Appendices

Center for Drug Evaluation and Research

Makena Hearing

October 17 – 19, 2022

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Appendix 1

Reproductive Health Drugs Advisory Committee
Meeting on Gestiva August 26, 2006

Federal agencies, state and local governments, schools of public health, colleges and universities, private industry, nonprofit foundations, professional associations, clinicians, researchers, administrators, and health planners. There are no costs to the respondents other than their time. The total estimated annualized burden hours are 8,645.

ESTIMATED ANNUALIZED BURDEN HOURS

Respondents	Number of respondents	Number of responses/respondent	Avg. burden per response (in hrs)
Office-based physicians (eligible):			
Physician Induction Interview	2,662	1	35/60
Patient Record form	2,263	30	5/60
Pulling and re-filing Patient Record form	399	30	1/60
CCSS	712	1	15/60
Office-based physicians (ineligible):			
Patient Induction Interview	888	1	5/60
Community Health Center Directors:			
Community Health Center Induction Interview	104	1	20/60
CHC Providers:			
Physician Induction Interview	312	1	35/60
Patient Record Form	265	30	5/60
Pulling and re-filing Patient Record form	47	30	1/60
CCSS	312	1	15/60

Dated: July 11, 2006.

Joan F. Karr,

Acting Reports Clearance Officer, Centers for Disease Control and Prevention.

[FR Doc. E6–11521 Filed 7–19–06; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Psychopharmacologic Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Psychopharmacologic Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on September 7 and 8, 2006, from 8 a.m. to 5 p.m.

Location: Hilton Hotel,The Ballrooms, 620 Perry Pkwy., Gaithersburg, MD 20877.

Contact Person: Cicely Reese, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane (for express delivery, 5630 Fishers Lane, rm. 1093) Rockville, MD 20857, 301–827–7001, FAX: 301–827–6776, e-mail: *Cicely.Reese@fda.hhs.gov*, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 3014512544. Please call the Information Line for up-to-date information on this meeting. The background material will become available no later than the day before the meeting and will be posted on FDA's Web site at *http://www.fda.gov/ohrms/dockets/ac/acmenu.htm* under the heading ''Psychopharmacologic Drugs Advisory Committee (PDAC).'' (Click on the year 2006 and scroll down to PDAC meetings.)

Agenda: On September 7, 2006, the committee will discuss new drug application (NDA) 21–999, paliperidone extended-release (ER) tablets, Janssen, L.P./Johnson & Johnson Pharmaceutical Research and Development, L.L.C., proposed indication for treatment of schizophrenia. On September 8, 2006, the committee will discuss NDA 21–992, desvenlafaxine succinate (DVS 233), ER tablets, Wyeth Pharmaceuticals, proposed indication for treatment of major depressive disorder.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person on or before August 23, 2006. Oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. on both days. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation on or before August 23, 2006.

Persons attending FDA's advisory committee meetings are advised that the agency is not responsible for providing access to electrical outlets.

FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to a disability, please contact Cicely Reese at least 7 days in advance of the meeting.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: July 13, 2006.

Randall W. Lutter,

Associate Commissioner for Policy and Planning.

[FR Doc. E6–11537 Filed 7–19–06; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Advisory Committee for Reproductive Health Drugs; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Advisory Committee for Reproductive Health Drugs.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on August 29, 2006, from 8 a.m. to 5:30 p.m.

Location: Hilton Hotel, The Ballrooms, 620 Perry Pkwy., Gaithersburg, MD.

Contact Person: Teresa Watkins, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane (for express delivery, 5630 Fishers Lane, rm. 1093), Rockville, MD 20857, 301–827–7001, FAX: 301–827–6776, e-mail: *Teresa.Watkins@fda.hhs.gov* or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 3014512537. Please call the Information Line for up-to-date information on this meeting. When available, background materials for this meeting will be posted 1 business day prior to the meeting on the FDA Website at *http://www.fda.gov/ohrms/dockets/ac/acmenu.htm*. Click on the year 2006 and scroll down to the Advisory Committee for Reproductive Health Drugs.)

Agenda: The committee will discuss new drug application (NDA) 21–945, proposed trade name Gestiva, 17 alpha-hydroxyprogesterone caproate injection, 250 mg/mL, Adeza Biomedical, for the proposed indication prevention of preterm delivery in women with a history of a prior preterm delivery.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person on or before August 15, 2006. Oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation on or before August 15, 2006.

Persons attending FDA's advisory committee meetings are advised that the agency is not responsible for providing access to electrical outlets.

FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to a disability, please contact Teresa Watkins at least 7 days in advance of the meeting.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: July 13, 2006.

Randall W. Lutter,

Associate Commissioner for Policy and Planning.

[FR Doc. E6–11538 Filed 7–19–06; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2006D–0246]

Draft Manufactured Food Regulatory Program Standards; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft document entitled ''Manufactured Food Regulatory Program Standards'' (draft program standards). The draft program standards, which establish a uniform foundation for the design and management of State programs responsible for regulation of plants that manufacture, process, pack, or hold foods in the United States, are being distributed for comment purposes only. This document is neither final nor is it intended for implementation at this time.

DATES: Written comments on the draft program standards may be submitted by September 18, 2006. General comments on the draft program standards are welcome at any time. Submit written comments on the information collection provisions by September 18, 2006.

ADDRESSES: Submit written comments on the information collection provisions to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments*. Identify comments with the docket number found in brackets in the heading of this document.

Submit written requests for single copies of the draft program standards to the Division of Federal-State Relations (HFC–150), Office of Regional Operations, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist the office in processing your request, or fax your request to 716–551–3845. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft program standards.

FOR FURTHER INFORMATION CONTACT: Beverly Kent, Division of Federal-State Relations, Food and Drug Administration, 300 Pearl St., suite 100, Buffalo, NY 14202, 716–541–0331.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft document entitled ''Manufactured Food Regulatory Program Standards.'' The standards were developed after the Department of Health and Human Services, Office of Inspector General (OIG) audited FDA's oversight of food firm inspections conducted by States through contracts. In June 2000, the OIG released its findings. The OIG recommended that FDA take steps to promote ''equivalence among Federal and State food safety standards, inspection programs, and enforcement practices.'' The report is on the Internet at *http://www.oig.hhs.gov/oei/reports/oei-01-98-00400.pdf*. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

In response to the OIG's findings, FDA established a committee to draft a set of quality standards for manufactured food regulatory programs. The committee was comprised of officials from FDA and from State agencies responsible for the regulation and inspection of food plants.

These draft program standards establish a uniform foundation for the design and management of a State program that is an operational unit(s) responsible for the regulatory oversight of food plants that manufacture, process, pack, or hold foods in the United States. The elements of the draft program standards describe best practices of a high-quality regulatory program. Achieving conformance with these program standards will require comprehensive self-assessment on the part of a State program and will encourage continuous improvement and innovation. All self-assessment

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

Advisory Committee for Reproductive Health Drugs Meeting
August 29, 2006

Hilton, Gaithersburg, MD
8:00 a.m. – 5:30 p.m.

AGENDA

The Committee will discuss new drug application (NDA) 21-945, proposed trade name Gestiva, 17 alpha-hydroxyprogesterone caproate injection, 250 mg/mL (once weekly), Adeza Biomedical, for the proposed indication prevention of preterm delivery in women with a history of a prior preterm delivery.

8:00	Call to Order and Introductions	Ezra Davidson, M.D. Acting Chair, Advisory Committee for Reproductive Health Drugs (ACRHD)
	Conflict of Interest Statement	Teresa Watkins, PharmD. Designated Federal Official (ACRHD)
8:15	Welcome and Comments	Scott Monroe, M.D. Acting Director, Division of Reproductive and Urologic Products
8:20	**FDA Invited Speaker** Causes of Premature Birth: The Premature Parturition Syndrome	Roberto Romero, M.D. Chief, Perinatology Research Branch Intramural Division, NICHD, NIH, DHHS
9:00	**Sponsor Presentation** 17P for the Prevention of Recurrent Preterm Birth	Durlin E. Hickok, MD, MPH Vice President, Medical Affairs Adeza Biomedical
	The Unmet Medical Need to Reduce Preterm Birth	Michael P. Nageotte, MD Professor, Obstetrics and Gynecology University of California, Irvine Past President of Society for Maternal-Fetal Medicine (SMFM)
10:30	Break	
10:45	**FDA Presentation** Efficacy and Safety Findings and Issues	Barbara Wesley, MD, MPH Medical Officer Division of Reproductive and Urologic Products

11:45	Clarifying questions from the committee to either FDA or Adeza	
12:00	Lunch	
1:00	Open Public Hearing	
2:00	Statistical Presentation	Daniel Gillen, Ph.D. Assistant Professor, Department of Statistics University of California, Irvine
	Committee Discussion	
4:00	Committee vote	
4:30	Adjournment	

Advisory Committee for Reproductive Health Drugs

August 29, 2006

Committee Members expected to attend

Arthur L. Burnett, M.D.
Diane Merritt, M.D.
James R. Scott, M.D.
William D. Steers, M.D.
Lorraine J. Tulman, DNSc, RN, FAAN
O. Lenaine Westney, M.D.

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SGE Patient Representative (voting) - Elizabeth Shanklin-Selby, Frederick, M.D.

Guest Speaker (non-voting)
Roberto Romero, M.D.
Chief, Perinatology Research Branch
Intramural Division, NICHD
National Institutes of Health
4704 St Antoine Blvd
Detroit MI 48201

Guest (non-voting)
Steven Ryder, M.D., F.A.C.P. – Acting Industry Representative
Senior Vice President and Therapeutic Area Group Head
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~~~~~~

FDA Center for Drug Evaluation and Research Participants at the Table (non-voting)

Julie Beitz, M.D.
Director, Office of Drug Evaluation III

Daniel Shames, M.D.
Acting Deputy Director, Office of Drug Evaluation III

Scott Monroe, M.D.
Acting Director, Division of Reproductive and Urologic Drugs

Lisa Kammerman, Ph.D.
FDA Statistician

Barbara Wesley, M.D., M.P.H.
Medical Officer, Division of Reproductive and Urologic Drugs
~~~~~~

Advisory Committee Briefing Document

For

17 α-Hydroxyprogesterone Caproate Injection, 250 mg/mL

NDA 21-945

Adeza Biomedical Corporation
1240 Elko Drive
Sunnyvale, CA 94089

25 July 2006

Available for Public Disclosure without Redaction

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LIST OF ABBREVIATIONS

17-HPC	17 α-hydroxyprogesterone caproate (active drug substance of 17P)
17P	17 α-hydroxyprogesterone caproate injection, 250 mg/mL; contains 17 α-hydroxyprogesterone caproate 250 mg, benzyl benzoate, castor oil, and benzyl alcohol
ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
AE	adverse event
Apgar	score reflecting condition of newborn; based on appearance, pulse, grimace, activity, and respiration
ASQ	Ages and Stages Questionnaire
BMI	body mass index
BPD	bronchopulmonary dysplasia
CI	confidence interval
CT	completed study
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
FU	follow-up
IF	Initial Formulation
ITT	intent-to-treat
IVH	intraventricular hemorrhage
MedDRA	Medical Dictionary for Regulatory Activities
MFMU	Maternal Fetal Medicine Units
NDA	New Drug Application

NEC	necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NICU	neonatal intensive care unit
PDA	patent ductus arteriosus
pPROM	preterm premature rupture of membranes
PSAI	preschool activities inventory
PTB	preterm birth
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
SAE	serious adverse event
SD	standard deviation
SPTD	spontaneous preterm delivery
US	United States

1. EXECUTIVE SUMMARY

Treatment with 17 α-hydroxyprogesterone caproate injection, 250 mg/mL (17P) has been shown to significantly reduce the rate of recurrent preterm birth among women at high risk for preterm birth. In a controlled clinical study conducted by the National Institute of Child Health and Human Development (NICHD), weekly injections of 17P reduced the incidence of preterm birth and serious perinatal and neonatal morbidities. In 2003, the results of the NICHD study were published by Meis and colleagues in the *New England Journal of Medicine* and led to a recommendation from the American College of Obstetricians and Gynecologists Committee on Obstetric Practice that progesterone be used to prevent recurrent preterm birth.[1,2] At this time, no Food and Drug Administration (FDA)-approved formulation of 17P is available and the only source is from compounding pharmacies. Recognizing the benefits of having a product manufactured and marketed under FDA oversight, Adeza Biomedical (Adeza) has submitted a 505(b)(2) New Drug Application (NDA) submission to market GESTIVA (17P) for the prevention of recurrent preterm birth.

Preterm birth, defined as birth before the 37th week of gestation, is the leading cause of neonatal mortality and morbidity in the United States (US) and represents a major health problem.[3] The incidence of preterm birth continues to rise in the US. In 2004, the Centers for Disease Control and Prevention reported over 500,000 preterm births in the US, which equates to approximately 1 every minute. According to the Centers for Disease Control and Prevention, 12.5% of the 4 million births in 2004 occurred preterm, which represents an 18% increase since 1990 and a 33% increase since 1981.[4] There are multiple risk factors that increase the likelihood of a woman experiencing preterm birth including low prepregnancy weight, drug and alcohol abuse, non-Caucasian race, lower socioeconomic status, and medical complications during pregnancy. One of the most significant risk factors for preterm birth is previous pregnancy history, as women who have had a prior preterm birth have a 2.5-fold greater risk than women with no prior history of preterm birth.[5,6]

Infants born preterm are at increased risk of experiencing serious complications such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), periventricular leukomalacia, necrotizing enterocolitis (NEC), apnea, jaundice, anemia, and infections due to immature immune systems.[7,8] Preterm birth is also associated with significant long-term morbidities such as retinopathy of prematurity (ROP), cerebral palsy, and mental retardation. The increased risks of neonatal morbidities are apparent not only for those infants born very premature, but also for late preterm infants born at 34, 35, and even 36 weeks of gestation.[9,10,11]

The costs associated with preterm birth are staggering. The March of Dimes estimates that the hospital expenditures for preterm or low birth weight infants totaled $18.1 billion in 2003, which represents nearly half of all infant-related hospital spending.[12] The cost of inpatient and outpatient care throughout the first year of life for preterm infants is estimated to be 15 times that of term infants.[12] While neonatal hospital costs are higher on a per case basis for those infants born at the earliest gestational ages, total neonatal costs are relatively consistent from 25 to 37 weeks because of the larger numbers of births with advancing gestational age.[13]

Currently, there is no effective FDA-approved product for preventing preterm birth. Despite widespread use, prophylactic methods, including pharmacological intervention, bed rest, and cervical cerclage have failed to demonstrate effectiveness in most studies.[14,15] Tocolytic drugs may be administered to reduce the frequency of uterine contractions after the onset of labor, but these drugs have not been demonstrated to prevent preterm birth.

Among the prophylactic interventions studied, progesterone agents have demonstrated the greatest potential to prevent preterm birth.[16,17] One such agent, 17 α-hydroxyprogesterone caproate (17-HPC), is a long-acting esterified derivative of the naturally occurring hormone 17 α-hydroxyprogesterone. 17-HPC has substantial progestational activity, a prolonged duration of action relative to its endogenous precursor, and no androgenic activity.[18,19] The safety of products containing 17-HPC as the active ingredient during pregnancy is supported by a long history of use, dating to the approval of Delalutin by the FDA in 1956. Delalutin was indicated for the treatment of habitual and recurrent abortion, threatened abortion, and postpartum after pains.

A number of historical clinical trials have shown the potential benefit of 17-HPC in preventing preterm birth in women at high risk for preterm delivery.[20,21,22,23,24] Among the 6 studies that examined the effectiveness of 17-HPC in preventing preterm birth in women with singleton pregnancies, 4 showed a significant reduction in the rate of preterm birth following treatment with 17-HPC.[21,22,23,24] Another study showed the same pattern of a reduced rate of preterm births with 17-HPC, but utilized a small sample size and appeared underpowered for statistical significance.[20] One study showed no benefit in using 17-HPC for prevention of preterm birth, but that study enrolled active military women who were pregnant, regardless of their previous pregnancy history.[25] A subsequent meta-analysis was performed by Keirse based upon the data from these 17-HPC clinical trials and confirmed the effectiveness of 17-HPC in reducing preterm birth.[16] In this meta-analysis, odds ratios demonstrated significant reductions in preterm birth, preterm labor, and birth weight <2500 g following 17-HPC use.

Although the individual studies and the meta-analysis supported a benefit of 17-HPC in reducing preterm birth, differences in methodology and treatment regimens in the individual studies did not allow for a consensus on the appropriate use of 17-HPC to prevent preterm birth. As a result, the Maternal Fetal Medicine Units (MFMU) Network of the NICHD designed and conducted a study to definitively evaluate the safety and efficacy of 17P for the prevention of recurrent preterm birth. The results from this study, hereafter referred to as Study 17P-CT-002, form the primary basis for the efficacy claim of Adeza's 505(b)(2) NDA submission.

The NICHD conducted a multicenter, randomized, double-masked, placebo-controlled study to evaluate the safety and efficacy of 17P for the prevention of recurrent preterm birth. This study enrolled a high-risk population of pregnant women between 16 weeks and 20 weeks 6 days gestation with a history of previous singleton spontaneous preterm delivery (SPTD). A total of 463 patients were randomized in a 2:1 ratio to receive weekly injections of either 17P (310 patients) or placebo (153 patients) through 36 weeks of gestation or birth, whichever occurred first.

The results from this study confirmed the efficacy of 17P in preventing preterm birth. Treatment with 17P significantly reduced the incidence of preterm birth less than 37 weeks of gestation compared with placebo (P<0.001) (Table 1-1). 17P treatment also significantly (P<0.05) reduced the incidence of preterm births when defined as <35^0 or <32^0 weeks of gestation, significantly prolonged the duration of pregnancy from time of enrollment (P=0.0024), and significantly increased the mean gestational age at birth (P=0.0024).

Table 1-1. Summary of Efficacy Endpoints

Outcome	**17P**	**Placebo**	***P* value**
ITT Data[a]	**N=310**	**N=153**	
Birth <37^0 weeks, n (%)	115 (37.1)	84 (54.9)	0.0003
Birth <35^0 weeks, n (%)	67 (21.6)	47 (30.7)	0.0324
Birth <32^0weeks, n (%)	39 (12.6)	30 (19.6)	0.0458
Prolongation of pregnancy, median days	131.0	125.0	0.0024
All Available Data[a,b]	**N=306**[a]	**N=153**	
Birth <37^0 weeks, n (%)	111 (36.3)	84 (54.9)	0.0001
Birth <35^0 weeks, n (%)	63 (20.6)	47 (30.7)	0.0165
Birth <32^0weeks, n (%)	35 (11.4)	30 (19.6)	0.0180
Mean gestational age at birth, wk	36.2	35.2	0.0024

Abbreviations: intent-to-treat (ITT)

[a] The ITT and all-available-data analyses included miscarriages, stillbirths, and patients lost to follow-up as treatment failures.

[b] Four patients in the 17P group were lost to follow-up (at 18^4, 22^0, 34^3, and 36^4 weeks of gestation) and were excluded from the all-available-data population. The results published by Meis and colleagues were based on the all available data.[1]

Treatment with 17P also led to significantly (P<0.05) lower incidence rates of low birth weight (<2500 g) infants, neonates with NEC, neonates having any IVH, neonates requiring supplemental oxygen, and neonates requiring admission to the neonatal intensive care unit (NICU) (Table 1-2). Although the differences did not reach statistical significance, incidence rates of RDS, ventilator support, and patent ductus arteriosus (PDA) were also reduced following 17P treatment.

Table 1-2. Summary of Infant Outcomes

Outcome	17P	Placebo	*P* value
All Available Infant Data[a]	**N=301**	**N=151**	
Mean infant birth weight, g	2760	2582	0.0736
Percent of infants <2500 g at birth, n (%)	82 (27.2)	62 (41.1)	0.0029
Percent of infants <1500 g at birth, n (%)	26 (8.6)	21 (13.9)	0.0834
Live Births	**N=295**	**N=151**	
Admitted to NICU, n (%)	82 (27.8)	55 (36.4)	0.0434
Necrotizing enterocolitis, n (%)	0	4 (2.7)	0.0127
Supplemental oxygen, n (%)	45 (15.4)	36 (24.2)	0.0248
Any IVH, n (%)	4 (1.4)	8 (5.3)	0.0258
Composite neonatal morbidity index, n (%)	35 (11.9)	26 (17.2)	0.1194
Mean days of respiratory therapy	1.7	2.7	0.0438
Integrated Data[c]	**N=404**	**N=209**	
Miscarriages, n (%)	6 (1.5)	1 (0.5)	0.2629
Stillbirths, n (%)	7 (1.7)	4 (1.9)	0.8769
Neonatal deaths, n (%)	10 (2.5)[d]	9 (4.3)[e]	0.1928

Abbreviations: neonatal intensive care unit (NICU); intraventricular hemorrhage (IVH)

a The all-available-data analyses included miscarriages and stillbirths as treatment failures.

b Four patients in the 17P group were lost to follow-up (at 18^4, 22^0, 34^3, and 36^4 weeks of gestation) and were excluded from the all-available-data population. The results published by Meis and colleagues were based on the all available data.[1]

c Integrated data include data from a terminated study initiated by NICHD prior to the definitive study. Details on this study and the integration of data are provided in Section 3.

d Percentage based on all randomized 17P patients; the rate for liveborn infants was 2.6% (10/386).

e Percentage based on all randomized placebo patients; the rate for liveborn infants was 4.5% (9/202).

The effectiveness of 17P treatment in the NICHD study was accompanied by a favorable safety profile. Weekly intramuscular injections of 17P were well tolerated by pregnant women, with injection site reactions being the most commonly reported adverse event (AE). *In utero* exposure to 17P was safe for the developing fetus and neonate as demonstrated by comparable rates of combined miscarriages, stillbirths, and neonatal deaths between the 17P and placebo groups, and rates of congenital anomalies identified at birth in the NICHD study (approximately 2% in both groups) that were consistent with those reported in general population surveys.

To assess the long-term outcome of infants exposed to 17P *in utero*, a follow-up observational study (Study 17P-FU) was conducted by the NICHD that examined the health and development of the infants born during the 17P-CT-002 study. This study was developed after completion of the 17P-CT-002 study and was specifically designed to assess safety outcomes. The study design was discussed with the FDA prior to initiation. This was a noninterventional safety study that collected data on children using the Ages and Stages Questionnaire (ASQ), a Survey Questionnaire tailored for this study, and a physical examination. The ASQ is a standard measurement tool completed by the parent/guardian that evaluates development from 4 months to 5 years of age in communication, gross motor, fine motor, problem solving, and personal-social skills (see Appendix 1). The Survey Questionnaire was specifically designed for this study and collected information from the parent/guardian on the child's gender-specific play, physical growth, activity levels, motor control, vision or hearing difficulties, and any diagnoses since discharge from birth hospitalization that were made by a health professional. The physical examination included measurements of the child's current weight, height, head circumference, and blood pressure, as well as documentation of any major physical abnormality, with specific documentation for genital abnormalities.

The long-term follow-up assessments demonstrated no untoward effect of 17P on development or physical health. At the time of evaluation, children were between 2.5 and 5.4 years of age. Of the infants discharged from birth hospitalization, 68% of the infants in the 17P group and 59% of the infants in the placebo group were enrolled in Study 17P-FU. The demographics of the children were comparable between the 2 groups. There were no differences in the percentage of children with delay in at least one developmental area measured by the ASQ (communication, gross motor, fine motor, problem solving, and personal-social). The percentages of children with delay in each of the 5 developmental areas were also not statistically different. The data from the Survey Questionnaire did not identify any safety concerns related to the use of 17P during pregnancy. Physical examination findings included reports of genital or reproductive anomalies in 2.6% of the children exposed *in utero* to 17P and 1.2% of children exposed *in utero* to placebo. After a review of the study data and additional medical records for some of the children, no genital or reproductive anomaly was considered related to *in utero* exposure to 17P based on the physical finding, the gestational age at first exposure, or the presence of other likely contributing factors.

The safety of 17P during pregnancy is further supported by a number of published clinical and epidemiological studies. In the clinical trials examining the use of 17-HPC for prevention of preterm birth, 17-HPC exposure was not associated with neonatal deaths or the development of congenital anomalies.[20,21,22,23,24] Similarly, no adverse effects of 17-HPC on pregnancy outcomes or the developing fetus were observed in a study of threatened abortion.[26] Epidemiological studies have not shown an association between 17-HPC and the development of congenital anomalies. A study from the Mayo clinic examined a cohort of 24,000 pregnancies and found that the 649 offspring exposed to 17-HPC showed no increase in congenital anomalies compared with controls over a mean followup period of 11.5 years.[27] A collaborative cohort study of more than 13,000 women in West Germany included 462 first trimester exposures to 17-HPC and similarly found no increase in malformations.[28] In a study of 1608 infants born to mothers who received progestins during the first trimester, Katz and colleagues found no differences in the incidence of congenital anomalies, including genital anomalies, among infants exposed to progestins (including 17-HPC) compared with controls.[29] Overall, the results of these published studies support the NICHD study findings that 17P is not teratogenic and does not endanger the developing infant.

In conclusion, clinical studies demonstrate that weekly injections of 17P result in a substantial reduction in the rate of recurrent preterm birth among women at increased risk for preterm birth, and also reduce the likelihood of clinically significant perinatal and neonatal morbidities. The administration of weekly injections of 17P is not associated with greater overall occurrences of adverse effects in pregnant women or any sequelae, including developmental delay in their infants, when compared with placebo. 17P is effective and has a favorable safety profile when used in the treatment of recurrent preterm birth in pregnant women.

The proposed indication for GESTIVA (17P) is for the prevention of preterm birth in pregnant women with a history of at least 1 spontaneous preterm birth.

2. INTRODUCTION

2.1 PRETERM BIRTH: UNMET MEDICAL NEED

2.1.1 Prevalence and Complications of Preterm Birth

Preterm birth, defined as birth before the 37th week of gestation, is a very serious health concern recognized as the leading cause of neonatal mortality and morbidity in the US.[3] In spite of advances in perinatal care, its incidence continues to rise in the US. According to the Centers for Disease Control and Prevention, 12.5% of the 4 million births in 2004 occurred preterm, which represents an 18% increase since 1990 and a 33% increase since 1981.[4] At its current rate, 1 preterm birth occurs nearly every minute in the US. In January 2003, the March of Dimes recognized this increase in preterm birth rate as a growing public health concern and started a multimillion dollar campaign to reduce preterm births as its primary initiative.

A number of factors have been identified that place women at-risk for preterm birth including previous pregnancy history, low prepregnancy weight, drug and alcohol abuse, non-Caucasian race, lower socioeconomic status, and medical complication during pregnancy. Women with prior preterm birth have demonstrated a substantially elevated risk (up to 2.5-fold higher).[5,6,30] Furthermore, the lower the gestational age of a prior preterm birth, the greater the risk of subsequent preterm birth. Mercer et al reported that women who delivered at 23 to 27 weeks gestation in a prior pregnancy had a 27.1% chance of delivering at less than 37 weeks in the current pregnancy.[5] When the prior delivery was at 28 to 34 weeks and 35 to 36 weeks, the probability for delivering before 37 weeks was 24.0% and 20.9%, respectively.

The NICHD has noted that a reduction in preterm delivery will reduce one of the primary causes of perinatal and neonatal morbidity and mortality.[7] Complications in the neonatal period that can occur with prematurity include RDS, IVH, periventricular leukomalacia, NEC, apnea, jaundice, anemia, and infections due to immature immune systems.[7] Long-term morbidities associated with preterm birth include retinopathy of prematurity, mental retardation, and cerebral palsy, which is 40 times more likely to occur in preterm infants than term infants.[30] Additionally, preterm infants without obvious neurological deficits remain at increased risk for cognitive problems such as attention deficit disorders throughout childhood.[10]

Preterm births impart a substantial financial burden on the US healthcare system. In evaluating the costs of preterm birth, Gilbert et al estimated the neonatal hospital cost for a preterm infant born at 25 weeks of gestation in California in 1996 was $202,700.[13] By contrast an infant born at 38 weeks of gestation would incur neonatal hospital costs of only $1100. The March of Dimes estimated that the total US hospital expenditures for all infants in 2003 was $36.7 billion, of which nearly half, $18.1 billion, was for preterm or low birth weight infants.[12] The average hospital stay for infants with any diagnosis of prematurity or low birth weight is 13.6 days compared with 2.0 days for term infants without complications. While these costs are primarily attributable to increased hospital stays during the neonatal period, the cost of inpatient and outpatient care throughout the first year of life for preterm infants is estimated to be 15 times that of term infants.[12] Additional estimates have reported prematurity and low birth weight combined to account for 35% of all direct infant care expenditures in the US.[31]

The benefits of prolonging pregnancy by even 1 week are considerable. Along with birth weight, gestational age is one of the most important determinants of an infant's likelihood of survival and subsequent health.[3] Among extremely low gestational age infants, the chances for survival increase dramatically with each additional week of gestation.[32,33] In addition to neonatal mortality, major neonatal morbidities are also decreased with increasing gestational ages. Incidence rates of PDA, NEC, and IVH are known to markedly decrease with increasing gestational age up to 32 weeks, while incidence rates of respiratory distress syndrome and the need for ventilator assistance have been shown to decrease with gestational age up to 37 weeks.[13,34] Lastly, as shown in Figure 2-1, each additional week of gestation from 25 to 37 weeks is associated with reduced neonatal hospitalization stays and associated costs.

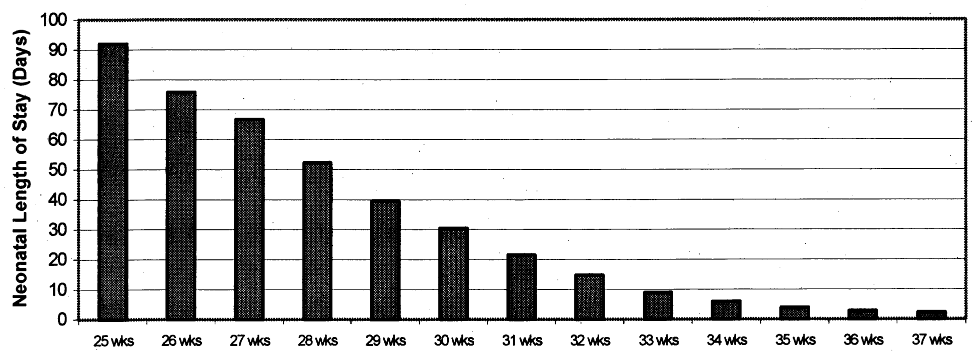


Figure 2-1. Neonatal Length of Hospital Stay by Gestational Age

The neonatology literature has historically focused on the outcomes of very low birth weight (<1500 g at birth) or very preterm infants, a population with the highest rate of mortality and morbidity.[32] Recently, considerable attention has been paid to preterm infants of greater gestational ages due to an increasing recognition that they contribute significantly to the total number of neonatal deaths. An analysis of gestational age distribution among preterm singleton infants born in 2002 shows that greater than 80% were delivered between 33 and 36 weeks of gestation.[35] In fact, most of the 33% increase in the rate of preterm births since 1981 can be attributed to the increases in late preterm infants.[36]

Late preterm infants born at 34 to 36 weeks have a mortality risk approximately 3 times that of term infants and that surviving late preterm infants are at increased risk for neonatal morbidities and cognitive problems throughout childhood.[9,10,11] Recently published studies have demonstrated that newborns born at 35 to 36 weeks of gestation experience significant mortality and morbidity, with a greater incidence of hypoglycemia, hypothermia, jaundice, and RDS compared with term infants.[37] In addition, late preterm term infants have longer hospital stays with higher associated costs, and are considerably more likely to require rehospitalization.[11,37] Based upon these new data, it is clear that the at-risk neonatal population includes all births prior to 37 weeks, and that treatment strategies need to address both very preterm and late preterm birth.

2.1.2 Current Treatment Strategies for Preterm Birth

Prophylactic methods for prevention of preterm birth, including drugs, bed rest, or other interventions such as prophylactic cerclage, have been shown in most studies to be ineffective.[14,15] Despite widespread use, conclusive clinical evidence to support the use of prophylactic cerclage in preventing preterm birth is limited. Four randomized trials evaluating cerclage in women with historic risk factors failed to demonstrate a reduction in birth before 37 weeks gestation as well as any positive effect on neonatal outcomes.[38,39,40,41] Three other studies evaluating cerclage in preventing preterm birth in women with a demonstrated short cervix upon second trimester ultrasound have been conducted, with only 1 study demonstrating potential benefit.[42,43,44] Althuisius et al investigated the efficacy of cervical cerclage plus bed rest versus bed rest alone, and demonstrated that cervical cerclage can reduce birth before 34 weeks gestation, however, no difference between groups were observed for neonatal outcomes.[42] In summary, the evidence supporting cervical cerclage does not support its use in all populations of pregnant women; however, ongoing research may shed light on specific populations that may benefit.[45]

Available data indicate that tocolytic drugs are not effective in preventing preterm birth or in improving perinatal outcomes but may be given to reduce the frequency of uterine contractions after the onset of labor. A number of trials have evaluated the efficacy of tocolytic therapy for the prevention of preterm birth. Only 1 trial was successful in increasing the rate of term births and increasing birth weight.[46] Among the other studies, 1 trial showed an increase in the mean estimated gestational age at delivery, 2 trials prolonged delivery in terms of days, and 2 other studies did not observe any benefit.[47,48,49,50,51] While the aforementioned trials evaluated beta-mimetics versus placebo, other trials have investigated magnesium sulfate. One trial evaluating magnesium sulfate demonstrated a significant pregnancy prolongation of greater than 48 hours (acute tocolysis), although the gestational age at birth was higher in the placebo group overall.[52] A recently published meta-analysis of 9 trials comparing various tocolytic agents exhibited mixed results and concluded that maintenance therapy with tocolytics is of little to no value.[53]

One of the few preventive measures to have shown effectiveness in randomized trials is the use of progesterone agents.[16,17] Progesterone has been shown to support gestation and to inhibit uterine activity.

2.2 17 α-HYDROXYPROGESTERONE CAPROATE

2.2.1 Rationale for Use in Prevention of Preterm Birth

17 α-hydroxyprogesterone caproate (17-HPC) is a long-acting esterified derivative of the naturally occurring hormone, 17 α-hydroxyprogesterone. Like its endogenous precursor, 17-HPC has no androgenic activity. Unlike its endogenous precursor, 17-HPC has

substantial progestational activity and a prolonged duration of action.[18,19] The mechanisms by which 17P prevents preterm birth are unknown and most likely pleiotropic in nature. Putative mechanisms include a direct relaxation of the myometrium or possibly genomic effects, which may include changes in transcription of genes and differential expression of progesterone receptor isoforms.[54] Other genomic mechanisms that have been proposed include inhibition of proinflammation, which is associated with production of prostaglandins and down-regulation of estrogen receptors.[55,56,57,58,59] Lastly, a nongenomic mechanism has been hypothesized that involves inhibition of the uterotonic effects of oxytocin on the myometrium via direct interaction with the oxytocin receptor.[60]

17-HPC has a long history of use in pregnant women dating back numerous decades, including a number of published controlled studies supporting 17-HPC for prevention of preterm births.[20,21,22,23] However, the individual studies differed in the risk status of the populations studied, the use of concurrent interventions (such as cervical cerclage) and the timing and dosage of 17-HPC. A meta-analysis of data from these 17-HPC clinical trials was performed by Keirse.[16] The odds ratio for 17-HPC to reduce preterm birth was 0.5 (95% confidence interval [CI] 0.30–0.85), indicating a significant reduction in the incidence of preterm birth following 17-HPC treatment. Likewise, the odds ratio demonstrated significant reductions in preterm labor and birth weight <2500 g following 17-HPC use. Pooled odds ratios demonstrated no significant effect on rates of miscarriage, perinatal death, or neonatal complications. Although this meta-analysis confirmed the effectiveness of 17-HPC, the differences in methodology, treatment regimens, and small sample sizes in the previous studies of 17-HPC did not allow for a consensus on the appropriate use of 17-HPC to reduce preterm birth.

Recognizing these unresolved issues and the compelling need to reduce preterm birth, the NICHD MFMU Network investigated the efficacy and safety of 17P for the prevention of recurrent preterm birth in a randomized, multicenter, double-masked, placebo-controlled clinical study. The results of the NICHD study were published by Meis and colleagues in the *New England Journal of Medicine* in 2003.[1] In the same year following the publication, the American College of Obstetricians and Gynecologists Committee on Obstetric Practice recommended that progesterone supplementation be used to reduce the risk of subsequent preterm birth in women with a documented history of at least 1 prior preterm birth.[2] However, no FDA-approved formulation of 17-HPC is currently available.

2.2.2 Marketing History of 17-HPC

The FDA first approved the use of 17-HPC in 1956. The marketed product, Delalutin (E.R. Squibb & Sons, Inc.), was approved for the treatment of habitual and recurrent abortion, threatened abortion, and postpartum after pains. In 1972, the FDA approved the use of Delalutin for the indication of control and palliation of advanced adenocarcinoma of the corpus uteri.

Delalutin is no longer marketed in the US. The FDA withdrew approval for NDA 16-911 after notification by Bristol-Myers Squibb that the drug would no longer be marketed.

The FDA stated in its withdrawal notice that the product was not being withdrawn because of safety or efficacy issues.

While no FDA-approved product is currently available, surveys have shown that use of 17P is becoming more common.[61] In questionnaires completed by 522 maternal fetal medicine specialists between December 2003 and January 2004, over one-third of respondents noted that they currently prescribe progesterone for the prevention of preterm birth. Among the 198 specialists that indicated they prescribed progesterone, 74% indicated they prescribed 17P as described in the Meis publication. A more recent survey completed in 2005 shows that the percentage of specialists prescribing progesterone has increased to 67%.[62]

Currently, only pharmacies able to compound the product fill prescriptions for 17P. Compounding pharmacies play an important role by creating customized medication for an individual patient based on allergies, dose sensitivity, or an inability to take the medication in its current dosage form. However, 17P is a drug product which does not require customization for individual use and would therefore be more appropriately supplied as an FDA-approved product under FDA oversight.

There are many benefits to having an FDA-approved product. An FDA-approved product would come with standardized labeling, including information on precautions and warnings, as well as detailed instructions for administration and dosing. Additionally, FDA approval will ensure preparation of the product under Good Manufacturing Practices which will provide consistency of the quality of the final product. Additionally, an FDA-approved product is subject to regulations concerning postmarketing safety surveillance. Lastly, an FDA-approved product will allow broad scale distribution thereby increasing availability of 17P to physicians and patients who are unfamiliar with compounded products.

2.2.3 Adeza Biomedical Development of GESTIVA

Recognizing the benefit of having a 17P product manufactured under FDA requirements and subject to postmarketing safety surveillance, Adeza Biomedical (Adeza) has recently submitted a 505(b)(2) NDA to market GESTIVA (17P) as a weekly injection for the prevention of preterm birth in pregnant women with a history of at least 1 spontaneous preterm birth.

Adeza is a medical technology company with a primary focus on pregnancy-related and female reproductive disorders, including preterm birth and infertility. Adeza requested and was granted nonexclusive access to the NICHD MFMU Network data previously published by Meis et al.[1] In preparation for their NDA submission for GESTIVA, Adeza had multiple meetings with the FDA to discuss the development of the NDA and the appropriateness of the data to be submitted. As requested by the FDA, full clinical study data collected by the NICHD MFMU Network were submitted as part of the NDA as well as follow-up data on the infants born to women enrolled in the NICHD study. A discussion of the clinical studies of 17P follows in Section 3.

It is important to note that the to-be-marketed formulation of 17P is identical to the 17P product used in the NICHD clinical studies and was formulated using the same source of active ingredient and has the same components, composition and packaging as the 17P used in the NICHD clinical studies. The 17P product is supplied as a sterile solution containing 17 α-hydroxyprogesterone caproate 25% (v/v), benzyl benzoate 46% (v/v), castor oil 28.6% (v/v), and benzyl alcohol 2% (v/v), as preservative.

3. NICHD CLINICAL STUDIES OF 17P

The NICHD conducted a multicenter, randomized, double-masked, placebo-controlled study to evaluate the use of 17 α-hydroxyprogesterone caproate injection, 250 mg/mL (17P) for the prevention of recurrent preterm birth. The study enrolled a high-risk population of pregnant women at 19 study centers. Women enrolled in the study had a current pregnancy at a gestational age of 16^0 to 20^6 weeks with a history of previous singleton spontaneous preterm delivery (SPTD). The main exclusion criteria were multifetal gestation, known major fetal anomaly or fetal demise, prior progesterone treatment or heparin therapy during current pregnancy, history of thromboembolic disease, or maternal medical/obstetrical complications (eg, current or planned cerclage, hypertension requiring medication, and seizure disorder). After 463 of the 500 proposed patients were enrolled, enrollment in this study was stopped on the recommendation of an independent Data and Safety Monitoring Committee (DSMC) when an interim analysis of 351 completed patients demonstrated a beneficial effect of 17P in reducing preterm birth $<37^0$ weeks of gestation. Those patients already enrolled in the study continued receiving study drug in a blinded fashion until the study was completed per protocol. The results from this completed study, hereafter referred to as Study 17P-CT-002, form the primary basis for the efficacy claim for 17P.

The NICHD also conducted a follow-up safety study to provide long-term follow-up data from infants born in the NICHD study. The FDA discussed with Adeza and the NICHD the required design aspects of a follow-up study, noting that long-term data would be required from a substantial number of babies (at least 35%-50% of babies in each treatment arm of the study) through at least 2 years of age. This study was not designed to assess efficacy. Rather, Study 17P-FU was designed and implemented to determine whether there is a difference in achievement of developmental milestones and physical health between children exposed *in utero* to 17P and those exposed *in utero* to placebo in Study 17P-CT-002. Women who were enrolled in Study 17P-CT-002 whose liveborn infant survived to be discharged from the hospital were contacted and asked if their child would participate in a follow-up study of the child's health status. Only patients enrolled in Study 17P-CT-002 at study sites that were active members of the MFMU Network in 2005 were considered eligible for the study. The results from Study 17P-FU are included in the safety evaluation of 17P.

Prior to conducting Study 17P-CT-002, the NICHD had initiated an earlier study with the same protocol design, inclusion and exclusion criteria, and study procedures but with a different manufacturer of study drug (Study 17P-IF-001). The study was terminated after only one-third of the proposed patients were enrolled because the study drug (17P) was recalled by the manufacturer due to violations of manufacturing practices. The recall was applicable to all products manufactured by the plant and was not limited to 17P. The study drug used in the terminated study is referred to as the Initial Formulation (IF). Because only 104 of a planned 500 patients were not withdrawn from Study 17P-IF-001 due to termination of the study, the efficacy data from the terminated study are not considered adequate to allow for any meaningful interpretation of differences in preterm birth rates between 17P and placebo. However, rather than dismissing these data, data from this terminated study were combined with the data from Study 17P-CT-002 to further explore the efficacy and safety of 17P.

The primary assessment of efficacy presented in the 505(b)(2) submission and in this document focuses on the completed Study 17P-CT-002. While the efficacy data from the terminated study were not considered meaningful on their own, the 17P-IF-001 data were combined with the 17P-CT-002 data for analyses to further assess the efficacy of 17P. In evaluating the clinical safety of 17P in pregnant women, data from both Study 17P-IF-001 and Study 17P-CT-002 were integrated into 1 database, compiling safety data from the 2 studies. Long-term follow-up data on the health and development of infants born during the 17P-CT-002 study collected in the noninterventional 17P-FU study are also included in the overall safety assessment.

Table 3-1 presents a summary of the clinical studies summarized in the efficacy and safety evaluation of 17P for the prevention of preterm birth.

Table 3-1. NICHD Clinical Studies of 17P

Protocol #; Status	Study Design	Study Population	Treatment Dose	Duration of Drug Treatment	Number of Patients	Mean Age (Range)
17P-CT-002; Completed [a] Aug 2002	Double-masked, placebo-controlled, randomized 2:1 17P to placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation through 36^6 wks gestation or birth[b]	463 17P: 310 Placebo: 153	26.2 yr (16, 43)
Study 17P-FU; Completed Nov 2005	Observational long-term safety follow-up for Study 17P-CT-002	Infants discharged live in Study 17P-CT-002	None	No study treatment was administered	278 17P: 194 Placebo: 84	47.4 mo (30, 64)
17P-IF-001; Terminated [c] Feb 1999	Double-masked, placebo-controlled, randomized 2:1 17P to placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation through 36^6 wks gestation or birth[b]	150 17P: 94 Placebo: 56	26.2 yr (17, 42)

[a] An independent DSMC reviewed study data after 400 patients had completed the study. Based on that interim data set, the DSMC recommended that enrollment be discontinued because 17P had shown significant benefit for the primary outcome (preterm birth $<37^0$ weeks). At the time the DSMC made its recommendation to stop enrollment, 463 patients had been enrolled, which was 93% of the proposed sample size of 500 patients.

[b] Gestational age is reported in weeks with days in superscript. For example, a gestational age of 36 weeks 6 days is presented as 36^6, and 37 weeks 0 days is presented as 37^0.

[c] Study 17P-IF-001 was terminated early by NICHD when the manufacturer recalled the study drug. The last patient visit was in August 1999. Only 104 patients (65 in the 17P group and 39 in the placebo group) were not withdrawn from the study due to study termination.

4. EFFICACY EVALUATION

4.1 EFFICACY OF 17P IN NICHD CLINICAL STUDIES

4.1.1 Patient Disposition

The disposition of patients in Study 17P-CT-002 is summarized in Figure 4-1. A total of 463 patients were enrolled and randomized to treatment; 310 in the 17P group and 153 in the placebo group. A comparable percentage of patients in each treatment group completed injections through 36^6 weeks gestation or birth, whichever occurred first. Early withdrawal from study drug occurred at a similar rate in both treatment groups. Most of these patients discontinued due to nonclinical reasons, which were not further defined. Four patients, all in the 17P group, were lost to follow-up.

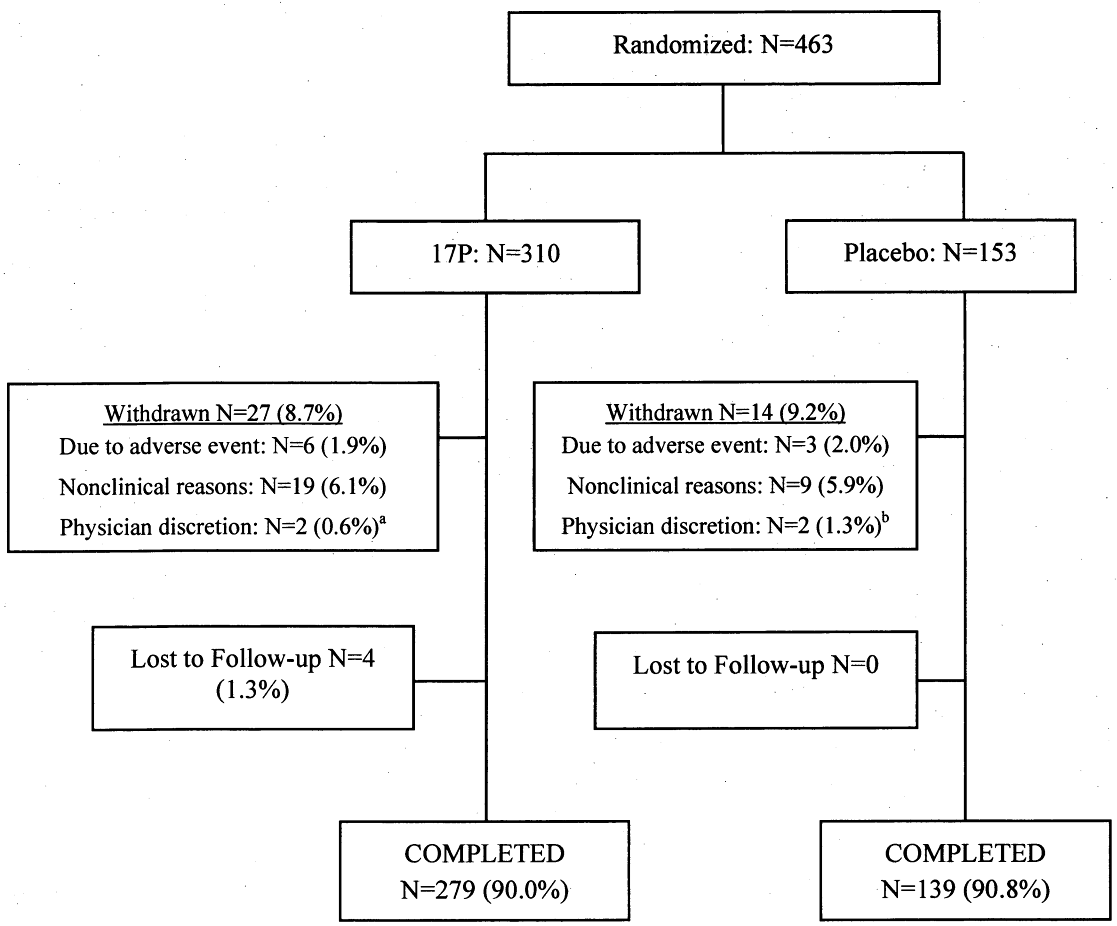


Figure 4-1. Patient Disposition

Note: "Withdrawn from the study" was defined as the patient no longer received study drug. "Lost to follow-up" was defined as the patient's delivery data could not be obtained.

a In the 17P group, an investigator stopped the participation of one patient due to injection site reactions. Therefore, 7 (2.2%) patients in the 17P group discontinued due to AEs.

b In the placebo group, an investigator stopped the participation of 1 patient due to a potential allergic reaction. Therefore, 4 (2.6%) patients in the placebo group discontinued due to AEs.

4.1.2 Patient Demographics and Baseline Characteristics

The baseline characteristics of patients enrolled in Study 17P-CT-002 were comparable between treatment groups (Table 4-1). More than half of the patients were African American (59%). The age of the patients ranged from 16 to 43 years.

Table 4-1. Demographics and Baseline Characteristics

Characteristic	17P N=310	Placebo N=153	*P* value
Age, yr			0.2481[d]
Mean (SD)	26.0 (5.6)	26.5 (5.4)	
Min, Max	16, 43	16, 40	
Race or ethnic group, n (%)[a]			0.8736[b]
African American	183 (59.0)	90 (58.8)	
Caucasian	79 (25.5)	34 (22.2)	
Hispanic	43 (13.9)	26 (17.0)	
Asian	2 (0.6)	1 (0.7)	
Other	3 (1.0)	2 (1.3)	
Marital status, n (%)			0.6076[b]
Married or living with partner	159 (51.3)	71 (46.4)	
Divorced, widowed, or separated	32 (10.3)	18 (11.8)	
Never married	119 (38.4)	64 (41.8)	
Prepregnancy BMI (kg/m^2)			0.3310[d]
Mean (SD)	26.9 (7.9)	26.0 (7.0)	
Min, Max	15.2, 72.2	16.1, 50.7	
Years of education			0.2175[d]
Mean (SD)	11.7 (2.3)	11.9 (2.3)	
Min, Max	2, 16	3, 16	
Diabetes, n (%)	13 (4.2)	4 (2.6)	0.3954[b]
Smoked cigarettes during pregnancy, n (%)	70 (22.6)	30 (19.6)	0.4647[b]
Alcoholic drinks during pregnancy, n (%)	27 (8.7)	10 (6.5)	0.4172[b]
Used street drugs during pregnancy, n (%)	11 (3.5)	4 (2.6)	0.7822[c]

Abbreviations: body mass index (BMI)

a Race or ethnic group was self-assigned by the women.

b *P* value from the chi-square test.

c *P* value from the Fisher exact test.

d *P* value from the Wilcoxon rank sum test.

Obstetrical histories of patients enrolled in Study 17P-CT-002 were comparable with the exception of statistically significant (*P*=0.0068) difference in the number of previous preterm deliveries (Table 4-2). Likewise, the percentage of patients who had >1 previous preterm birth was significantly (*P*=0.0036) lower in the 17P group (28%) compared with the placebo group (41%). Adjustments were made to the analysis of the primary endpoint (preterm birth <37^0 weeks gestation) that demonstrated that this imbalance did not impact the efficacy results of the study.

Table 4-2. Previous and Current Obstetrical History

Obstetrical History	17P N=310	Placebo N=153	*P* value
No. of previous preterm deliveries			0.0068[c]
Mean (SD)	1.4 (0.7)	1.6 (0.9)	
Min, Max	1, 5	1, 6	
>1 Previous preterm birth, n (%)	86 (27.7)	63 (41.2)	0.0036[a]
No. of previous SPTD			0.0017[c]
Mean (SD)	1.3 (0.7)	1.5 (0.9)	
Min, Max	1, 5	1, 6	
No. of previous term deliveries			0.6650[c]
Mean (SD)	0.8 (1.1)	0.7 (1.0)	
Min, Max	0, 7	0, 5	
Duration of gestation at randomization, wk			0.5929[c]
Mean (SD)	18.9 (1.4)	18.8 (1.5)	
Min, Max	16, 21	16, 21	
Gestational age of qualifying delivery, wk			0.2078[c]
Mean (SD)	30.6 (4.6)	31.3 (4.2)	
Min, Max	20, 36	20, 36	
Previous miscarriage, n (%)	93 (30.0)	57 (37.3)	0.1166[a]
Previous stillbirth, n (%)	31 (10.0)	13 (8.5)	0.6039[a]
Infection during pregnancy (before randomization), n (%)	98 (31.6)	55 (35.9)	0.3510[a]
Corticosteroids during pregnancy (before randomization), n (%)	5 (1.6)	8 (5.2)	0.0359[b]

Abbreviations: spontaneous preterm delivery (SPTD)

[a] *P* value from the chi-square test.

[b] *P* value from the Fisher exact test.

[c] *P* value from the Wilcoxon rank sum test.

4.1.3 Efficacy Results

4.1.3.1 Prevention of Preterm Birth <37^0 Weeks

The primary efficacy outcome was preterm birth <37^0 weeks (as determined by project gestational age). All deliveries occurring from randomization through 36^6 weeks gestation, including any miscarriages and elective abortions, were to be counted in the primary outcome.

Treatment with 17P was effective in reducing preterm birth prior to 37^0 weeks of gestation as shown in Table 4-3. The incidence of deliveries prior to 37^0 weeks gestation was significantly lower in the 17P group than the placebo group whether examined using the intent-to-treat (ITT) population (P=0.0003) or all-available-data population, which excluded the 4 patients lost to follow-up. The incidence of preterm birth was reduced

32% following 17P treatment compared with placebo in the ITT population, yielding a relative risk for preterm birth of 0.68 (95% CI: 0.55 – 0.83) for 17P. The incidence of preterm birth was reduced 34% following 17P treatment compared with placebo in the all-available-data population.

The effect of 17P was apparent even after adjusting for the imbalance in the number of preterm deliveries. The adjusted incidence of deliveries prior to 37^0 weeks gestation remained significantly lower among the 17P group (*P*=0.0010) indicating that the baseline imbalance was not driving the differences between the 17P and placebo groups.

Table 4-3. Preterm Birth <37^0 Weeks

	17P		Placebo		
Data Source	**N**	**n (%)**	**N**	**n (%)**	***P* value**
ITT population (all data)	310	115 (37.1)	153	84 (54.9)	0.0003[a] 0.0010[b]
All available data	306	111 (36.3)	153	84 (54.9)	0.0001[a] 0.0006[b]

Note: ITT population was all randomized patients. Patients with missing outcome data were classified as having a preterm birth <37^0 weeks (treatment failure). All-available-data population excludes 4 patients lost to follow-up and is synonymous with that presented by Meis et al.[1]

[a] *P* value from chi-square test.

[b] *P* value from a logistic regression adjusting for the number of previous preterm deliveries.

As with the overall rate of deliveries <37^0 weeks, the incidence of SPTD <37^0 weeks gestation was significantly lower in the 17P group compared with the placebo group (*P*=0.0017). This difference was primarily due to the rate of spontaneous births <37^0 weeks gestation with preterm labor (*P*=0.0026).

Table 4-4. Spontaneous Preterm Delivery <37^0 Weeks

Pregnancy Outcome	**17P N=310 n (%)**	**Placebo N=153 n (%)**	***P* value[b]**
Spontaneous delivery[a] <37^0	94 (30.3)	69 (45.1)	0.0017
SPTD <37^0 due to pPROM	26 (8.4)	16 (10.5)	0.4656
SPTD <37^0 due to preterm labor	67 (21.6)	53 (34.6)	0.0026
SPTD <37^0 due to preterm labor or pPROM	89 (28.7)	69 (45.1)	0.0005
Indicated delivery <37^0	25 (8.1)	15 (9.8)	0.5309

Abbreviations: preterm premature rupture of membranes (pPROM)

Note: Data presented are from the ITT analysis. The ITT population was all randomized patients. Patients with missing outcome data were classified as having a preterm birth <37^0 weeks (treatment failure).

[a] Spontaneous delivery includes delivery following preterm labor or pPROM and miscarriages <20 weeks gestation.

[b] *P* value from chi-square test.

4.1.3.2 Prevention of Preterm Birth <37^0 Weeks in Subsets of the Overall Population

Treatment with 17P was effective in reducing preterm birth prior to 37^0 weeks gestation irrespective of the gestational age of the qualifying delivery, race, or number of previous preterm births (Table 4-5). Subgroup analyses were performed after stratifying patients by number of previous preterm deliveries (1, 2, ≥3), by gestational age of the previous qualifying SPTD (20^0-<28^{0}weeks, 28^0-<32^0 weeks, 32^0-<35^0 weeks, 35^0-<37^0 weeks), and by race (African American, non-African American). A Breslow-Day test demonstrated that the treatment effect of 17P was consistent across strata as indicated by nonsignificant *P* values. These results are particularly important as prior preterm deliveries, gestational age of a previous preterm birth, and African American race are all risk factors for preterm birth.[5,6,30,63]

Table 4-5. Preterm Birth <37^0 Weeks by Number of Previous Preterm Deliveries, Gestational Age of Qualifying Delivery, and Race

Characteristic	**17P n/N[a] (%)**	**Placebo n/N[a] (%)**	***P* value[b]**
Number of previous preterm births (PTBs)			0.4681
1 prior PTB	74/224 (33.0)	40/90 (44.4)	
>1 prior PTB	41/86 (47.7)	44/63 (69.8)	
2 prior PTB	27/56 (48.2)	31/46 (67.4)	
≥3 prior PTB	14/30 (46.7)	13/17 (76.5)	
Previous SPTD (qualifying delivery) by gestational age			0.7261
20^0 - <28^{0}weeks	33/82 (40.2)	19/29 (65.5)	
28^0 - <32^0 weeks	21/66 (31.8)	17/30 (56.7)	
32^0 - <35^0 weeks	30/84 (35.7)	27/55 (49.1)	
35^0 - <37^0 weeks	31/78 (39.7)	21/39 (53.8)	
Race			0.7021
African American	66/183 (36.1)	47/90 (52.2)	
Non-African American	49/127 (38.6)	37/63 (58.7)	

Abbreviation: spontaneous preterm delivery (SPTD), preterm birth (PTB).

Note: Data based on ITT population (all randomized patients). Patients with missing outcome data were classified as having a preterm birth <37^0 weeks (treatment failure).

[a] n represents the number of patients in a specific category who delivered <37^0 weeks gestation; N represents the number of patients overall in a specific category.

[b] *P* value from the Breslow-Day test for consistency of response across categories.

4.1.3.2.1 Number of Previous Preterm Births

Treatment with 17P reduced the rate of preterm births <37^0 weeks gestation regardless of whether the patient had 1, 2 or ≥3 previous preterm births (Table 4-5). In both treatment groups, patients who had more than 1 previous preterm birth had higher rates of preterm birth <37^0 week gestation than patients who had only one previous preterm birth. The incidence of preterm birth <37^0 weeks was reduced by 26% compared with placebo following 17P treatment among women with 1 previous preterm birth (from 44.4% in the placebo group to 33% in the 17P group) and was reduced by 32% compared with placebo following treatment with 17P among women with >1 previous preterm birth (from 69.8% in the placebo group to 47.7% in the 17P group).

4.1.3.2.2 Gestational Age of Qualifying Delivery

Treatment with 17P reduced the rate of preterm birth <37^0 weeks in all 4 gestational age categories (Figure 4-2). Following treatment with 17P, the incidence of preterm birth was reduced by 39% compared with placebo for women with a qualifying prior preterm birth between 20^0 and <28^0 weeks gestation (from 65.5% in the placebo group to 40.2% in the 17P group). The incidence of preterm birth following treatment with 17P was reduced by 44% compared with placebo for women who had a qualifying prior preterm birth between 28^0 and <32^0 weeks gestation (from 56.7% in the placebo group to 31.8% in the 17P group). The incidence of preterm birth following treatment with 17P was reduced by 27% compared with placebo for women who had a qualifying prior preterm birth between 32^0 and <35^0 weeks gestation (from 49.1% in the placebo group to 35.7% in the 17P group). And finally, the incidence of preterm birth following treatment with 17P was reduced by 26% compared with placebo for women who had a qualifying prior preterm birth between 35^0 and <37^0 weeks gestation (from 53.8% in the placebo group to 39.7% in the 17P group).

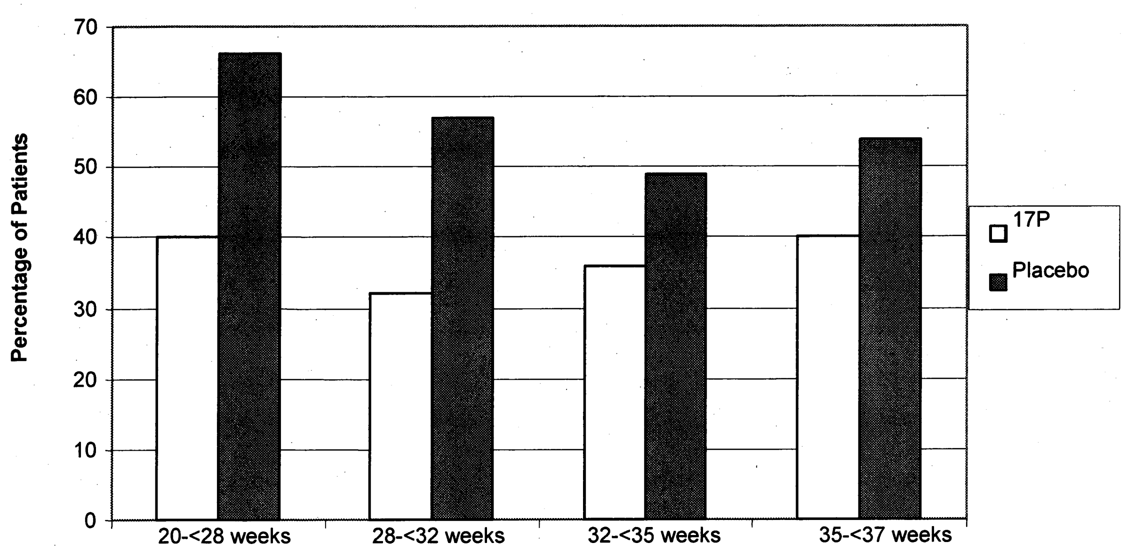


Figure 4-2. Preterm Birth <37^0 Weeks by Gestational Age of Qualifying Delivery and Treatment

4.1.3.2.3 Race (African American versus Non-African American)

Treatment with 17P reduced the rate of preterm birth <37^0 weeks gestation in both African American and non-African American women (Figure 4-3). Following treatment with 17P, the incidence of preterm birth <37^0 weeks was reduced by 31% compared with placebo among African American women (from 52.2% in the placebo group to 36.1% in the 17P group) and by 34% compared with placebo among non-African American women (from 58.7% in the placebo group to 38.6% in the 17P group).

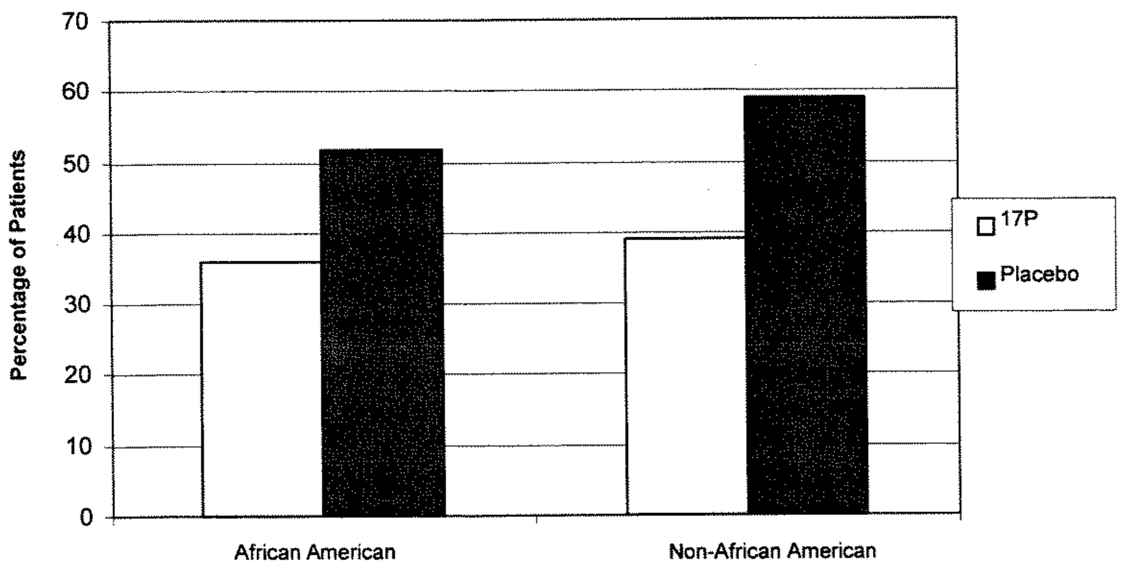


Figure 4-3. Preterm Birth <37^0 Weeks by Race and Treatment

4.1.3.3 Prevention of Preterm Birth <35^0, <32^0, and <30^0 Weeks

Treatment with 17P was effective in reducing preterm birth whether preterm was defined as <37^0, <35^0, <32^0, or <30^0 weeks gestation. As shown in Table 4-6, rates of deliveries <35^0 weeks gestation (*P*=0.0324), <32^0 weeks gestation (*P*=0.0458), and <30^0 weeks gestation (*P*=0.0329) were all significantly lower in the 17P group compared with the placebo group.

Table 4-6. Secondary Pregnancy Outcomes

Pregnancy Outcome	17P N=310 n (%)	Placebo N=153 n (%)	Relative Risk (95% CI)	*P* value[a]
Preterm Birth <35^0	67 (21.6)	47 (30.7)	0.70 (0.51 – 0.97)	0.0324
Preterm Birth <32^0	39 (12.6)	30 (19.6)	0.64 (0.42 – 0.99)	0.0458
Preterm Birth <30^0	28 (9.0)	24 (15.7)	0.58 (0.35 – 0.96)	0.0329
Preterm Birth <28^0	27 (8.7)	16 (10.5)	0.83 (0.46 – 1.50)	0.5422
Preterm Birth <24^0	15 (4.8)	5 (3.3)	1.48 (0.55 – 4.00)	0.4342

Abbreviations: confidence interval (CI)

Note: Data presented are from the ITT analysis. The ITT population was all randomized patients. Patients with missing outcome data were classified as having a preterm birth <37^0 weeks (treatment failure).

[a] *P* value from chi-square test.

Figure 4-4 illustrates the effectiveness of 17P in reducing preterm birth irrespective of the definition applied. Following treatment with 17P, the incidence of preterm birth was reduced by approximately 42%, 36%, 30%, and 32% and when defined as <30^0, <32^0, <35^0, and <37^0 weeks, respectively.

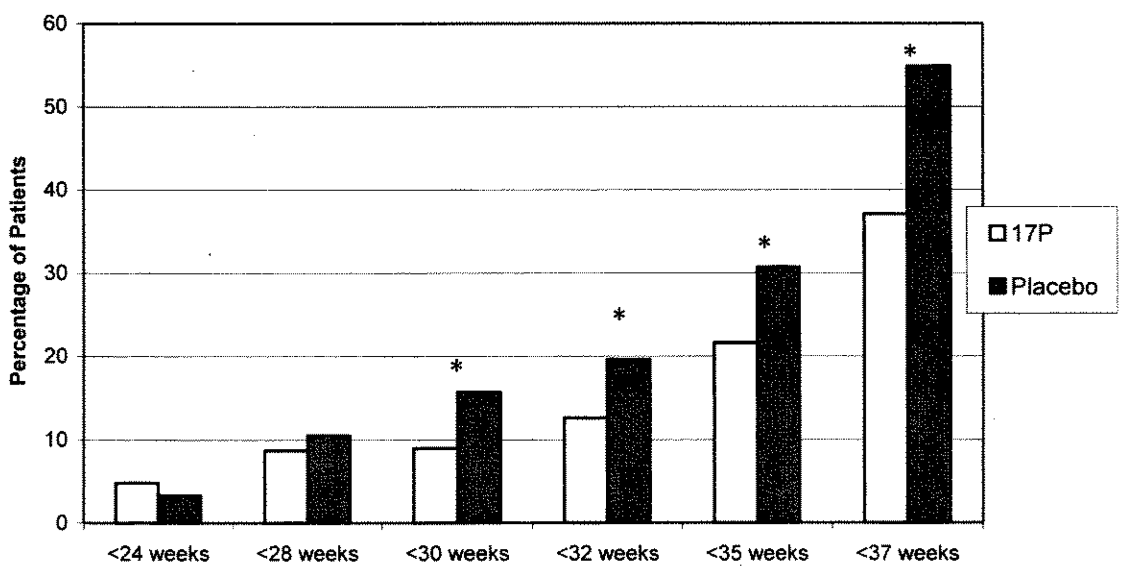


Figure 4-4. Preterm Birth <37^0, <35^0, <32^0, <30^0, <28^0, and <24^0 Weeks

*Statistically significant difference; $P < 0.05$.

4.1.3.4 Prolongation of Pregnancy

Treatment with 17P significantly prolonged pregnancy when compared with placebo. Treatment with 17P prolonged gestation (from the time of randomization) from a mean of 125 days for women who received placebo to 131 days for women who received 17P (P=0.0024). Accordingly, the mean gestational age at the time of birth was 1 week higher in the 17P group (36.2 weeks) compared with placebo (35.2 weeks; P=0.0024).

Treatment with 17P also resulted in a distinct shift in the distribution of gestational ages at birth. As shown in Table 4-7, the percentage of infants born at term (>37^0 weeks) was markedly higher in the 17P group (62.9%) compared with the placebo group (45.1%). In contrast, the percentage of infants born at all gestational ages less than 32 weeks was nearly half in the 17P group (11.9%) compared with the placebo group (19.6%). This shift in distribution illustrates the effectiveness of 17P in preventing preterm birth and prolonging pregnancy.

Table 4-7. Distribution of Gestational Ages at Birth

Gestational Age at Birth	17P N=310 n (%)	Placebo N=153 n (%)
>37^0 weeks (term births)	195 (62.9)	69 (45.1)
35^0-<37^0 weeks	49 (15.8)	37 (24.2)
32^0-<35^0 weeks	29 (9.4)	17 (11.1)
28^0-<32^0 weeks	8 (2.6)	14 (9.2)
24^0-<28^0 weeks	12 (3.9)	11 (7.2)
20^0-<24^0 weeks	11 (3.5)	5 (3.3)
16^0-<20^0 weeks	6 (1.9)[a]	0 (0)

Note: Data from 4 patients lost to follow-up are included in this analysis. These patients are considered to have delivered at the gestational age interval when they were lost to follow-up.

[a] Includes miscarriages <20^0 weeks.

The ability of 17P treatment to prolong pregnancy is further demonstrated by the hazard ratios for delivery at each gestational age time interval. The hazard ratio is the probability that a 17P patient who has not delivered at the start of a gestational age interval will deliver in that interval compared with a placebo patient. As shown in Table 4-8, a woman treated with 17P is less likely to give birth at each gestational age interval from 24 weeks of gestation up to 37 weeks of gestation than a woman receiving placebo.

Table 4-8. Hazard Ratio for Delivery – 17P Relative to Placebo

Gestational Age	Hazard Ratio (95% CI)
>37^0 weeks (term births)	ND
35^0-<37^0 weeks	0.52 (0.28 – 0.94)
32^0-<35^0 weeks	0.73 (0.31 – 1.70)
28^0-<32^0 weeks	0.27 (0.08 – 0.90)
24^0-<28^0 weeks	0.54 (0.17 – 1.72)
20^0-<24^0 weeks	1.01 (0.23 – 4.50)
16^0-<20^0 weeks	ND

Abbreviations: not determined (ND).

Note: The hazard ratio for the interval from 16^0-<20^0 weeks could not de determined since the hazard function in the placebo group is 0. The hazard ratio for >37^0 weeks (term births) is 1 because all patients eventually deliver. Therefore, no standard error can be calculated and no confidence interval can be constructed.

4.1.3.5 Neonatal Outcomes

Treatment with 17P significantly reduced the number of low birth weight infants. As shown in Table 4-9, the percentage of infants weighing <2500 g was significantly (*P*=0.0029) lower in the 17P group (27.2%) than in the placebo group (41.1%). Treatment with 17P also reduced the incidence of infants weighing <1500 g, but the difference did not reach statistical significance (*P*=0.0834).

Treatment with 17P also resulted in fewer admissions to the NICU. A significantly smaller percentage of live infants in the 17P group were admitted to the NICU compared with live infants in the placebo group (*P*=0.0434) (Table 4-9). Also, the median time spent in the NICU was shorter for the 17P group than the placebo group, but the difference was not statistically significant (*P*=0.1283). Likewise, the overall mean days in the hospital among all infants was lower in the 17P group compared with the placebo group, but the difference was not statistically significant (*P*=0.3612).

There were no differences between treatment groups in mean birth weight, head circumference, scores reflecting condition of newborn (Apgar scores), or the appearance of congenital anomalies. Congenital anomalies identified at birth are discussed in more detail in Section 5.1.3.3.2.

Table 4-9. Neonatal Outcomes

Neonatal Outcome	17P	Placebo	*P* value
Birth weight (g)	N=301	N=151	--
Mean (SD)	2760 (859)	2582 (942)	0.0736[c]
Min, Max	208, 4900	300, 4855	--
Birth weight <2500 g, n (%)	82 (27.2)	62 (41.1)	0.0029[a]
Birth weight <1500 g, n (%)	26 (8.6)	21 (13.9)	0.0834[a]
Congenital anomalies, n (%)	N=302	N=153	--
	6 (2.0)	3 (2.0)	1.0000[b]
Admitted to NICU or miscarriage/stillbirth/neonatal death, n (%)	N=306	N=153	--
	93 (30.4)	57 (37.3)	0.1395[a]
Admitted to NICU (live births), n (%)	N=295	N=151	--
	82 (27.8)	55 (36.4)	0.0434[c]
Days in NICU[d]	N=76	N=52	--
Median	9.1	14.1	0.1283[c]
Min, Max	0.1, 194.8	0.1, 147.0	--
Infant hospital days[e]	N=285	N=140	--
Mean (SD)	8.7 (16.0)	13.3 (26.5)	0.3612[c]
Min, Max	2, 123	2, 148	--

Abbreviations: neonatal intensive care unit (NICU)

Note: Birth weight data were missing for some infants.

[a] *P* value from the chi-square test.

[b] *P* value from the Fisher exact test.

[c] *P* value from the Wilcoxon rank sum test.

[d] For neonatal deaths, days in the NICU were calculated until date of death. However, it was set to the maximum value for the determination of the *P* value. Days in NICU could not be determined for 3 patients in the 17P group and 2 patients in the placebo group.

[e] Determined only for infants who did not die during the study.

4.1.3.6 Neonatal Morbidity and Mortality

Maternal treatment with 17P was effective in reducing serious neonatal morbidities associated with preterm birth. As shown in Table 4-10, the incidence rates of any type of IVH (P=0.0258) and of NEC (P=0.0127) were significantly lower in the 17P group compared with placebo. Likewise, the use of supplemental oxygen (P=0.0248) and the mean number of days of respiratory therapy were also significantly lower following 17P treatment (P=0.0438). The rates of bronchopulmonary dysplasia, PDA, other intracranial hemorrhages, and confirmed pneumonia were lower following 17P treatment, but the differences did not reach statistical significance.

A composite neonatal morbidity index was determined as a post hoc analysis. While there is no universal standard for defining a composite morbidity index, this assessment was based on the number of neonates who died or experienced respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 IVH, proven sepsis, or NEC. The composite morbidity was lower in the 17P group, however, the difference was not statistically significant (*P*=0.1194).

Neonatal mortality was lower following treatment with 17P, but the difference between treatment groups was not statistically significant (*P*=0.1159). Overall fetal and neonatal mortality is discussed in detail in the safety discussion in Section 5.1.3.3.

Table 4-10. Neonatal Morbidity and Mortality for Live Births

Morbidity	17P N=295 n (%)	Placebo N=151 n (%)	*P* value
Transient tachypnea	11 (3.7)	11 (7.3)	0.0990[a]
Respiratory distress syndrome (RDS)	29 (9.9)	23 (15.3)	0.0900[a]
Bronchopulmonary dysplasia (BPD)	4 (1.4)	5 (3.3)	0.1730[b]
Persistent pulmonary hypertension	2 (0.7)	1 (0.7)	1.0000[b]
Ventilator support	26 (8.9)	22 (14.8)	0.0616[a]
Supplemental oxygen	45 (15.4)	36 (24.2)	0.0248[b]
Patent ductus arteriosus	7 (2.4)	8 (5.4)	0.1004[a]
Seizures	3 (1.0)	0	0.5541[b]
Any intraventricular hemorrhage (IVH)	4 (1.4)	8 (5.3)	0.0258[b]
Grade 3 or 4 IVH	2 (0.7)	0	0.5511[b]
Other intracranial hemorrhage	1 (0.3)	2 (1.3)	0.2628[b]
Retinopathy of prematurity	5 (1.7)	5 (3.3)	0.3164[b]
Proven newborn sepsis	9 (3.1)	4 (2.6)	1.0000[b]
Confirmed pneumonia	3 (1.0)	4 (2.7)	0.2330[b]
Necrotizing enterocolitis (NEC)	0	4 (2.7)	0.0127[b]
Composite Neonatal Morbidity Index[c]	35 (11.9)	26 (17.2)	0.1194[a]
Neonatal mortality	8 (2.7)	9 (6.0)	0.1159[b]

a *P* value is from the chi-square test.

b *P* value is from the Fisher exact test.

c The composite neonatal morbidity measure counted any liveborn infant who experienced 1 or more of the following: death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC.

4.1.3.7 Integrated Analysis

To further explore the efficacy of 17P, the primary efficacy data collected from patients enrolled in the terminated study (Study 17P-IF-001) were combined with the primary efficacy data from Study 17P-CT-002. Analyses of integrated data from the 17P-IF-001 and 17P-CT-002 studies demonstrated the same reduction in preterm birth following 17P treatment as was observed with Study 17P-CT-002 data alone. The integrated analysis was based on a combined ITT population and included data from all patients in Study 17P-IF-001 whether or not they completed treatment.

The incidence rates of deliveries <37^{0} weeks gestation, <35^{0} weeks gestation, and <32^{0} weeks gestation were all significantly lower in the 17P patients than in the placebo patients (Figure 4-5). The risk of giving birth <32^{0}, <35^{0}, and <37^{0} weeks gestation were reduced by 32% (from 19.1% in the placebo group to 12.9% in the 17P group), 27% (from 30.6% in the placebo group to 22.3% in the 17P group), and 23% (from 49.8% in the placebo group to 38.1% in the 17P group), respectively, following treatment with 17P.

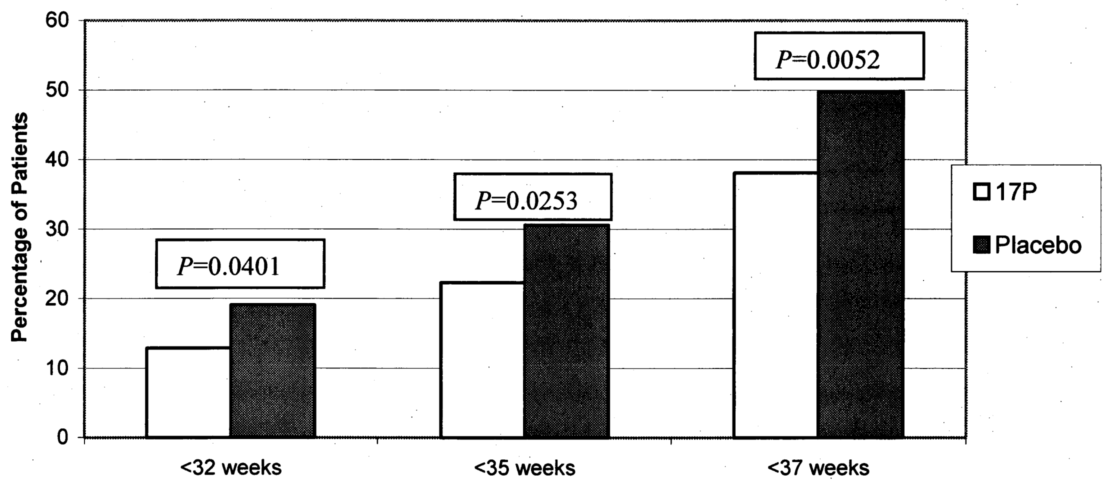
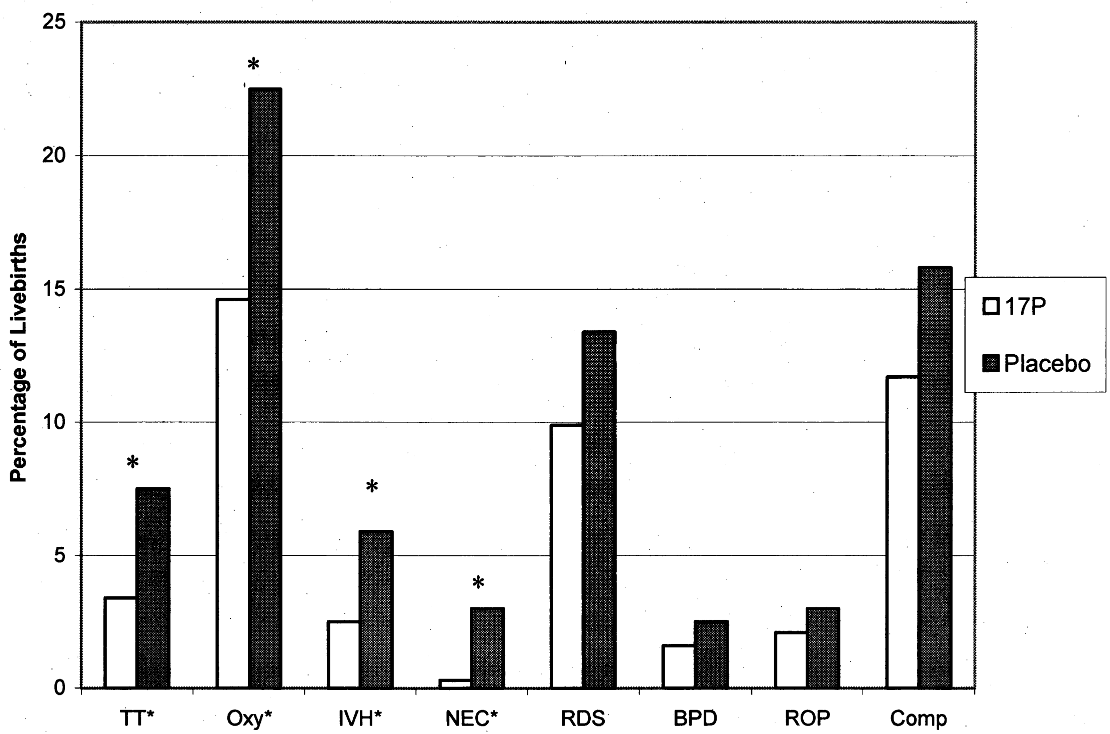


Figure 4-5. Integrated Analysis of Preterm Births <37^{0}, <35^{0}, and <32^{0} Weeks

As with the data from the completed study alone, data from the integrated analysis demonstrate that 17P treatment decreased the occurrence of neonatal morbidities. As shown in Figure 4-6, treatment with 17P significantly reduced the incidence rates of transient tachypnea (from 7.5% in the placebo group to 3.4% in the 17P group), supplemental oxygen (from 22.5% in the placebo group to 14.6% in the 17P group), any type of IVH (from 5.9% in the placebo group to 2.3% in the 17P group), and NEC (from 3.0% in the placebo group to 0.3% in the 17P group). There were also nonstatistically significant reductions in RDS, BPD, ROP, and ventilator support.



Abbreviations: transient tachypnea (TT); supplemental oxygen (Oxy); intraventricular hemorrhage (IVH); necrotizing colitis (NEC); respiratory distress syndrome (RDS); bronchopulmonary dysplasia (BPD); retinopathy of prematurity (ROP); composite neonatal morbidity measure (Comp).

Figure 4-6. Integrated Analysis of Neonatal Morbidity

*Statistically significant difference; $P < 0.05$.

4.1.4 Efficacy Conclusions from NICHD Studies

The efficacy results from the completed NICHD Study 17P-CT-002 demonstrate that treatment with 17P significantly reduces:

- preterm birth whether defined as $<37^0$ (P=0.0003), $<35^0$ (P=0.0324), $<32^0$ (P=0.0458), or $<30^0$ (0.0329) weeks gestation. Pregnancy was significantly prolonged by 17P treatment (P=0.0024) and the mean gestational age at birth was one week higher following treatment with 17P.
- preterm birth $<37^0$ weeks regardless of the gestational age of the qualifying prior preterm delivery, race (African American and non-African American), or the number of previous preterm deliveries.
- the incidence of low birth weight infants. Maternal treatment with 17P resulted in a significant reduction in the incidence of infants weighing <2500 g at birth (27.2% for 17P compared with 41.1% for placebo; P=0.0029) and a nonstatistically significant reduction in the percentage of infants weighing <1500 g (8.6% for 17P compared with 13.9% for placebo; P=0.0834).

- the incidence of live born infants admitted to the NICU (*P*=0.0434).
- the occurrence of serious neonatal morbidities such as NEC (*P*=0.0127) and any grade of IVH (*P*=0.0258). Maternal treatment with 17P also resulted in a significant reduction in the need for supplemental oxygen (*P*=0.0248) and the number of days of respiratory therapy (*P*=0.0438) in neonates.

In summary, the results of Study 17P-CT-002 indicate that 17P, administered as weekly intramuscular injections, when initiated from 16^0 to 20^6 weeks gestation and continued through 36^6 weeks gestation or birth, significantly reduces the risk of preterm birth and neonatal morbidities in the high-risk population of women with a prior preterm birth.

4.2 EFFICACY OF 17-HPC IN SCIENTIFIC LITERATURE

4.2.1 Controlled Clinical Studies of 17-HPC in Singleton Pregnancies

The NICHD clinical study results reinforce the positive findings from a number of smaller studies of 17-HPC. Prior to the publication of data from the completed NICHD study by Meis and colleagues, 6 controlled clinical trials had been previously published on the efficacy of 17-HPC for the prevention of preterm birth with singleton pregnancies.[20,21,22,23,24,25] These studies differed in the risk status of patients, the use of other interventions, and the timing and dosage of 17-HPC. Table 4-11 provides a summary of the incidence of preterm births reported in the previous controlled clinical trials of 17-HPC.

Table 4-11. Summary of Incidence Rates of Preterm Birth in Women with Single Gestation – Literature Review

Study	Gestation Week 17-HPC Treatment Initiated	17-HPC Rate of Preterm Birth		Placebo Rate of Preterm Birth		Odds Ratio (95% CI)
		N	n (%)	N	n (%)	
Controlled Studies in US						
LeVine 1964[20]	≤16	15	2 (13)	15	3 (20)	0.63 (0.10-4.15)[a]
Johnson 1975[22]	<24	18	2 (11)	25	12 (48)	0.19 (0.05-0.70)[a]
Hauth 1983[25]	16 to 20	80	5 (6)	88	5 (5.7)	ND[b]
Controlled Studies Outside US						
Papiernik-Berkhauer 1970[21]	28 to 32	50	2 (4)	49	9 (18)	0.24 (0.07-0.82)[a]
Yemini 1985[23]	mean 12.2	39	5 (13)	40	14 (35)	0.30 (0.11-0.84)[a]
Suvonnakote 1986[24]	16 to 20	35	5 (14)	39[c]	19 (49)	-- (*P*=0.0036)

Abbreviations: not determined (ND)

[a] Odds ratios reported in Keirse 1989.

[b] Odds ratio was not determined, but differences in rates of preterm birth were not significant.

[c] Placebo group was not used in this study; the control group received no specific study treatment.

The first study indicating a benefit of 17-HPC to reduce prevent birth was published by LeVine in 1964. This single-center, double-blind study evaluated the use of 17-HPC for prevention of habitual abortion.[20] The primary outcome of interest was spontaneous abortion, but preterm delivery was also reported. To be enrolled in the study, patients were required to have had 3 consecutive spontaneous abortions prior to their present pregnancy. Patients were to have a current pregnancy <16 weeks gestation and have no symptoms of threatened abortion. Patients were alternately assigned to receive weekly injections of either 500 mg 17-HPC or placebo. Fifty-six patients started the study, but the outcomes were reported for only the 30 patients (15 per treatment group) who continued the injections until delivery or 36 weeks gestation. Of the 15 patients treated with 17-HPC, 4 aborted spontaneously and 3 delivered preterm. By comparison, patients treated with placebo had 7 spontaneous abortions and 3 preterm deliveries. Therefore, the rate of delivery at $>37^0$ weeks gestation of a live infant was 53% (8/15) in the 17-HPC group versus 33% (5/15) in the placebo group. The odds ratio for preterm birth determined for this study suggested a benefit of 17-HPC use (0.63 [95% CI: 0.10-4.15]), but the sample size was too small to achieve statistical significance.

Six years later, Papiernik-Berkhauer published the results of a randomized, placebo-controlled trial of 17-HPC for the prevention of preterm labor.[21] A total of 50 pregnant women with a high risk for preterm birth received 250 mg 17-HPC intramuscularly every 3 days starting at 28 to 32 weeks gestation and stopping after 8 doses. Forty-nine women received the placebo on the same schedule. Preterm delivery occurred in 4.1% of the pregnancies in the 17P group and 18.8% of the pregnancies in the placebo group. The odds ratio for preterm birth determined for this study was 0.24 (95% CI: 0.07-0.82), signifying a significant reduction in the incidence of preterm birth with 17-HPC treatment.

Johnson and colleagues published the results of a randomized, double-blind study to evaluate 17-HPC for the prevention of preterm birth in 1975.[22] Qualifying patients had a history of 2 spontaneous abortions, 1 preterm birth, and 1 spontaneous abortion immediately preceding the index pregnancy, or at least 2 preterm births at any previous time. The women received weekly injections of 250 mg 17-HPC or placebo beginning prior to 24 weeks of gestation until 37 weeks of gestation or delivery, whichever occurred first. The primary outcome was delivery <36 weeks gestation. None of the eighteen 17-HPC patients delivered before 36 weeks, whereas 9 (41%) of the 22 placebo patients delivered prematurely ($P<0.01$). The odds ratio for preterm birth determined for this study was 0.19 (95% CI: 0.05-0.70). The mean duration of pregnancy and the mean birthweight were significantly greater in the 17-HPC group (38.6 weeks and 2836 g) compared with the placebo group (35.2 weeks and 2361 g; $P<0.025$), while perinatal mortality rate was significantly lower following 17-HPC treatment (0% compared with 27% in the placebo group; $P<0.05$).

Yemini and colleagues published the results of a randomized, double-blind, placebo-controlled study to evaluate 17-HPC for prevention of preterm birth in 1985.[23] Eighty pregnant women who had a history of at least 2 spontaneous abortions, 2 preterm births, or a combination of these were randomized to receive weekly intramuscular injections of either 250 mg 17-HPC or placebo from study entry (mean gestational age at study enrollment was 12.2 weeks) until 37 weeks gestation or delivery. Baseline characteristics and obstetric histories were similar between the treatment groups, with the exception of a higher number of induced abortions in the 17P group (1.8 compared with 1.4 in the placebo group; $P<0.01$). This trial differs from others in that all patients received a cervical cerclage, but the results still support the use of 17-HPC to reduce the risk of preterm delivery. The rate of preterm births was significantly lower in the17-HPC group (16.1%) than in the Placebo group (37.8%; $P<0.05$), as was the rate of threatened preterm labor (29.0% vs 59.4%; $P<0.025$). The odds ratio for preterm birth determined for this study was 0.30 (95% CI: 0.11-0.84). Mean birth weights were significantly higher in the 17-HPC group (3112 g) compared with the placebo group (2680 g, $P<0.05$), and infants born in the 17-HPC had fewer neonatal morbidities. There were no reported cases of perinatal death or fetal malformations in either group, though the rate of miscarriages was higher in the 17-HPC group (20.4%) than in the placebo group (7.5%).

Suvonnakote and colleagues published the results of a nonrandomized study that evaluated the use of 17-HPC to prevent preterm labor in high-risk patients in 1986.[24] Seventy-five pregnant women with a past history of unsuccessful pregnancies (1 preceding preterm birth, at least 2 previous mid-trimester abortions, or a mixture of term, preterm births, and mid-trimester abortions) were either administered 250 mg 17-HPC (n=36) or placed in the control group and given no study drug (n=39). 17-HPC was administered weekly beginning at 16 to 20 weeks gestation until 37 weeks gestation or until symptoms of labor were established. The percentage of women with preterm births was significantly lower in the 17-HPC group (14% [5/35]) compared with the untreated group (49% [19/39]; $P=0.0036$). The 17-HPC group also had a higher percentage of infants (68.6%) with birth weight >2500 g compared with the untreated group (51.3%), but the difference was not statistically significant ($P=0.2022$). The lack of randomization and of a placebo control diminishes the value of this study, but the results support the benefit of using 17-HPC to reduce the risk of preterm birth.

Among the published studies in singleton pregnancies, only 1 failed to show a benefit of 17-HPC in reducing preterm birth. Hauth and colleagues performed a double-blind trial designed to prospectively evaluate pregnant women in a US active-duty military population and to collect data both on the risks of pregnancy complications and the efficacy of 17-HPC for prevention of preterm labor.[25] Active-duty women from 16 to 20 weeks gestation were analyzed in 1 of 3 groups: 80 who received 1000 mg 17-HPC weekly until 36 weeks gestation; 88 who received placebo consisting of castor oil, 46% benzyl benzoate, and 2% benzyl alcohol; and 78 who declined to participate in the protocol. The 3 groups were similar for parity, history of previous abortion, race, cigarette smoking, and marital status. There were no significant differences in the 3 groups when comparisons were made for low-birth weight infants, perinatal mortality, and the incidence of preterm delivery. The incidence of preterm delivery in the 17-HPC group, placebo group, and declined-to-participate group were 6.3%, 5.7%, and 10.2%, respectively. The lack of effectiveness demonstrated in this study may have been the result of evaluating a relatively low risk population of women who did not all have a history of spontaneous preterm delivery.

In conclusion, despite small sample sizes and differences in study methodologies and treatment regimens, the historical clinical trials provide supportive evidence of the effectiveness of 17-HPC in preventing preterm birth.

4.2.2 Meta-Analyses of Progesterones for Prevention of Preterm Birth

Meta-analyses of the published data also support the use of 17-HPC for prevention of preterm birth.[1,16,64,65,66] Keirse performed a meta-analysis published in 1990 that focused only on trials that employed 17-HPC.[16] The odds ratio for 17-HPC to reduce preterm birth was 0.5 (95% confidence interval [CI] 0.30–0.85), indicating a significant reduction in the risk of preterm birth following 17-HPC treatment. Likewise, significant reductions in the odds of preterm labor (0.43 [95% CI 0.20-0.89]) and birth weight <2500 g (0.46 [95% CI 0.27-0.80]) were also observed following 17-HPC use.

Three subsequent meta-analyses that included the NICHD data published by Meis and colleagues also support the conclusion that 17-HPC is effective in preventing preterm birth.[64,65,66] As shown in Table 4-12, the relative risk of experiencing preterm birth $<37^0$ weeks gestation or an infant weighing <2500 g when treated with 17-HPC versus placebo was very similar whether the meta-analysis included only the earlier 17-HPC studies or if the meta-analysis included Study 17P-CT-002 data. This consistency is striking considering that the earlier studies were all small (sample sizes between 30 and 168 patients) compared with Study 17P-CT-002 (463 patients). These data strongly support the efficacy of 17P in reducing preterm birth and the incidence of low weight (<2500 g) infants. The data also suggest a reduction in perinatal mortality following maternal treatment with 17P, but too few data were available to achieve statistically significance.

Table 4-12. Results of Meta-Analyses of the Effects of 17-HPC

Outcome	Meta-Analysis	Relative Risk 17-HPC vs Placebo	95% Confidence Interval
Preterm birth <37^0 wks gestation	Keirse 1990	0.5	0.30 - 0.85
	Dodd 2005[a]	0.59	0.48 – 0.70
	Sanchez-Ramos 2005[a]	0.48	0.35 – 0.66
	Mackenzie 2006[a]	0.57	0.36 – 0.90
Infant birth weight <2500 g	Keirse 1990	0.46	0.27 - 0.80
	Dodd 2005[a]	0.62	0.49 – 0.78
	Sanchez-Ramos 2005[a]	0.50	0.36 – 0.71
	Mackenzie 2006[a]	0.66	0.51 – 0.87
Perinatal mortality	Keirse 1990	NR	NR
	Dodd 2005[a]	0.60	0.32 – 1.12
	Sanchez-Ramos 2005[a]	0.69	0.38 – 1.26
	Mackenzie 2006[a,b]	0.55	0.14 – 2.15

Abbreviations: not reported (NR)

[a] Included data for Study 17P-CT-002 as published in Meis 2003.[1]

[b] Includes only data from Study 17P-CT-002.

In summary, meta-analyses of earlier studies produced similar relative risk reductions before and after Study 17P-CT-002 data were included, further supporting the consistency of the observation that 17-HPC can prevent recurrent preterm births.[16,64,65,66]

5. SAFETY EVALUATION

5.1 SAFETY OF 17P IN NICHD CLINICAL STUDIES

As previously described, safety data from both Study 17P-IF-001 and Study 17P-CT-002 were integrated into one database for a comprehensive assessment of the safety of 17P.

5.1.1 Extent of Exposure

A total of 613 pregnant women were randomized and received at least 1 injection of study drug in Studies 17P-IF-001 and 17P-CT-002: 404 received 17P and 209 received placebo. Across the 2 studies, 336 women completed the full course of therapy with 17P (ie, weekly injections from study entry until 36^6 weeks of gestation or birth, whichever occurred first). Table 5-1 presents dosing information for Studies 17P-IF-001 and 17P-CT-002, including numbers of injections and patient compliance.

Table 5-1. Dosing Information

	17P	Placebo	*P* value
Study 17P-IF-001	N=65[a]	N=39[a]	
Number of injections			
Mean (SD)	13.3 (5.9)	11.3 (6.2)	0.1497[b]
Min, Max	1, 21	1, 20	
Greater than 90% compliance			
n (%)	54 (83.1)	26 (66.7)	0.0545[c]
Study 17P-CT-002	N=310	N=153	
Number of injections			
Mean (SD)	14.1 (5.6)	13.7 (5.0)	0.1781[b]
Min, Max	1, 21	2, 21	
Greater than 90% compliance			
n (%)	271 (87.4)	134 (87.6)	0.9604[c]

Note: Compliance was defined as the number of injections received divided by the number of expected injections multiplied by 100.

a Only includes patients who were not withdrawn from the study due to study termination.

b *P* value is from the Wilcoxon rank sum test.

c *P* value is from the chi-square test.

5.1.2 Pregnancy Complications

The occurrence of pregnancy-related procedures and pregnancy-related complications was similar for patients treated with 17P and patients treated with placebo (Table 5-2). Among the pregnancy-related procedures, admission to the hospital or labor and delivery unit for preterm labor prior to hospitalization for the actual delivery was experienced by 14.8% of the 17P patients and 15.6% of the placebo patients. The most common pregnancy complications (those reported by >5% of patients) were preeclampsia or gestational hypertension and gestational diabetes. No significant differences between groups were observed.

Table 5-2. Pregnancy Complications and Maternal Outcomes

Complication or Outcome	17P N=399[a] n (%)	Placebo N=205[a] n (%)	*P* value
Hospital or labor/delivery admission for preterm labor	59 (14.8)	32 (15.6)	0.7834[c]
Gestational diabetes	25 (6.3)	7 (3.4)	0.1792[d]
Oligohydramnios	13 (3.3)	3 (1.5)	0.2851[d]
Significant antepartum bleeding	10 (2.5)	7 (3.4)	0.5654[c]
Preeclampsia or gestational hypertension	33 (8.3)	9 (4.4)	0.0795[c]
Abruption	7 (1.8)	6 (2.9)	0.3565[c]
Confirmed clinical chorioamnionitis	13 (3.3)	5 (2.4)	0.8011[d]
Cerclage placement	5 (1.3)	3 (1.5)	1.0000[d]
Other complication	10 (2.6)[b]	6 (3.0)[b]	0.7928[d]

a Of the 404 patients randomized to 17P and the 209 patients randomized to placebo, data on pregnancy complications and maternal outcomes were available for 399 and 205 patients, respectively.

b N=389 for 17P group and N=202 for placebo group.

c *P* value is from the Cochran-Mantel-Haenszel statistic.

d *P* value is from the Fisher exact test.

5.1.3 Adverse Events

5.1.3.1 Incidence of Adverse Events

Adverse events were reported by a comparable percentage of patients following treatment with 17P and treatment with placebo (Table 5-3). The most common AEs in each of the treatment groups, based on system organ class, were general disorders and administration site conditions, which included injection site reactions. The percentages of patients reporting AEs coded to each system organ class were comparable between the 2 treatment groups.

Table 5-3. Incidence of Adverse Events by System Organ Class

MedDRA System Organ Class	17P N=404 n (%)	Placebo N=209 n (%)
Any Adverse Event [a]	239 (59.2)	118 (56.5)
General Disorders and Administration Site Conditions	195 (48.3)	94 (45.0)
Skin and Subcutaneous Tissue Disorders	75 (18.6)	34 (16.3)
Gastrointestinal Disorders	35 (8.7)	17 (8.1)
Injury, Poisoning and Procedural Complications	26 (6.4)	20 (9.6)
Nervous System Disorders	19 (4.7)	5 (2.4)
Pregnancy, Puerperium and Perinatal Conditions	16 (4.0)	6 (2.9)
Musculoskeletal and Connective Tissue Disorders	9 (2.2)	6 (2.9)
Congenital, Familial and Genetic Disorders	9 (2.2)	4 (1.9)
Metabolism and Nutrition Disorders	6 (1.5)	8 (3.8)

Note: Table presents system organ classes in which at least 2% of patients experienced an adverse event.

[a] Patients reporting a particular AE more than once were counted only once for that AE. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 8.0.

Injection site reactions were the most commonly reported adverse events in both treatment groups (Table 5-4). Individual injection site reactions reported by ≥2% of patients in at least 1 treatment group included: pain; swelling; pruritus; nodule; and irritation. Swelling was the only injection site reaction that was reported by significantly (*P*=0.0055) more patients in the 17P group than in the placebo group.

Table 5-4. Most Frequently Reported Adverse Events

Preferred Term	17P N=404 n (%)	Placebo N=209 n (%)
Any adverse event[a]	239 (59.2)	118 (56.5)
Injection site reactions:	180 (44.6)	85 (40.7)
Injection site pain	149 (36.9)	74 (35.4)
Injection site swelling	68 (16.8)	18 (8.6)
Injection site pruritus	25 (6.2)	10 (4.8)
Injection site nodule	17 (4.2)	7 (3.3)
Injection site irritation	5 (1.2)	5 (2.4)
Urticaria	51 (12.6)	24 (11.5)
Pruritus	28 (6.9)	11 (5.3)
Contusion	26 (6.4)	20 (9.6)
Nausea	20 (5.0)	8 (3.8)
Vomiting	11 (2.7)	6 (2.9)
Death[b]	10 (2.5)	9 (4.3)
Diarrhea	9 (2.2)	1 (0.5)
Edema	8 (2.0)	2 (1.0)
Abdominal pain	6 (1.5)	6 (2.9)
Anorexia	5 (1.2)	7 (3.3)

Note: Table presents adverse events experienced by at least 2% of patients in either treatment group.

[a] Patients reporting a particular AE more than once were counted only once for that AE. AEs were coded using MedDRA Version 8.0.

[b] The MedDRA coding included only the neonatal deaths under this preferred term. Miscarriages and stillbirths were coded to other preferred terms and were experienced by less than 2% of patients in each treatment group.

5.1.3.2 Adverse Events Leading to Discontinuation

The rate of early discontinuations of study drug due to AEs was comparable in the 17P (2.2%) and placebo groups (3.3%) (Table 5-5). Injection site reactions were the adverse events most commonly leading to discontinuation in both groups.

Table 5-5. Adverse Events Leading to Discontinuation

Preferred Term	17P N=404 n (%)	Placebo N=209 n (%)
Discontinued due to any AE	9 (2.2)	7 (3.3)
Injection site reactions	4 (1.0)	3 (1.4)
Allergic reaction	1 (0.2)	1 (0.5)
Urticaria	2 (0.5)	1 (0.5)
Pruritus	0	2 (1.0)
Weight gain	1 (0.2)	0
Arthralgia	1 (0.2)	0

5.1.3.3 Serious Adverse Events

Serious adverse events in the 17P-IF-001 and 17P-CT-002 studies were collected in accordance with NICHD MFMU practices. Specifically, all deaths (maternal, fetal, or neonatal) and life-threatening events required completion of a written safety report using the MFMU Network AE Form. In addition, adverse events that were serious and unexpected in nature, severity, or frequency also required completion of the MFMU Network AE Form.

Serious adverse events were reported by a comparable percentage of patients in the 2 treatment groups (Table 5-6). The most common SAEs were neonatal deaths, stillbirths, and miscarriages (discussed in Section 5.1.3.3.1) and congenital anomalies (discussed in Section 5.1.3.3.2).

Table 5-6. Serious Adverse Events by Preferred Term – Maternal, Fetal, and Neonatal Events

Preferred Term[a]	17P N=404 n (%)	Placebo N=209 n (%)
Any SAE and unexpected AE	38 (9.4)	22 (10.5)
Maternal		
Injection site reactions[b]	4 (1.0)	2 (1.0)
Respiratory distress	1 (0.2)	0
Choking	1 (0.2)	0
Hypersensitivity	1 (0.2)	0
Cellulitis	1 (0.2)	0
Endometritis	1 (0.2)	0
Arthralgia	1 (0.2)	0
Uterine rupture	1 (0.2)	0
Pulmonary embolism	1 (0.2)	0
Adverse drug reaction	0	1 (0.5)
Pruritus	0	1 (0.5)
Neonatal/Fetal		
Death[c]	10 (2.5)	9 (4.3)
Stillbirth	7 (1.7)	4 (1.9)
Miscarriage	6 (1.5)	1 (0.5)
Congenital anomalies	9 (2.2)	4 (1.9)
Testicular infarction	1 (0.2)	0

a SAEs and unexpected AEs reported on the MFMU Network AE Form were coded using MedDRA Version 8.0.

b Injection site reaction is the higher level term; the incidences by preferred terms of injection site reactions reported on the MFMU Network AE Form were also not different between treatment groups.

c The MedDRA coding included only the neonatal deaths under this preferred term. Miscarriages and stillbirths were coded separately.

5.1.3.3.1 Deaths

The overall rate of combined fetal and neonatal deaths was comparable between the 2 treatment groups (Table 5-7). None of the fetal or neonatal deaths were considered by the investigator to be related to study drug. While the overall incidence of miscarriage was comparable based on the integrated data, there was a higher rate of miscarriage in the 17P group in Study 17P-CT-002. In that study, 5 of the 310 patients (1.6%) in the 17P group had miscarriages compared with none of the 153 patients in the placebo group ($P>0.05$). None of the individual miscarriages were considered by the investigator to be related to the use of 17P and appeared more related to prior pregnancy history, pregnancy complications, and social factors than study drug. Specifically, 2 of the women who miscarried had threatened abortions prior to being randomized at 17^{3} or 17^{5} weeks of gestation and received only 1 injection of 17P before the event. One of these women was a cocaine user who had gone through rehabilitation during the study pregnancy (1 month before being randomized). A third woman developed bacterial vaginosis, experienced preterm premature rupture of membranes at 18^{6} weeks after 3 injections of 17P, and chose to terminate the pregnancy.

In summary, while the incidence of miscarriage was higher following 17P treatment, none were considered related to administration of 17P. The overall rate of miscarriages across the 2 studies was low considering that approximately one-third of the women reported having at least 1 previous miscarriage. Additionally, the overall rate of miscarriage reported in this study was lower than that previously reported by Mercer et al, who noted a 3.9% second-trimester miscarriage rate was among 1711 multiparous women with a history of least 1 prior preterm birth.[6]

Table 5-7. Fetal and Neonatal Deaths

Fetal/Neonatal Deaths	17P N=404	Placebo N=209	*P* value[a]
Miscarriages, n (%)	6 (1.5)	1 (0.5)	0.2629
Stillbirths, n (%)	7 (1.7)	4 (1.9)	0.8769
Neonatal deaths, n (%)	10 (2.5)[b]	9 (4.3)[c]	0.1928
TOTAL	23 (5.7)	14 (6.7)	0.5977

a *P* value is from the Cochran-Mantel-Haenszel statistic.

b Percentage based on all randomized 17P patients; the rate for liveborn infants was 2.6% (10/386).

c Percentage based on all randomized placebo patients; the rate for liveborn infants was 4.5% (9/202).

5.1.3.3.2 Congenital Anomalies

The percentage of infants with congenital abnormalities identified at birth across the 2 studies was comparable between the 2 treatment groups. The types of congenital anomalies were not different between treatment groups and the majority were congenital anomalies that are known to occur during embryogenesis in the first trimester, ie, before women qualified to receive the first injection of study drug (at least 16 weeks of gestation). Specific details of the congenital anomalies identified at birth are provided in Table 5-8.

Table 5-8. Congenital Anomalies Identified at Birth

Patient ID	Treat-ment	GA at first injection	Number of injections	GA at birth	Sex	Event(s) of Interest
Study 17P-IF-001						
002-005	17P	17^0	3	40^6	male	Breast malformation
014-001	17P	19^2	15	34^2	male	Limb reduction defect (transverse deficiency of upper limb)
015-001	17P	19^3	16	39^1	male	Hydrocele of tunica vaginalis
015-004	Placebo	20^5	12	35^3	male	Hydrocele of tunica vaginalis
Study 17P-CT-002						
002-024	17P	19^2	3	38^4	female	Cardiovascular anomaly (cardiomegaly; diverticulum [left ventricle]; pericardial effect)
014-016	17P	20^6	8	38^1	male	Genitourinary abnormality (renal pelvis; ureter)
015-015	17P	17^1	14	37^0	male	Hydrocele of tunica vaginalis
015-025	17P	18^1	10	35^6	female	Polydactyly (accessory fingers; other talipes calcaneovarus)
015-028	17P	19^1	11	30^4	male	Cardiovascular anomaly (other circulatory system anomalies)
021-022	17P	18^1	18	35^3	male	Pes planus, rocker bottom flat foot
002-047	Placebo	20^6	7	28^3	male	Cardiovascular anomaly (stenosis and other circulatory anomalies); polydactyly (accessory fingers)
004-046	Placebo	20^2	16	39^0	male	Genitourinary abnormality (bladder; urethra)
021-011	Placebo	17^3	19	39^4	male	Talipes equinovarus

5.1.4 Safety Conclusions from NICHD Studies

The safety results from Studies 17P-IF-001 and 17P-CT-002 demonstrate that administration of 17P was:

- safe and well tolerated by pregnant women. Adverse events were reported by a comparable percentage of patients in each group and the rate of discontinuation due to adverse events was low.
- safe for the developing fetus and neonate. The percentage of combined stillbirths, miscarriages, and neonatal deaths was comparable between the 2 treatment groups and the rates of congenital anomalies reported at birth were comparable to those reported in population surveys.

Taken together, the safety results of the 17P-IF-001 and 17P-CT-002 studies indicate that weekly injections of 17P do not pose a significant risk to pregnant women or their developing offspring.

5.2 LONG-TERM INFANT FOLLOW-UP

Long-term follow-up data on the health and development of infants born during the 17P-CT-002 study were collected in the noninterventional Study 17P-FU.

5.2.1 Infant Disposition and Demographics

Only patients enrolled in Study 17P-CT-002 at study sites that were active members of the MFMU Network in 2005 were considered eligible for Study 17P-FU. Based on these criteria, 348 (78%) of the 446 infants born to women enrolled in Study 17P-CT-002 and who survived to be discharged from birth hospitalization were eligible to participate in Study 17P-FU. Among the 234 children exposed to 17P who were eligible for enrollment, 82.9% were enrolled in Study 17P-FU. Likewise, 73.7% of the 114 eligible children exposed to placebo were enrolled. The disposition of children enrolled in the follow-up study is presented in Figure 5-1.

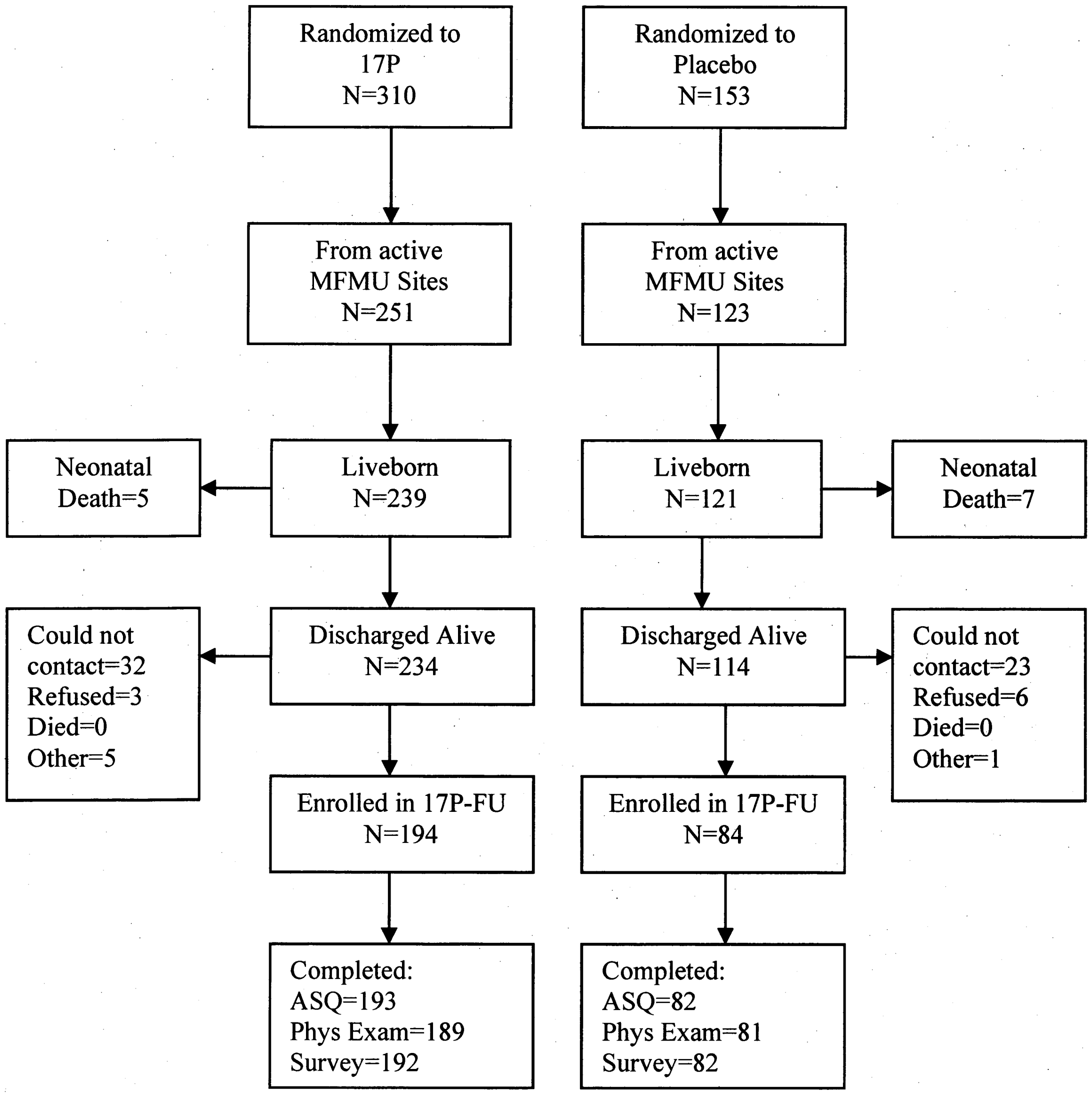


Figure 5-1. Disposition of Children Enrolled in Follow-Up Study

At the time of enrollment in the follow-up study, the demographics of the children enrolled were comparable between the 2 groups (Table 5-9). Children in the 17P group were born at later gestational ages and had a higher mean birth weight than children in the placebo group, which reflects the lower incidence of preterm births in Study 17P-CT-002.

Table 5-9. Demographics of Children Enrolled in Follow-Up Study

Characteristic	17P N=194	Placebo N=84
Age at enrollment (months)		
Mean (SD)	47.2 (8.6)	48.0 (8.3)
Min, Max	30.2, 63.9	33.5, 64.3
Race/Ethnicity, n (%)		
African American	105 (54.1)	47 (56.0)
Caucasian	55 (28.4)	20 (23.8)
Hispanic	29 (14.9)	15 (17.9)
Asian	2 (1.0)	1 (1.2)
Other	3 (1.5)	1 (1.2)
Sex, n (%)		
Male	113 (58.2)	40 (47.6)
Female	81 (41.8)	44 (52.4)
Treatment assignment disclosed, n (%)		
Yes	16 (8.3)	6 (7.1)
Gestational age at birth (wks)		
Mean (SD)	37.3 (3.2)	36.2 (3.7)
Min, Max	25.0, 41.7	25.1, 41.9
Birth weight (g)		
Mean (SD)	2914 (707.8)	2756.7 (813.7)
Min, Max	714, 4900	615, 4855

Among the 278 children enrolled in the follow-up study, the treatment assignment from Study 17P-CT-002 was known by the parent/guardian of 22 children (16 who were exposed to 17P *in utero* and 6 who were exposed to placebo). In these cases, the parent/guardian had knowledge of treatment prior to completing the questionnaires in the follow-up study.

5.2.2 Ages and Stages Questionnaire Results

The primary safety measure in Study 17P-FU used the Ages and Stages Questionnaire (ASQ), a commonly used screening tool to be completed with the parent/guardian that allows identification of children considered to be at medical risk that may require further evaluation and early intervention. The ASQ is composed of questionnaires containing 30 items addressing 5 developmental areas: communication, gross motor, fine motor, problem solving, and personal-social. The ASQ was scored based upon the sum of scores for each question in a category (Yes=10, Sometimes=5, and Not Yet=0). The ASQ uses predefined cut-off points designed to identify children considered to be at medical risk who may require further evaluation and early intervention.

In utero exposure to 17P was not associated with a delay in development based upon ASQ findings. As presented in Table 5-10, the percentage of children who scored below a specified cutoff for at least 1 developmental area on the ASQ was not significantly different (P=0.9206) between the 17P and placebo groups. The percentages of children who scored below the ASQ cutoff in each of the 5 developmental areas were also comparable between the 17P and placebo groups.

Table 5-10. Ages and Stages Questionnaire

Area of Development	17P N=193 n (%)	Placebo N=82 n (%)	*P* value
Occurrence of score below cutoff on at least 1 area of development	53 (27.5)	23 (28.0)	0.9206[a]
Communication	22 (11.4)	9 (11.0)	0.9191[a]
Gross Motor	5 (2.6)	3 (3.7)	0.6989[b]
Fine Motor	40 (20.7)	15 (18.3)	0.6445[a]
Problem Solving	20 (10.4)	9 (11.0)	0.8797[a]
Personal-Social	7 (3.6)	1 (1.2)	0.4427[b]

a *P* value is from the chi-square test.
b *P* value is from the Fisher exact test.

5.2.3 Survey Questionnaire Results

In addition to the ASQ, the 17P-FU study utilized a Survey Questionnaire tailored specifically for this study that was comprised of questions that were derived from the following validated instruments: the 2001 Child Health Supplement of the National Health Interview Survey, the 1991 National Maternal and Infant Health Survey, Early Childhood Longitudinal Survey (Department of Education), and the Avon Longitudinal Study of Parents and Children.

The Survey Questionnaire asked the parent/guardian to provide information on the child's gender-specific play (based on the preschool activities inventory [PSAI]), physical growth, activity levels, motor control, vision or hearing difficulties, and any diagnoses since discharge from birth hospitalization that were made by a health professional, such as asthma, allergic disorders, sensory disorders, and neurodevelopmental disorders (attention deficit hyperactivity disorder [ADHD] or attention deficit disorder [ADD]).

Based on the information provided by the parent/guardian on the Survey Questionnaire, no safety concerns related to the use of 17P during pregnancy were identified.

5.2.3.1 Gender Specific Play

There were no differences in gender-specific roles between the 17P and placebo groups (Table 5-11).

Table 5-11. Gender Specific Roles

PSAI	17P	Placebo	*P* value[a]
Number of enrolled children with completed questionnaire	192	82	
PSAI in males, n (%)	112 (58)	39 (48)	
Mean (SD)	66.48 (8.32)	67.28 (10.59)	0.3437
Min, Max	51.55, 90.05	44.74, 90.05	
PSAI in females, n (%)	80 (42)	43 (52)	
Mean (SD)	31.78 (8.45)	33.11 (8.83)	0.5432
Min, Max	10.85, 55.95	14.97, 55.95	

Abbreviations: preschool activities inventory (PSAI)

[a] *P* value is from the Wilcoxon rank sum test.

5.2.3.2 Physical Growth, Motor Skills, and Activity Levels

No significant differences in physical growth, motor skills, or activity levels were observed between the 2 treatment groups (Table 5-12).

Table 5-12. Physical Growth, Motor Skills, and Activity Levels

	17P	Placebo	*P* value[a]
Percentile of normal height (cm)	N=182	N=77	
Mean (SD)	54.4 (29.5)	57.0 (28.9)	--
Min, Max	1.2, 99.7	0.5, 98.5	--
Below normal height, n (%)	7 (3.8)	4 (5.2)	0.7371
Percentile of normal weight (kg)	N=189	N=80	
Mean (SD)	55.2 (29.7)	57.0 (29.6)	--
Min, Max	0.1, 100.0	0.0, 100.0	--
Below normal weight, n (%)	11 (5.8)	6 (7.5)	0.5921
	N=192	N=82	
Diagnosis of problem in overall activity, n (%)	2 (1.0)	1 (1.2)	1.0000
Diagnosis of problem in coordination or use of limbs, n (%)	1 (0.5)	1 (1.2)	0.5097

Note: Ns represent numbers of children included in the assessment based on available data.

[a] *P* value is from the Fisher exact test.

5.2.3.3 Hearing, Vision, and Use of Special Equipment

Results from the Survey Questionnaire on hearing, vision, and the use of special equipment were comparable between the 2 treatment groups (Table 5-13). No significant differences in any finding were noted.

Table 5-13. Hearing, Vision, and Use of Special Equipment

Categories	17P N=192[a] n (%)	Placebo N=82[a] n (%)	*P* value[b]
Hearing			
Good	188 (97.9)	77 (93.0)	0.1327
Little trouble	4 (2.1)	5 (6.1)	0.1327
Lot of trouble	0	0	--
Wears hearing aid	0	0	--
Deaf	0	0	--
Vision			
No trouble seeing	188 (97.9)	80 (97.6)	0.7972
Trouble seeing and wears glasses	3 (1.6)	1 (1.2)	--
Trouble seeing and does not wear glasses	1 (0.5)	1 (1.2)	--
Use of special equipment			
Wheelchair	0	1 (1.2)	0.5097
Brace	1 (0.5)	0	--
Impairment or health problem that limits ability to walk, run, or play	5 (2.6)	5 (6.1)	0.1714

[a] The number of children for whom the Survey Questionnaire was completed; 2 children in each treatment group did not have a completed Survey Questionnaire.

[b] *P* value is from the Fisher exact test.

5.2.3.4 Communication and Problem Solving

No significant differences in results from the Survey Questionnaire on communication and problem solving were reported between the 2 treatment groups (Table 5-14). Mental retardation was reported for 1 child in the 17P group who had Down syndrome and autism.

Table 5-14. Communication and Problem Solving

	17P N=192[a]	Placebo N=82[a]	*P* value[b]
Diagnosis of problem in ability to communicate, n (%)	9 (4.7)	7 (8.5)	0.2605
Age at first diagnosis (months)			
Mean (SD)	17.6 (14.55)	16.7 (11.87)	--
Median	12	12	
Min, Max	0.0, 48.0	1.0, 36.0	--
Diagnosis of problem in ability to pay attention/learn, n (%)	8 (4.2)	5 (6.1)	0.5387
Learning disability	1 (0.5)	0	--
ADHD or ADD	1 (0.5)	2 (2.4)	--
Developmental delay[c]	5 (2.6)	3 (3.7)	--
Autism or pervasive developmental disorder	1 (0.5)	0	--
Mental retardation	1 (0.5)	0	--
Other	2 (1.0)	1 (1.2)	--
Age at first diagnosis (months)	N=8	N=4	
Mean (SD)	22.4 (20.80)	18.3 (15.11)	--
Median	12	18	
Min, Max	0.0, 60.0	1.0, 36.0	--

Abbreviations: attention deficit hyperactivity disorder (ADHD); attention deficit disorder (ADD)

[a] The number of children for whom the Survey Questionnaire was completed; 2 children in each treatment group did not have a completed Survey Questionnaire.

[b] *P* value is from the chi-square or Fisher exact test.

[c] Parent/guardian reported a diagnosis of developmental delay specific to the child's ability to pay attention, learn, think, and problem solve.

5.2.3.5 Overall Health

The overall health was comparable between the 17P and placebo groups (Table 5-15). There were lower rates of chronic (>3 months) medication use and lower surgical interventions in the 17P group, but the differences were not statistically significant.

Table 5-15. Overall Health

	17P N=192[a] n (%)	Placebo N=82[a] n (%)	*P* value
Overall health			0.4797[b]
Excellent	117 (60.9)	46 (56.1)	--
Very good	43 (22.4)	22 (26.8)	--
Good	28 (14.6)	10 (12.2)	--
Fair	4 (2.1)	4 (4.9)	--
Compared to 12 months ago, health is:			0.6930[c]
Better	64 (33.3)	26 (31.7)	--
Worse	2 (1.0)	2 (2.4)	--
About the same	126 (65.6)	54 (65.9)	--
Health problem requiring medication for ≥3 months	21 (10.9)	16 (19.5)	0.0572[b]
Any operations	23 (12.0)	17 (20.7)	0.0602[b]
Hernia repair	4 (2.1)	2 (2.4)	--
Surgery for undescended testicles	1 (0.5)	0	--
Ear tubes inserted	8 (4.2)	7 (8.5)	--
Tonsils removed	5 (2.6)	1 (1.2)	--
Adenoids removed	5 (2.6)	1 (1.2)	--
Other	7 (3.6)	7 (8.5)	--

a The number of children for whom the Survey Questionnaire was completed; 2 children in each treatment group did not have a completed Survey Questionnaire.

b *P* value is from the chi-square test.

c *P* value is from the Fisher exact test.

5.2.3.6 Reported Diagnoses by Health Professionals

The incidence of reported diagnoses as communicated by the parent/guardian on the Survey Questionnaire was comparable between children exposed to 17P and children exposed to placebo (Table 5-16). Of note, developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age-mates in physical, mental, social/emotional, or speech development, was reported for a comparable percentage of children in the treatment groups.

Table 5-16. Reported Diagnoses by Health Professionals

Reported Diagnosis	17P N=192[a] n (%)	Placebo N=82[a] n (%)
Asthma	39 (20.3)	20 (24.4)
Asthma attack in past 12 months	20 (10.4)	8 (9.8)
Visit to ER or Urgent Care due to asthma in past 12 months	18 (9.4)	7 (8.5)
Eczema or skin allergy	35 (18.2)	12 (14.6)
Ear infections (3 or more)	20 (10.4)	7 (8.5)
Hay fever	19 (9.9)	5 (6.1)
Respiratory allergy	16 (8.3)	9 (11.0)
Developmental delay	14 (7.3)	7 (8.5)
Stuttering or stammering[b]	11 (6.4)	5 (6.6)
Frequent repeated diarrhea or colitis	5 (2.6)	1 (1.2)
Anemia	5 (2.6)	4 (4.9)
Food or digestive allergy	3 (1.6)	3 (3.7)
Seizures or convulsions with fever	3 (1.6)	1 (1.2)
Frequent or severe headaches or migraines	1 (0.6)	2 (2.6)
Diabetes	1 (0.5)	0
Arthritis	1 (0.5)	0
Seizures or convulsions without fever	0	1 (1.2)
Cerebral palsy	0	1 (1.2)
Sickle cell	0	1 (1.2)

Abbreviations: emergency room (ER)

[a] The number of children for whom the Survey Questionnaire was completed; 2 children in each treatment group did not have a completed Survey Questionnaire.

[b] Question answered only for children 3 years or older. Percentages were based on N=171 in 17P group and N=76 in placebo group.

5.2.4 Physical Examination Findings Including Genital and Reproductive Anomalies

As part of the follow-up study, a general physical examination was conducted by a pediatrician or nurse practitioner at the study center. These examinations included measurements of the child's current weight, height, head circumference, and blood pressure. While women in Study 17P-CT-002 received 17P beginning only in the second trimester, a time after which major congenital abnormalities would be expected to occur[67], the follow-up physical examination still targeted major physical abnormalities. Specific emphasis was placed on genital abnormalities. If the child was unable to attend the study visit, information from a previous physical examination (within 1 year) was abstracted from the child's medical records.

Physical examinations findings were comparable between the 17P infants and the placebo infants (Table 5-17). The most common abnormalities were of the skin and palpable inguinal nodes. Minor heart conditions, such as murmurs and irregular heart rhythm, were identified in 5% of the 17P group and 0% in the placebo group; the imbalance between groups was considered random chance since the incidence of murmurs in young children has been reported to be as high as 50%.[68]

Table 5-17. Follow-Up Study Physical Examination Results

Abnormality or Location of Abnormality	17P N=194	Placebo N=84
Skin, N	187	80
n (%)	23 (12.3)	6 (7.5)
Inguinal nodes palpable, N	184	80
n (%)	20 (10.9)	7 (8.8)
Mouth, N	187	81
n (%)	17 (9.1)	7 (8.6)
Neck, N	187	81
n (%)	11 (5.9)	4 (4.9)
Heart, N	188	81
n (%)	10 (5.3)	0
Ears,	188	81
n (%)	6 (3.2)	3 (3.7)
Supraclavicular nodes palpable, N	184	80
n (%)	6 (3.3)	2 (2.5)
Kidneys palpable, N	186	79
n (%)	4 (2.2)	0
Rhythm by auscultation, N	188	80
n (%)	3 (1.6)	0
Legs, N	188	80
n (%)	2 (1.1)	1 (1.3)
Epicanthal folds, N	185	77
n (%)	2 (1.1)	1 (1.3)

Medical events of special interest among the infants born during the 17P-CT-002 study included genital or reproductive anomalies identified upon physical examination or upon review of the completed Survey Questionnaire. During the follow-up study, 5 (2.6%) children in the 17P group and 1 (1.2%) child in the placebo group had genital or reproductive anomalies reported. These 6 children with reported anomalies are listed in Table 5-18.

Table 5-18. Genital and Reproductive Anomalies Identified During Follow-up Safety Assessments

Patient ID	Treat-ment Group	GA at first injection	Number of Injections	GA at birth	Sex	Event(s) of Interest	Age at FU Assessment (mo)
018-032	17P	20^4	7	38^1	female	Clitoral hypertrophy	48.8
020-023	17P	17^0	21	38^1	female	Labioscrotal fusion	60.3
025-002	17P	20^0	17	39^6	female	Early puberty at 3.5 yr of age	43.4
008-167	Placebo	18^0	7	25^1	female	Sparse pubic hair at 3.4 yr of age	41.7
008-076	17P	19^0	18	38^1	male	Micropenis; small scrotal sac	54.1
008-134	17P	18^2	14	33^5	male	Micropenis; Down syndrome	42.4

Abbreviations: gestational age (GA); follow-up (FU)

Two females had abnormalities of the genitalia noted, both in the 17P group. One female child was reported to have clitoral hypertrophy and another female child was reported to have labioscrotal fusion. For the child reported to have clitoral hypertrophy, the maternal birth and newborn records indicated that all assessments of genitalia were within normal limits. A repeat physical examination 4 months later by the same physician who performed the follow-up study physical examination found the female genitalia to be normal (clitoris <5 mm in transverse diameter). For the child reported to have labioscrotal fusion, the maternal birth records, newborn records, and ambulatory pediatric records from 1 week to 3 years of age were reviewed. The newborn assessment as well as pediatric records at 1, 4, 6, 9, 12, 15, 18, and 24 months all indicated that genitalia were within normal limits.

Signs of early puberty were reported for 1 female child in the 17P group. At 3.6 years of age, the child had breast buds (4-5 cm) noted during the physical examination and joint pain reported by the mother on the Survey Questionnaire that she considered related to early puberty. Potentially confounding the determination of breast development during the physical examination was the child's weight of 30 kg, which at a height of 107 cm placed her in the 100^{th} percentile for body mass index. Medical records revealed no abnormalities on physical examination at birth.

One female child in the placebo group had sparse pubic hair present at the time of the study physical examination, when she was 3.5 years of age. This child was born preterm at 25 weeks of gestation and had a protracted NICU stay, with no physical abnormalities noted at birth.

Two male infants in the 17P group and none in the placebo group were reported to have a small penis. Based upon review of all data, these events did not appear to be treatment related. The male child with the micropenis also had Down syndrome, a syndrome in which micropenis is not uncommon.[69,70] The second child was reported to have a small penis at 4.5 years of age. In this child's newborn medical records, 2 comments were made under Genitalia: "male – meatus present and testes palpable." No other comments were made regarding abnormalities of size or structure of the penis, testes, or scrotal sac.

Based upon review of all available data for these children, it is concluded that *in utero* exposure to 17P was unlikely to have contributed to any of the genital abnormalities reported.

5.2.5 Safety Conclusions from Follow-Up Study

The safety results from the long-term follow-up Study 17P-FU demonstrate that *in utero* exposure to 17P:

- does not lead to delay in development. The results from the ASQ demonstrated no significant differences between the 2 groups in the percentage of children falling below cutoffs for any developmental area.
- does not pose any safety concerns related to overall health or physical development. The results from the Survey Questionnaire demonstrated no significant differences between the 2 groups in any assessment, including gender-specific roles.
- is not associated with the development of genital or reproductive anomalies. While 2.6% of children in the 17P group were noted to have genital or reproductive anomalies abnormalities upon physical examination compared with 1.2% in the placebo group, none were considered to be associated with *in utero* exposure to 17P based on the nature of the physical finding, the gestational age at first exposure, or the presence of other likely contributing factors.

Taken together, the results of the NICHD 17P-FU study indicate that *in utero* exposure to 17P has no untoward effects on developmental milestones or physical health status of children.

5.3 SAFETY OF 17-HPC USE IN SCIENTIFIC LITERATURE

5.3.1 Clinical Trials and Epidemiological Studies

The safety of 17-HPC use in pregnancy is further supported by multiple scientific publications of controlled studies. As previously discussed, multiple studies have evaluated the effectiveness of 17-HPC for the prevention of preterm birth in singleton pregnancies.[20,21,22,23,24] In these studies, the publications consistently noted that administration of 17-HPC was not associated with maternal adverse effects other than discomfort or tenderness at the injection site. Overall, the publications did not suggest that 17-HPC exposure was associated with an excess rate of fetal or neonatal death. Rates of perinatal morbidity were not higher following 17-HPC treatment and were noted to be significantly reduced relative to the placebo group in one study.[22] One study noted that the percentage of live births was significantly higher following 17-HPC treatment, while another study noted that the miscarriage rate was significantly higher in the 17-HPC group.[20,23] Only 2 of the studies noted any observed abnormalities among infants at birth, but none of the abnormalities noted (anencephaly, accessory digits of the hand) were considered related to 17-HPC exposure by the authors.[22,24]

A number of published studies have examined the effects of *in utero* exposure of 17-HPC on the developing fetus. These studies include assessments of congenital anomalies and psychological development. The results from these studies support the findings that 17-HPC is not teratogenic and is safe for the developing fetus.[26,27,28,29,71]

Varma and Morsman conducted a retrospective evaluation of the safety of 17-HPC administered for prevention of threatened abortion.[26] Over a period of 7 years, 150 patients received weekly intramuscular injections of 17-HPC (250 to 500 mg) from 6 to 8 weeks up to 16 to 18 weeks of gestation. These patients were matched with control patients who did not receive hormone treatment. No evidence was found that 17-HPC had any adverse effect on the outcome of the pregnancy or the fetus. The rate of fetal anomalies was 0.7% in the 17-HPC group versus 2.0% in the control group. One infant in the 17-HPC group had a proven fetal anomaly (infant stillborn at 33 week gestation with hydrocephalus and other anomalies) compared with 3 infants (anencephaly, spina bifida, and multiple anomalies) in the control group. No incidence of masculinization of female infants was observed.

Resseguie and colleagues examined the medical records of 24,000 women to identify children who were exposed to sex hormones *in utero*.[27] A total of 649 children were identified that been exposed to 17-HPC. The median time of first exposure was 60 days of gestation and the median total exposure was estimated to be 1625 mg. No differences in the frequency or type of congenital anomalies were observed between children exposed to 17-HPC *in utero* and unexposed children. The incidence of any major anomaly was 5.5% among children exposed to 17-HPC *in utero* compared with 4.5% among unexposed children. Children exposed to 17-HPC had comparable rates of genitourinary anomalies, central nervous system anomalies, major cardiovascular anomalies, and hypospadias compared with the control group. A notable feature of this study was the long period of follow-up of the children, with a mean of 11.5 years. The results from this study supported the observation that progestin exposure and the occurrence of anomalies were independent events, even if only first-trimester exposure was considered.

In a cohort study of 13,643 pregnancies in West Germany, Michaelis and colleagues found no increase in malformations in infants exposed *in utero* to 17-HPC during the first trimester.[28] The study evaluated women treated with progesterone and 17-HPC to prevent abortion. Ten major malformations were observed in infants delivered among 462 women who received 17-HPC (2.2%). Of these 10, there were 6 whose mothers received one or more other sex hormones in addition to 17-HPC and 4 whose mothers received 17-HPC only. No major malformations were observed in infants delivered by 186 women who received progesterone. Women who received only progesterone or 17-HPC during the first 12 weeks (n=320) were combined and compared with selected controls in a matched-pair analysis. The number of major malformations was not increased in the active group (4 infants) compared with the control group (6 infants). The number of miscarriages was increased in the active group; however, this was to be expected since those women receiving progesterone treatment were those at higher risk for abortion.

Katz and colleagues compared 1608 infants who were exposed to progestogens during the first trimester of pregnancy to 1146 control infants delivered at the same hospital to examine the potential teratogenicity of progestogens.[29] The progestogens studied were oral medroxyprogesterone acetate administered at doses of 20 to 30 mg per day, 17-HPC administered as weekly injections of 500 mg, or a combination of the 2 drugs. The overall rate of malformations was not different between the progestogen group (120/1000) and the control group (124/1000). The authors concluded that there was no evidence of teratogenicity due to progestogens administered during the first trimester of pregnancy.

The long-term impact of *in utero* exposure to 17-HPC on psychological development has also been examined. Kester examined adolescent males exposed to 17-HPC to determine whether prenatal exposure impacted recreational interests and psychosexual development in boyhood.[71] Twenty-five males exposed to 17-HPC and closely matched unexposed controls were evaluated based on a number of psychological tests. No significant differences in psychological testing were noted for adolescents exposed to 17-HPC. The total dosage of 17-HPC, duration of exposure, and period of gestation had no significant impact on the findings.

In summary, the published literature provides no evidence that administration of 17-HPC during pregnancy results in significant risk to mother, fetus, or newborn. Importantly, epidemiological studies evaluating first trimester exposure demonstrate a lack of association between the use of 17-HPC and the incidence of congenital anomalies. Major congenital anomalies are unlikely to occur from drug exposure later than the first trimester of pregnancy, the time of organogenesis.[67] The proposed indication for 17P is to initiate treatment no earlier than 16 weeks of gestation, after the period of most vulnerability for the fetus. This timing further reduces any safety concern for the fetus.

5.3.2 FDA Assessment of Congenital Anomalies

The conclusion that exposure to 17P is not teratogenic is supported by the published findings of the FDA. The FDA conducted a thorough scientific review of all available data regarding the association between progesterone use and congenital malformations. The review was conducted to determine whether drugs containing natural progesterone or synthetic progestins should still carry a class warning about their use during the first trimester of pregnancy. At the conclusion of their review, the FDA proposed a rule in the 13 April 1999, *Federal Register*, that there was no need for special labeling.[72]

During their review, the FDA noted that most cases associating progestogen use during pregnancy with virilization of the genitalia in female infants involved high doses of ethisterone and norethindrone, both of which are androgen-derived progestins. They concluded that a warning of an increased risk of birth defects for all progestogens is not warranted and that:

> *"The reliable evidence, particularly from controlled studies, shows no increase in congenital anomalies, including genital abnormalities in male or female infants, from exposure during pregnancy to progesterone or hydroxyprogesterone."*

6. ASSESSMENT OF BENEFIT/RISK AND OVERALL CONCLUSIONS

Preterm birth is the leading cause of perinatal and neonatal morbidity and mortality in the US and, as such, is well recognized as a serious public health concern. Moreover, despite both educational and medical prenatal interventions, the rate of preterm births continues to rise: 12.5% of all births are now preterm (<37 weeks gestation), compared with a rate of 9.4% in 1981.

Multiple neonatal complications are associated with preterm birth, including respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and infections resulting from immature immune systems. However, the effects of preterm birth may extend well beyond the neonatal period, with increased risks of lifelong medical, developmental, and social problems. Long-term morbidities associated with prematurity include mental retardation, retinopathy of prematurity, and cerebral palsy. As one of the most pronounced manifestations of preterm birth, the relative risk for the development of cerebral palsy is nearly 40 times that for a term infant.

Many children born prematurely "catch up" developmentally in later childhood to term-born infants. The social and emotional costs of this process, for both children and their families, are difficult to completely quantify. However, financial costs are often utilized as a surrogate measure of neonatal morbidities. In 2003, US hospitals charged an estimated $18.1 billion to treat infants with a diagnosis of prematurity or low birth weight — nearly *half* of all hospital charges for all infants in the US. On average, these preterm infants spend 16.8 days in the hospital during their first year of life compared to 2.3 days for term infants; direct costs for that first year of care are estimated to be *15 times* that for healthy term infants.

While many factors lead to an increased risk of preterm birth, a woman's previous pregnancy history is one of the most important factors. The risk of a subsequent preterm delivery is 2.5 times greater for a woman who has experienced a prior spontaneous preterm birth — an easily identifiable population that is an appropriate target for pharmacological intervention.

Based on the NICHD studies described in detail in this document, as well as the data available in the literature of earlier studies, 17P has been proven not only effective, but also safe for 2 critical populations — both mother and child — and merits approval for the following indication:

> *GESTIVA (17P) is indicated for the prevention of preterm birth in pregnant women with a history of at least 1 spontaneous preterm birth.*

<u>Benefits of 17P</u>

The benefits of 17P have been described at length throughout this document. The product is not only highly effective at reducing the risk of preterm birth and prolonging pregnancy, but mothers treated with it give birth to healthier neonates.

- *Prevention of Preterm Birth*

17P has been proven effective in preventing recurrent spontaneous preterm birth in women with a singleton pregnancy. Evidence for this benefit was suggested in 6 other controlled clinical studies, published between 1964 and 1986 with varied study designs and dosing regimens, and confirmed in the well-controlled, randomized clinical study recently conducted by the NICHD at 19 study centers,

In the NICHD study, 17P was shown to reduce the incidence of recurrent preterm birth by 32%. There were significant reductions in the rate of preterm births, regardless of definition ($<30^0$, $<32^0$, $<35^0$, or $<37^0$ weeks of gestation). Moreover, 17P was equally efficacious in women regardless of the number or gestational age of previous preterm deliveries.

- *Prolongation of Pregnancy*

Treatment with 17P resulted in an extension of the gestational period that averaged one week across the pregnancies. Additionally, 17P treatment resulted in a shift in the distribution of gestational ages at birth, resulting in a greater percentage of infants born at term (62.9%) compared with the placebo group (45.1%). Similarly, treatment with 17P resulted in a lower percentage of infants born less than 32 weeks gestation (11.9%) compared with placebo (19.6%). Furthermore, compared with women who received placebo, women treated with 17P are less likely to give birth at each time interval from 24 weeks of gestation up to 37 weeks of gestation. This is an issue of critical importance since prolonging pregnancy by even 1 week can have profound effects on infant mortality and subsequent health.

- *Healthier Neonates*

The shift in distribution of gestational ages at birth following treatment with 17P resulted in healthier neonates. Three important measures support this claim: Infants born to mothers treated with 17P were significantly less likely to be born at low birth weight (<2500 g), to experience serious morbidities in the neonatal period (such as NEC and IVH), or to require supplemental oxygen.

The NICHD study also demonstrated that children born to mothers treated with 17P had fewer admissions to the NICU and, when admitted, had shorter lengths of stay. These observations were supported in a recent study by Mason and colleagues that examined 17P versus a control group on the rate of admission to the NICU, the length of stay in the NICU, and the associated costs for women treated with the drug.[73] In that study, treatment with 17P reduced the number of days spent in the NICU by 35% (149 compared with 231) and overall costs by 71% ($165,487 compared with $568,462).

Risks of 17P

In considering the risks of 17P, it has been demonstrated throughout this document that treatment with 17P is well tolerated and safe for the mother and, of importance, poses no identified risks for either fetus or child.

- *Risk for the Mother*

  17P is safe for the mother. Weekly administration of the drug was well tolerated by pregnant women, who demonstrated a very low level of discontinuations due to AEs. In fact, the most frequently reported AEs were injection site reactions that tended to be mild and short in duration, a common response to injectable products. Further, 17P treatment did not lead to increased rates of pregnancy complications or pregnancy-related procedures.

- *Risk for the Fetus and Neonate*

  There is no evidence, either from the 17P studies or the published literature, that 17P endangers the developing fetus or neonate. *In utero* exposure to 17P was safe for the developing fetus and neonate as demonstrated by comparable rates of combined miscarriages, stillbirths, and neonatal deaths between the 17P and placebo groups.

  Multiple animal and clinical studies have identified no teratogenic effects from 17-HPC. In the NICHD study, congenital anomalies occurred at similar rates in the 17P and placebo treatment groups, and these rates were consistent with overall rates in the general population. These findings were consistent with a previous analysis of *in utero* exposure to hydroxyprogesterone completed by the FDA in 1999. At that time, FDA concluded that the reliable evidence showed no increase in congenital abnormalities, including genital abnormalities, during pregnancy from exposure to hydroxyprogesterone.

  However, as a precautionary measure, 17P therapy for prevention of preterm birth is to be initiated no earlier than week 16, well into the second trimester. By avoiding treatment during critical embryonic development during the first trimester, the fetus is not exposed to 17P at the time of highest risk for development of congenital anomalies.

- *Risk for the Child*

  A follow-up safety study conducted by the NICHD examined children who had been exposed *in utero* to 17P using a broad range of developmental measures, which included information on communication, gross and fine motor skills, problem solving, and personal-social interaction and physical growth. The data from that study demonstrated that for children between 2.5 and 5.4 years of age, *in utero* exposure to 17P was not associated with developmental delays.

Multiple published studies explored the long-term medical or social effects of 17P in children up to 11 years of age and identified no evidence that *in utero* exposure to 17P posed a risk to the fetus.

In summary, 17P has been shown to be effective and safe for use in the prevention of recurrent preterm birth in singleton pregnancies. Based on the NICHD study and other published results regarding the efficacy and safety of the drug, in 2003 the American College of Obstetricians and Gynecologists Committee on Obstetric Practice recommended progesterone supplementation be used to prevent recurrent preterm birth. As a result, according to the preliminary results of a recent survey, progesterone is now being used by 67% of certified maternal-fetal medicine physicians.

The only current source for this treatment is product compounded by local pharmacies. FDA approval of 17P will ensure the availability of comprehensive labeling, which will provide standardized and accurate guidance on patient selection, dosing and administration instructions and relevant safety information. Additionally, an FDA-approved source will also ensure consistent drug quality, broader availability and a disciplined approach to safety surveillance.

17P represents an important advance for women and children who might otherwise suffer from the potentially damaging effects of preterm birth. The NICHD study demonstrates that 17P is highly effective, and that this benefit results in extended gestational periods and healthier neonates. The low numbers of at-risk women needed to treat further illustrates 17P's efficacy. Specifically, a physician would need to treat 5.6 patients to prevent 1 preterm birth $<37^0$ weeks, 11.0 patients to prevent 1 preterm birth $<35^0$, and 14.2 patients to prevent 1 preterm birth $<32^0$ weeks.

17P is also safe for the mother and her child, as it is well tolerated by the mother and does not cause congenital anomalies or developmental delays during childhood. The benefits far exceed the risks associated with its use. Given the clear unmet medical need and the highly favorable benefit/risk ratio, the case for the approval of 17P is compelling as it can result in a reduction in the number of preterm births in the United States and specifically addresses an important and unmet health care problem.

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ADEZA®

23 August 2006

Teresa Watkins
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Center for Drug Evaluation and Research
Office of Executive Programs
Advisors and Consultants Staff
Rockville, MD 20857

Re: NDA 21-945 Alternative Analysis for the Advisory Committee Meeting on August 29, 2006

Dear Teresa,

Please find attached a document which describes an alternative Intent-to-Treat analysis which Adeza Biomedical will present to the Advisory Committee on Tuesday. This analysis is an alternative to the ITT analysis provided in the Adeza Biomedical Advisory Committee Briefing Document dated 25 July 2006.

Also included in the document is an errata discussion correcting a mathematical error calculation that is specific to secondary pregnancy outcomes presented in Adeza Biomedical's Briefing Document dated 25 July 2006.

Thank you,

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Vice President, Strategic Projects

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Alternative Analysis

For

Advisory Committee Briefing Document

For

17 α-Hydroxyprogesterone Caproate Injection, 250 mg/mL

NDA 21-945

Adeza Biomedical Corporation
1240 Elko Drive
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23 August 2006

In the Adeza Biomedical Advisory Committee Briefing Document dated 25 July 2006, the Intent-to-Treat (ITT) analysis classified patients who were lost to follow-up as treatment failures at each definition of preterm delivery (ie, <37, <35, <32, <30, <28 and <24 weeks). This ITT analysis was conducted even though the last known date pregnant was available for the lost to follow-up patients. For example, the lost to follow-up patient delivered at 36^4 weeks was classified as a treatment failure in all six of the preterm delivery definitions.

An alternative, and perhaps more appropriate, ITT analysis that classifies lost to follow-up patients as delivering at their last known date pregnant was undertaken and is provided below. This analysis did not affect the primary outcome of preterm delivery at <37 weeks.

Table 1. ITT Population with Last Known Date Pregnant

Pregnancy Outcome	17P (N=310) N (%)	Placebo (N=153) N (%)	Relative Risk (95% CI)	*P* value*
Preterm Birth <37^0	115 (37.1%)	84 (54.9%)	0.68 (0.55-0.83)	0.0003
Preterm Birth <35^0	66 (21.3%)	47 (30.7%)	0.69 (0.50-0.95)	0.0263
Preterm Birth <32^0	37 (11.9%)	30 (19.6%)	0.61 (0.39-0.95)	0.0273
Preterm Birth <30^0	30 (9.7%)	24 (15.7%)	0.62 (0.37-1.02)	0.0581
Preterm Birth <28^0	29 (9.4%)	16 (10.5%)	0.89 (0.50-1.60)	0.7063
Preterm Birth <24^0	17 (5.5%)	5 (3.3%)	1.68 (0.63-4.46)	0.2918

Note: The 4 patients lost to follow-up were in the 17P group and are counted as treatment failures based on the last known date pregnant of 18^4, 22^0, 34^3, and 36^4 weeks.
* *P* value is for 17P vs. placebo and is from the chi-square test

Figure 1 reflects the numbers provided in Table 1 and illustrates the effectiveness of 17P in reducing preterm birth irrespective of the definition applied. Following treatment with 17P, the incidence of preterm birth was reduced by approximately 38%, 39%, 31%, and 32% and when defined as <30^0, <32^0, <35^0, and <37^0 weeks, respectively. Adeza Biomedical will present this alternative ITT analysis at the Advisory Committee Meeting on 29 August 2006.

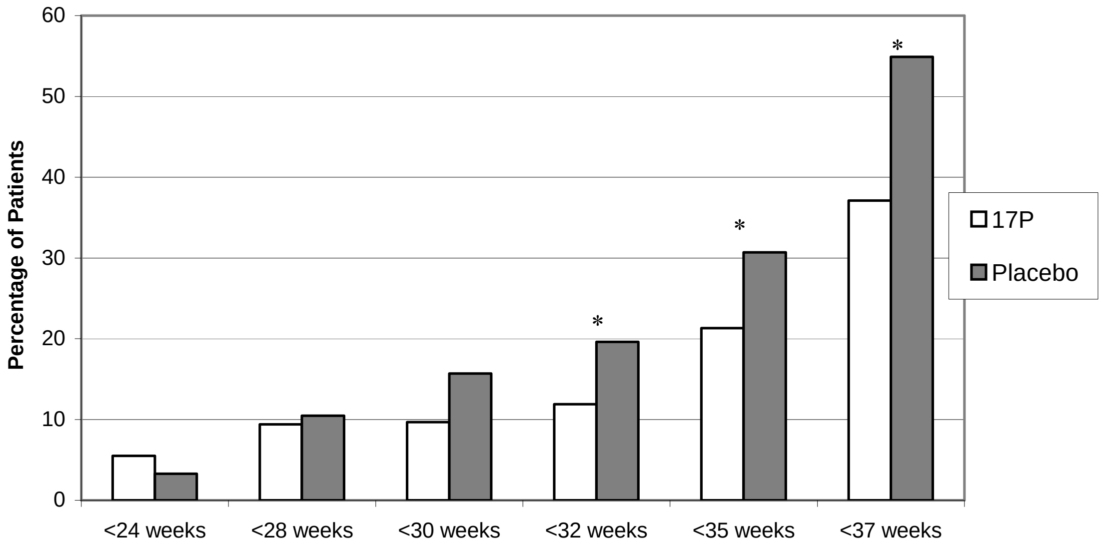


Figure 1. Preterm Birth <37^0, <35^0, <32^0, <30^0, <28^0, and <24^0 Weeks

*Statistically significant difference; *P* <0.05.

Errata

For

Advisory Committee Briefing Document

For

17 α-Hydroxyprogesterone Caproate Injection, 250 mg/mL

NDA 21-945

Adeza Biomedical Corporation
1240 Elko Drive
Sunnyvale, CA 94089

23 August 2006

Errata:

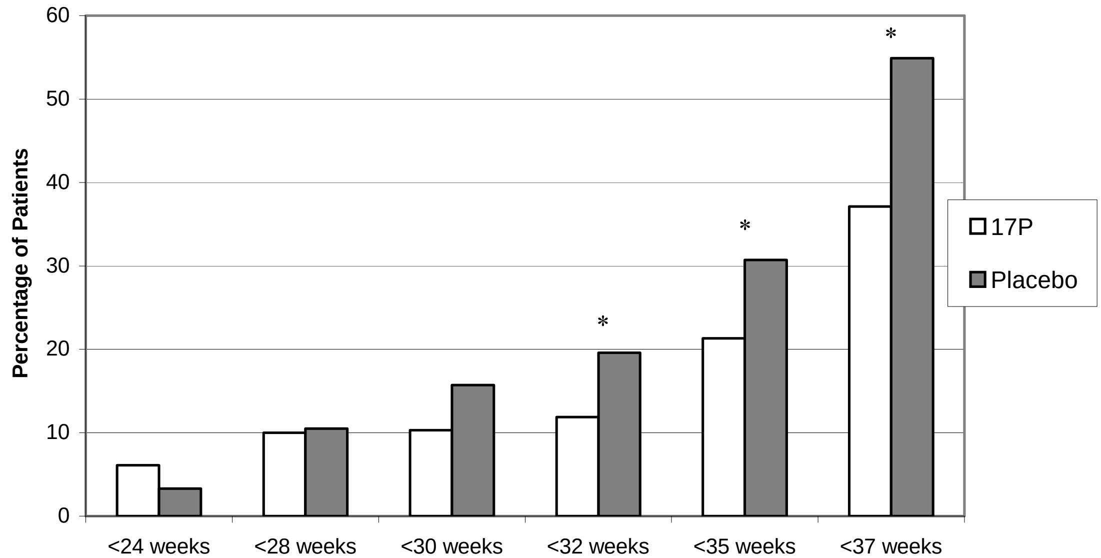
Table 4-6 entitled “Secondary Pregnancy Outcomes” (page 30) of the Adeza Biomedical Advisory Committee Briefing Document dated 25 July 2006 contains a mathematical error that is corrected with this document. Four patients who were lost to follow-up in the CT-002 study were inadvertently omitted from the secondary pregnancy outcomes of preterm delivery at <30, <28 and <24 weeks gestation. These patients should have been included in each of these outcomes as treatment failures. Note that the data for the <35 and <32 week definitions of preterm birth are correct in the original Briefing Document. The corrected Table 4-6 (corrections highlighted), associated Figure 4-4, and associated text are provided below.

Corrected Table 4-6. Secondary Pregnancy Outcomes

Pregnancy Outcome	17P (N=310) N (%)	Placebo (N=153) N (%)	Relative Risk (95% CI)	*P* value*
Preterm Birth $<35^0$	67 (21.6%)	47 (30.7%)	0.70 (0.51-0.97)	0.0324
Preterm Birth $<32^0$	39 (12.6%)	30 (19.6%)	0.64 (0.42-0.99)	0.0458
Preterm Birth $<30^0$	32 (10.3%)	24 (15.7%)	0.66 (0.40-1.08)	0.0959
Preterm Birth $<28^0$	31 (10.0%)	16 (10.5%)	0.96 (0.54-1.69)	0.8781
Preterm Birth $<24^0$	19 (6.1%)	5 (3.3%)	1.88 (0.71-4.93)	0.1915

Abbreviations: confidence interval (CI)
Note: Data presented are from the ITT analysis. The ITT population is all randomized patients. Patients with missing outcome data were classified as having a preterm birth at each preterm birth interval (ie, treatment failure).
* *P* value is for 17P vs. placebo and is from the chi-square test

Corrected Figure 4–4 illustrates the effectiveness of 17P in reducing preterm birth irrespective of the definition applied. Following treatment with 17P, the incidence of preterm birth was reduced by approximately 34%, 36%, 30%, and 32% when defined as $<30^0$, $<32^0$, $<35^0$, and $<37^0$ weeks, respectively.



Corrected Figure 4-4. Preterm Birth $<37^0$, $<35^0$, $<32^0$, $<30^0$, $<28^0$, and $<24^0$ Weeks

*Statistically significant difference; *P* <0.05.

As a result of this error, the *P* value associated with <30 weeks gestation was incorrectly reported as statistically significant. The text on pages 29 (Section 4.1.3.3), 36 (Section 4.1.4) and 66 (Section 6) incorrectly report that the preterm birth rate at <30 weeks is statistically significant. The correct *P* value is 0.0959.

Bibliography of Appendices

Appendix 1 Ages and Stages Questionnaire (36 month/3 Year Questionnaire)

Squires J, Bricker D, Mounts L, Potter LW, Nickel R, Twombly E, Farrell, J. *Ages & Stages Questionnaires (ASQ): A Parent-Completed, Child-Monitoring System (2nd ed.).* Paul H. Brookes Publishing Co.: Baltimore, MD. (1999).

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17 α-Hydroxyprogesterone Caproate Injection, 250 mg/mL NDA 21-945

Adeza Biomedical

Advisory Committee Meeting

Reproductive Health Drugs

August 29, 2006

Durlin E Hickok, MD, MPH

Vice President, Medical Affairs

Adeza Biomedical

Presentation

- Adeza Biomedical
- Medical Need
- Clinical Review
  - Efficacy
  - Safety
- Benefit / Risk

Presenters

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Vice President, Medical Affairs

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Adeza Biomedical

- Medical technology company
- Focused on pregnancy-related and female reproductive disorders
  - preterm birth
  - infertility
- Submitted NDA for FDA approval to market 17P in the US for the prevention of recurrent preterm birth

Nomenclature

17-HPC

- 17 α-hydroxyprogesterone caproate

17P

- Clinical study formulation of 17-HPC for injection used in the NICHD Study

Gestiva™

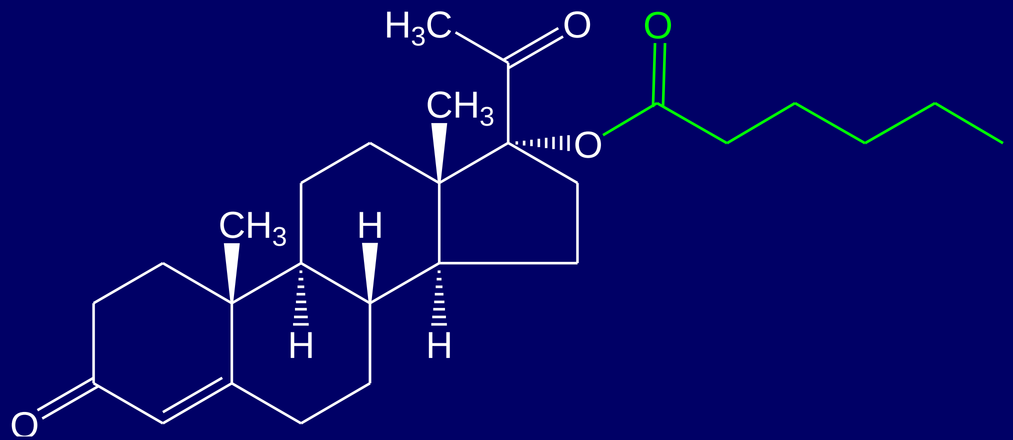
- Adeza's proposed trade name for 17P

Delalutin®

- Trade name of previously marketed 17-HPC

17-HPC

- 17 α-hydroxyprogesterone caproate
  - The active pharmaceutical ingredient of 17P
  - An esterified derivative of the naturally occurring 17 α-hydroxyprogesterone
  - Substantial progestational activity
  - Prolonged duration of action



17P

- 17P is a sterile solution for injection containing:
  - 17-HPC (250 mg/mL)
  - Castor oil USP
  - Benzyl benzoate USP
  - Benzyl alcohol NF
- 17P
  - Used in NICHD clinical studies
  - Identical in composition to previously marketed Delalutin

17-HPC – History

- Delalutin approved by FDA in 1956
  - Indications
    - treatment of habitual and recurrent miscarriage
    - threatened miscarriage
    - postpartum after pains
    - advanced uterine cancer
  - Voluntarily withdrawn from US market in 1999 for reasons not related to safety or effectiveness
- Multiple studies evaluated safety and efficacy of 17-HPC for prevention of preterm birth

17-HPC Studies for Preterm Birth

	Inclusion Factors	Initiated	Ended	Dose (mg/wk)	Odds Ratio
LeVine (1964)	3 miscarriages	<16 wks	36 wks	500	0.63 (0.10-4.15)[a]
Papiernik (1970)	High Preterm Risk Score	28-32 wks	≤8 doses	250 mg q 3days	0.24 (0.07-0.82)[a]
Johnson (1975)	2 miscarriages or 2 preterm births	First visit	37 wks	250	0.12 (0.02-0.85)[a]

[a]Odds ratios reported by Keirse 1989

17-HPC Studies for Preterm Birth (continued)

	Inclusion Factors	Initiated	Ended	Dose (mg/wk)	Odds Ratio
Hauth (1983)	Active duty military	16-20 wks	36 wks	1000	1.11 (0.31-3.97)
Yemeni (1985)	2 preterm births or 2 miscarriages	First visit (mean GA 12.2 wks)	37 wks	250	0.30 (0.11-0.84)[a]
Suvonnakote (1986)	1 preterm birth or 2 midtrimester miscarriages	16-20 wks	37 wks	250	0.29 (0.12-0.70)

[a]Odds ratios reported by Keirse 1989

17-HPC Studies for Preterm Birth – Forest Plot

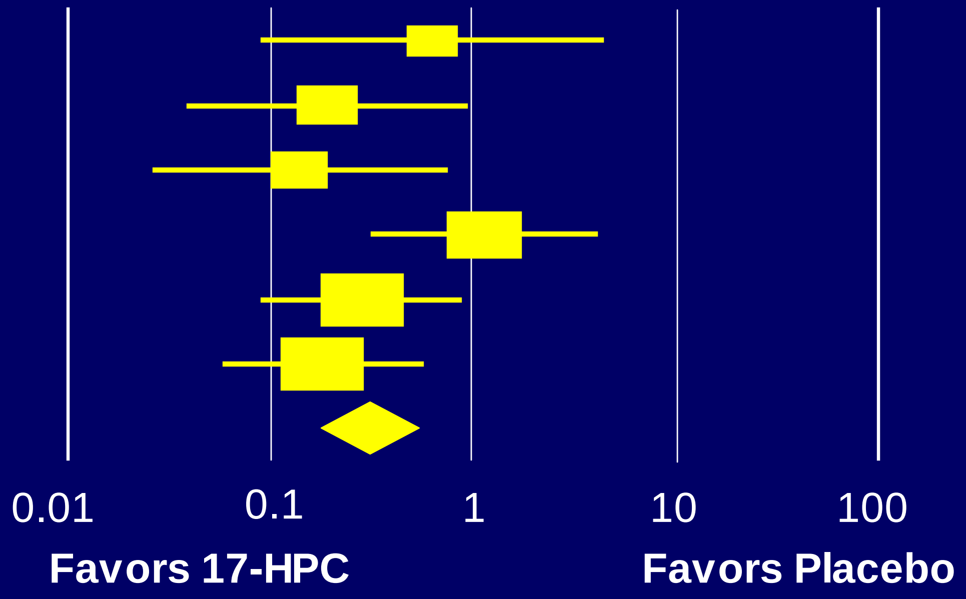
Treatment Effect of 17-HPC

Study name

LeVine, 1964
Papiernik, 1970
Johnson, 1975
Hauth, 1983
Yemini, 1985
Suvonnakote, 1986

Total = 0.30 (0.17 - 0.53)

Odds ratio and 95% CI



Meta Analysis

Development of 17P NDA Submission

- NICHD conducted controlled clinical study evaluating 17P for prevention of recurrent preterm birth
- Results published in *New England Journal of Medicine*, 2003
- Adeza allowed access to clinical database

Development of 17P NDA Submission

- Results from NICHD study provide primary basis for efficacy claim of Adeza's NDA submission for 17P
  - Large, multicenter study
  - Highly statistically significant efficacy findings
  - Study stopped early by DSMC for efficacy
  - Results consistent across subsets of patients

Proposed Indication for Gestiva (17P)

"Gestiva is indicated for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth."

Medical Need

Michael P Nageotte, MD

Professor, Obstetrics & Gynecology

University of California, Irvine

Immediate Past President

Society for Maternal-Fetal Medicine

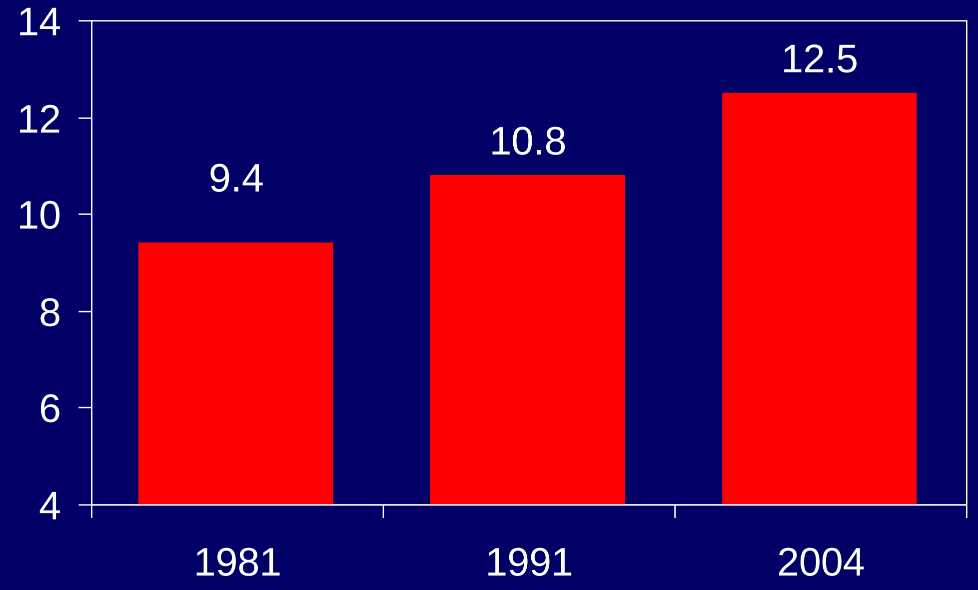
Definition of Preterm Birth

- Preterm birth is defined as birth before the 37th week of gestation

Preterm Birth in the US

- Incidence of preterm birth continues to rise[a]
- Costs exceed $26 billion annually
- One preterm birth occurs every minute in the US
- March of Dimes launched a multimillion dollar campaign to reduce preterm births
- Reduction in preterm births will alleviate primary cause of perinatal and neonatal morbidity and mortality[b]

33% increase since 1981



[a]Hamilton BE et al. *Natl Vital Stat Rep*. 54(8):1-17; 2005

[b]Spong CY. *Obstet Gynecol*. 101(6):1153-4; 2003

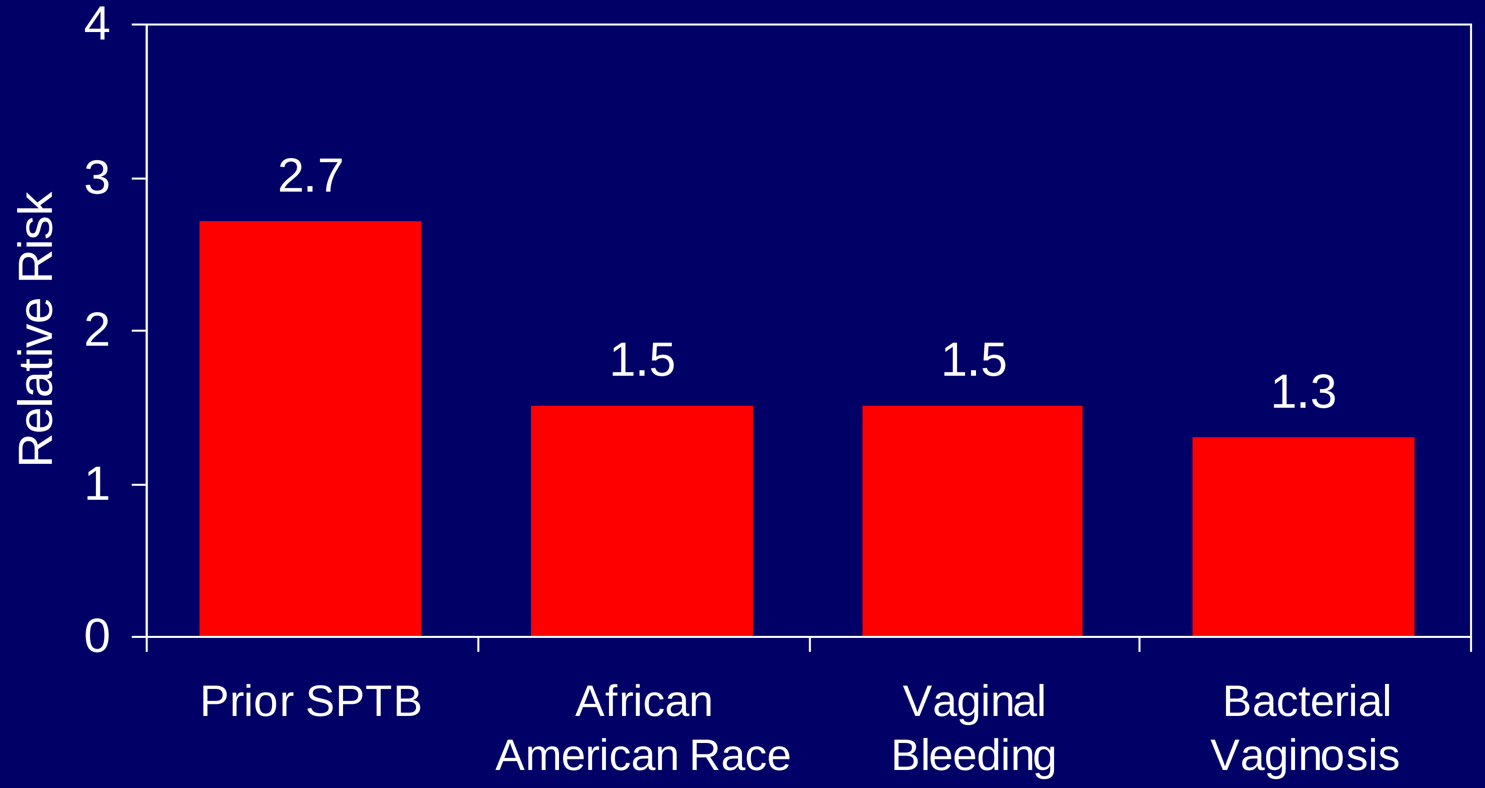
Morbidities Associated with Preterm Birth

- Respiratory distress syndrome (RDS)
- Intraventricular hemorrhage (IVH)
- Periventricular leukomalacia (PVL)
- Necrotizing enterocolitis (NEC)
- Apnea
- Jaundice
- Anemia
- Infections due to immature immune systems
- Neonatal death

Neonatal Long-Term Morbidities

- Potential long-term outcomes
  - Retinopathy
  - Cerebral palsy
  - Mental retardation
  - Learning disabilities
  - Attention deficit disorders

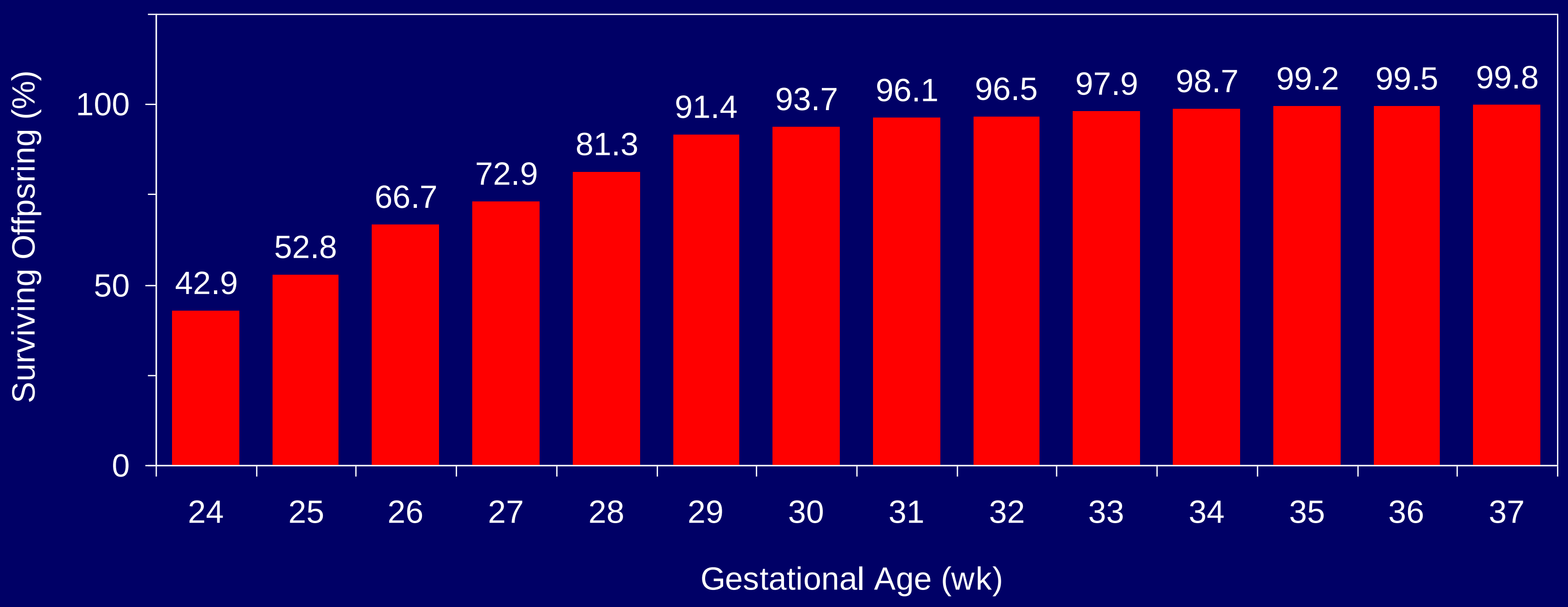
Risk Factors for Preterm Birth



From: Goldenberg RL et al. *Am J Public Health.* 88:233-238; 1998

Benefits of Prolonging Pregnancy – Mortality

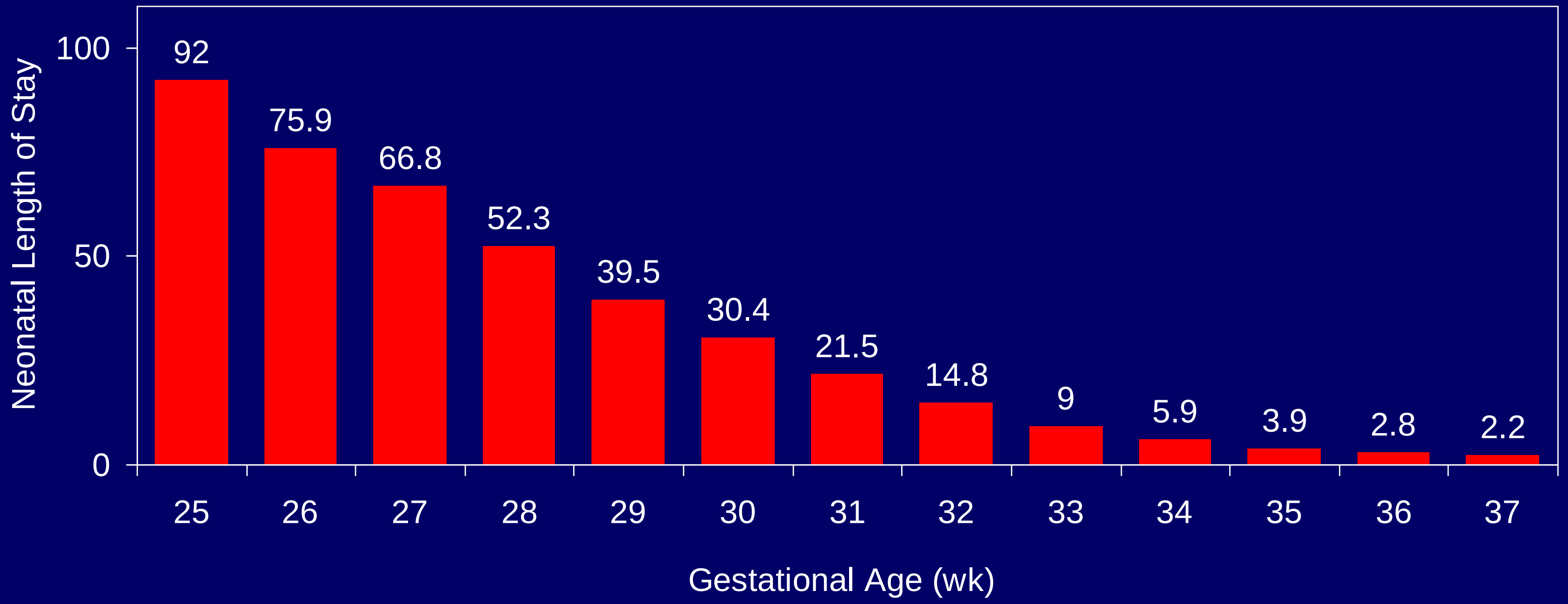
- Improved survival with gestational age



From: St. John EB et al. *J Obstet Gynecol.* 182:170-175; 2000

Benefits of Prolonging Pregnancy – Length of Stay

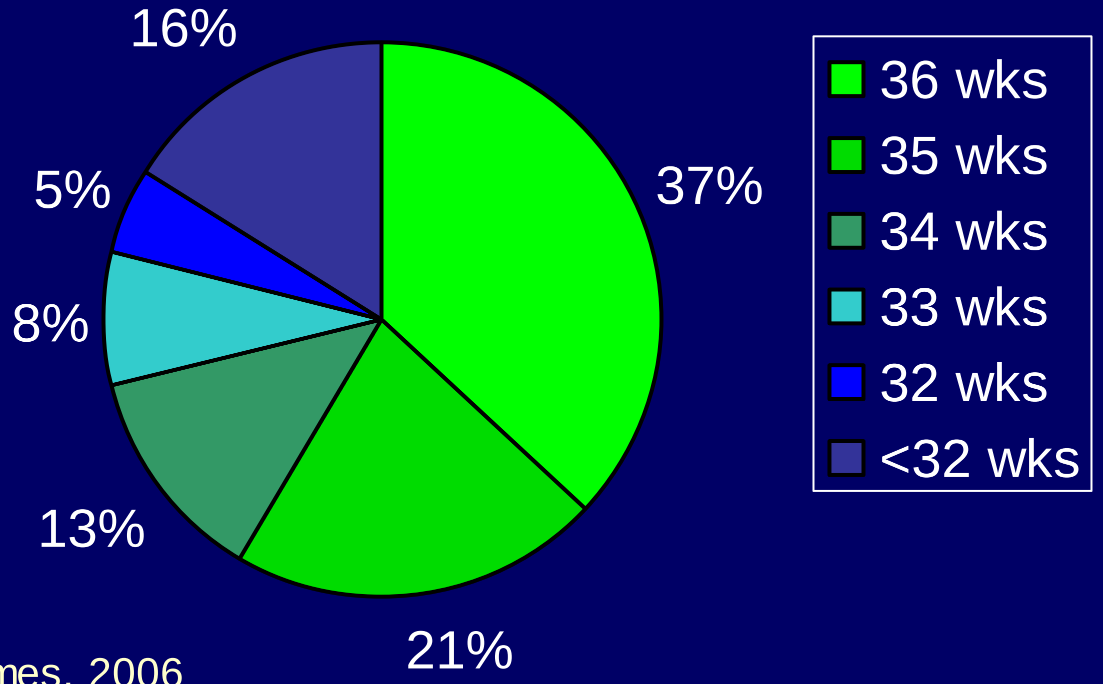
- Reduced neonatal hospital days



From: Gilbert WM et al. *Obstet Gynecol.* 102:488-492; 2003

Significance of Late Preterm Birth

- Contributes substantially to overall preterm births
  - 58% between 35-36 weeks
  - 79% greater than 32 weeks



From: March of Dimes, 2006

Significance of Late Preterm Birth

- Increased mortality[a]
  - Mortality risk approximately 3-fold higher at 35-36 weeks
- Increased morbidities[b,c]
  - Respiratory distress requiring O_2
  - Temperature instability
  - Hypoglycemia
  - Jaundice
  - Attention deficit disorders
- Increased hospitalizations and associated costs[b,c]
  - Initial hospitalization costs approximately 3-fold higher
  - Risk for rehospitalization from 2 weeks to 6 months post discharge increased

[a]Kramer MS et al. *JAMA*. 284:843-9; 2000
[b]Wang ML et al. *Pediatrics*. 114:372-6; 2004
[c]Escobar GJ et al. *Semin Perinatol*. 30(1):28-33; 2006

Available Treatments

- Treatment of preterm labor
  - Tocolytics effective for short-term prolongation after onset of labor
- Prevention of preterm birth
  - No effective treatments identified prior to 17P
  - American College of Obstetricians and Gynecologists (ACOG) recommends use to prevent recurrent preterm birth in 2003 after publication of the NICHD study[a,b]
  - 17P currently in use among Ob/Gyn community for prevention of recurrent preterm birth

[a]ACOG News Release, 2003
[b]ACOG Committee Opinion. *Obstet Gynecol*. 102(5 pt 1):1115-6; 2003

Current Availability of 17P

- Available only from compounding pharmacies
  - No consistent labeling/prescribing information
  - Limited FDA oversight
  - No regulations ensuring consistency of products between compounding pharmacies
  - No federal regulations requiring reporting of AE/SAEs (MedWatch)

Conclusions

- Compelling need to address rising incidence of preterm birth and associated costs and morbidities
- Benefits of prolonging pregnancy at any gestation
  - Prevention of early preterm births
  - Prevention of late preterm births
- Need for FDA-approved product

Clinical Review

National Institute of Child Health and Human Development (NICHD)

- Part of the National Institutes of Health (NIH)
- Objectives
  - Identify causes of prematurity
  - Evaluate safety and effectiveness of treatments
- Maternal-Fetal Medicine Units (MFMU) Network
  - Consists of major medical training institutions
  - Engages in multicenter collaborative investigations

NICHD MFMU Network Sites for 17P Study

- University of Pittsburgh
- University of Tennessee
- University of Alabama
- Wayne State University
- University of Cincinnati
- Wake Forest University
- University of Chicago
- Ohio State University
- University of Miami
- University of Texas Southwestern
- University of Texas San Antonio
- University of Utah
- Thomas Jefferson University
- Brown University
- Columbia University
- Case Western University
- University of Texas Houston
- University of North Carolina
- Northwestern University

Overview of NICHD Clinical Studies

- Study 002
  - Initiated in 1999, completed in 2002
  - Randomized, placebo-controlled, double-blind, multi-center clinical study
  - Weekly IM injections from 16^0 and 20^6 weeks of gestation until 36^6 weeks gestation or birth
  - Enrolled 463 patients in 2:1 ratio active to placebo
  - DSMC recommended study be halted early
    - Interim analysis conducted on 351 completed patients
    - Boundary for test of significance had been crossed
    - Indicated a benefit for 17P in reducing preterm birth
  - Results form primary basis for efficacy

Overview of NICHD Clinical Studies

- Study 001
  - Initiated in 1998
  - Terminated due to manufacturer and FDA recall of study drug
  - Enrolled only 150 of 500 planned patients

Overview of NICHD Clinical Studies

- Follow-Up Study
  - Observational follow-up safety study to assess the long term safety outcome of infants exposed to 17P in utero
  - Examined health and development of infants born during Study 002
  - Conducted at 15 MFMU Network study centers
  - Enrolled 278 children

Efficacy and Safety Databases

Efficacy Assessment

- Study 002

Safety Assessment

- Study 002
- Study 001
- Follow-Up Study

Efficacy

Enrollment Criteria

- Pregnant women with documented history of previous singleton spontaneous preterm delivery (SPTD)
- Gestational age of 16^0 to 20^6 weeks at randomization
- Exclusion criteria:
  - Multifetal gestation
  - Known major fetal anomaly or fetal demise
  - Prior progesterone treatment during current pregnancy
  - Prior heparin therapy during current pregnancy
  - History of thromboembolic disease
  - History of maternal medical/obstetrical complications (eg current or planned cerclage, HTN requiring medications, seizure disorder)

Patient Enrollment – Study 002

- Total of 463 patients
  - 2:1 randomization (active:placebo)
  - 310 in 17P group
  - 153 in Placebo group
- 418 (90.3%) patients completed injections through 36^6 weeks gestation or birth
  - 279 (90.0%) in 17P group
  - 139 (90.8%) in Placebo group

Baseline Demographics

Characteristic	17P (N=310)	Placebo (N=153)	P value
Age, yr mean (SD)	26.0 (5.6)	26.5 (5.4)	0.2481
Race or ethnic group			0.8736
African American	59.0%	58.8%	
Caucasian	25.5%	22.2%	
Hispanic	13.9%	17.0%	
Asian	0.6%	0.7%	
Other	1.0%	1.3%	
Marital status			0.6076
Married or living with partner	51.3%	46.4%	
Divorced, widowed or separated	10.3%	11.8%	
Never married	38.4%	41.8%	
Years of education, mean (SD)	11.7 (2.3)	11.9 (2.3)	0.2175

Baseline Pregnancy Characteristics

Characteristic	17P (N=310)	Placebo (N=153)	P value
Body mass index (kg/m^2), mean (SD)	26.9 (7.9)	26.0 (7.0)	0.3310
Diabetes	4.2%	2.6%	0.3954
Smoked cigarettes during pregnancy	22.6%	19.6%	0.4647
Alcoholic drinks during pregnancy	8.7%	6.5%	0.4172
Used street drugs during pregnancy	3.5%	2.6%	0.7822
Duration of gestation at randomization (wk), mean (SD)	18.9 (1.4)	18.8 (1.5)	0.5929

Previous Obstetrical History

Obstetrical History	17P (N=310)	Placebo (N=153)	P value
Number previous SPTD, mean (SD)	1.3 (0.7)	1.5 (0.9)	0.0017
>1 Previous PTB	27.7%	41.2%	0.0036
Gestational age qualifying delivery (wk), mean (SD)	30.6 (4.6)	31.3 (4.2)	0.2078
Previous miscarriage	30.0%	37.3%	0.1166

Efficacy Endpoints – Primary

- Preterm birth <37 weeks

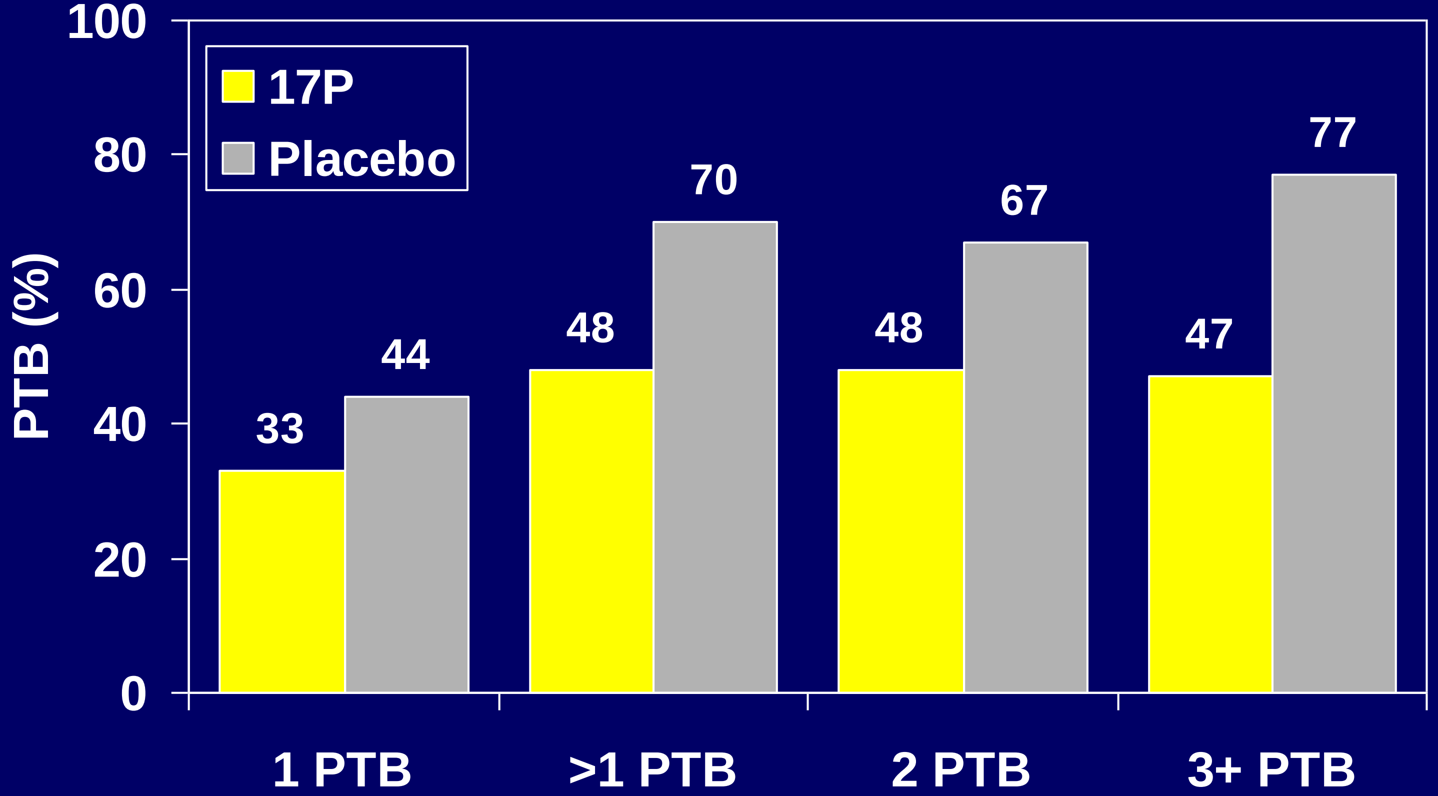
Primary Efficacy Results
Preterm Birth <37 Weeks

Population	17P N (%)	Placebo N (%)	P value
Intent-to-treat	310 (37.1)	153 (54.9)	0.0003
			0.0010[a]
All available data[b]	306 (36.3)	153 (54.9)	0.0001
			0.0006[a]

[a]P value from a logistic regression adjusting for the number of previous preterm deliveries
[b]Analysis population represents that reported by Meis et al (2003) and excludes 4 patients lost to follow-up

Preterm Birth <37 Weeks of Gestation

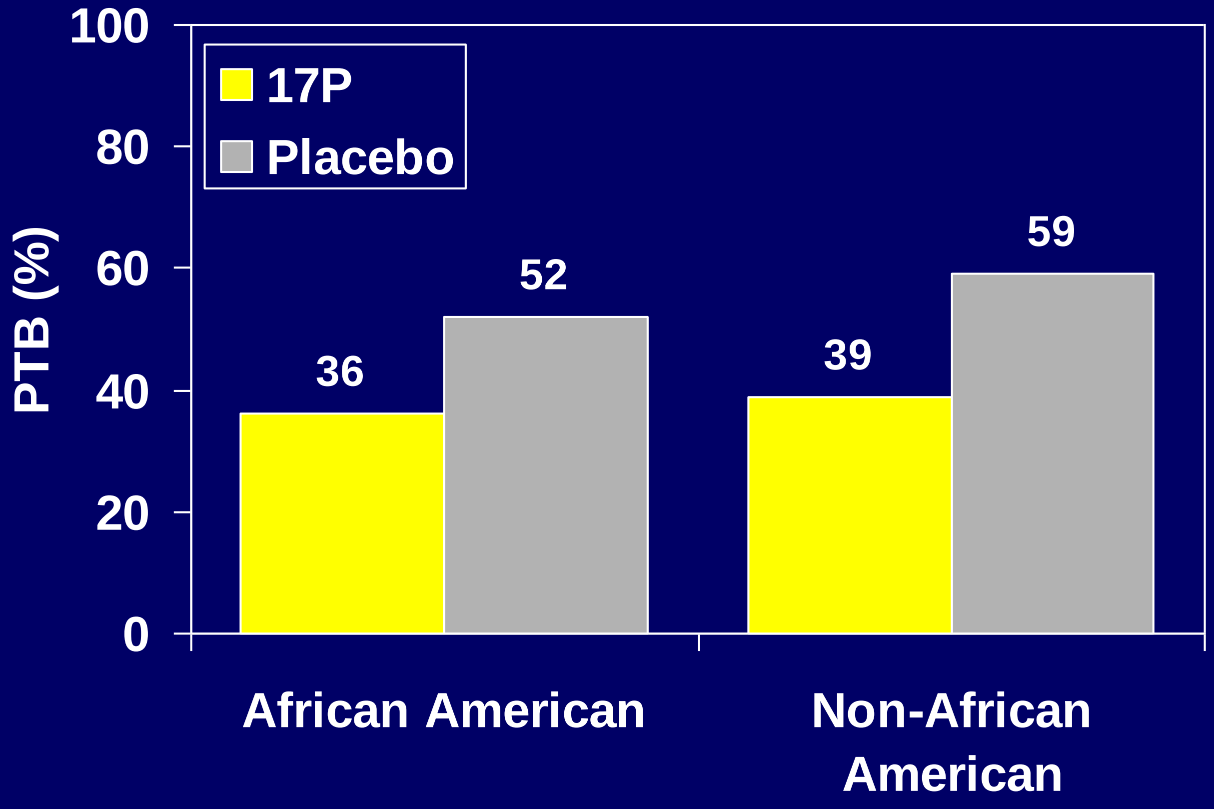
Number of Previous Preterm Births



Breslow-Day P value >0.05

Preterm Birth <37 Weeks of Gestation

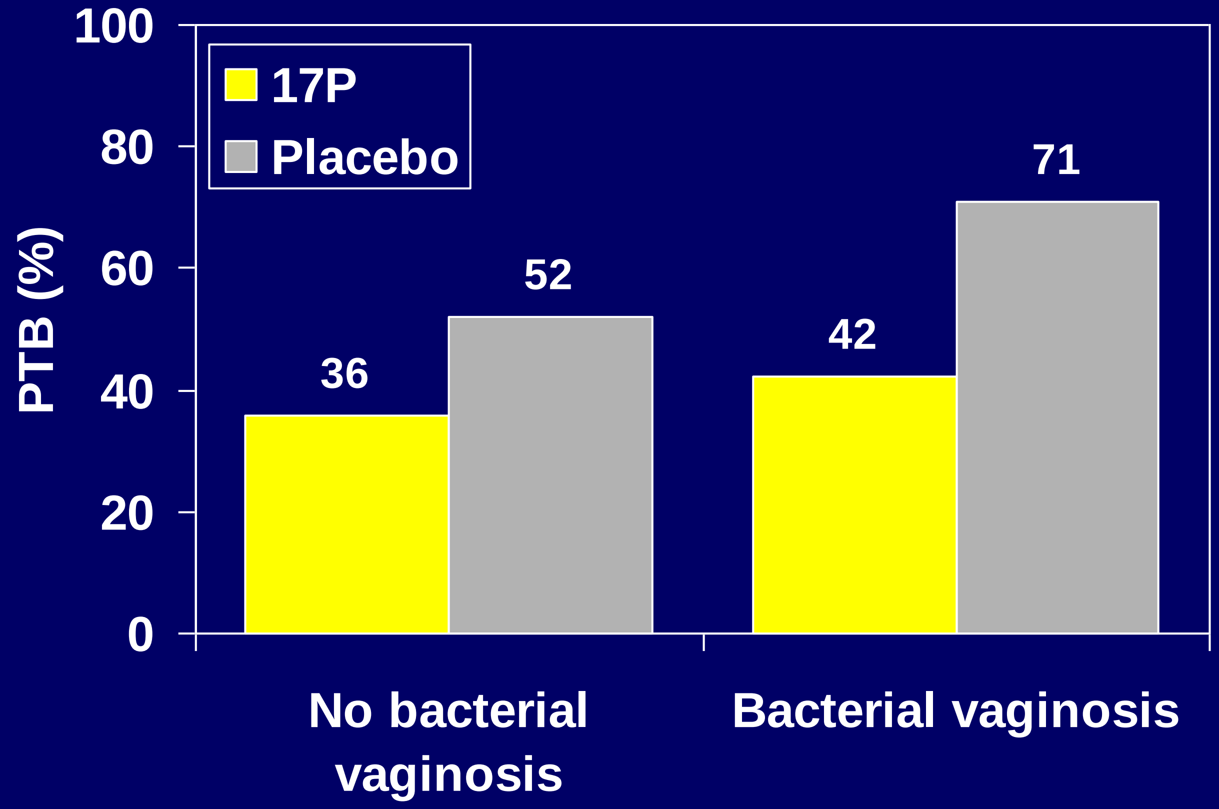
Race



Breslow-Day P value >0.05

Preterm Birth <37 Weeks of Gestation

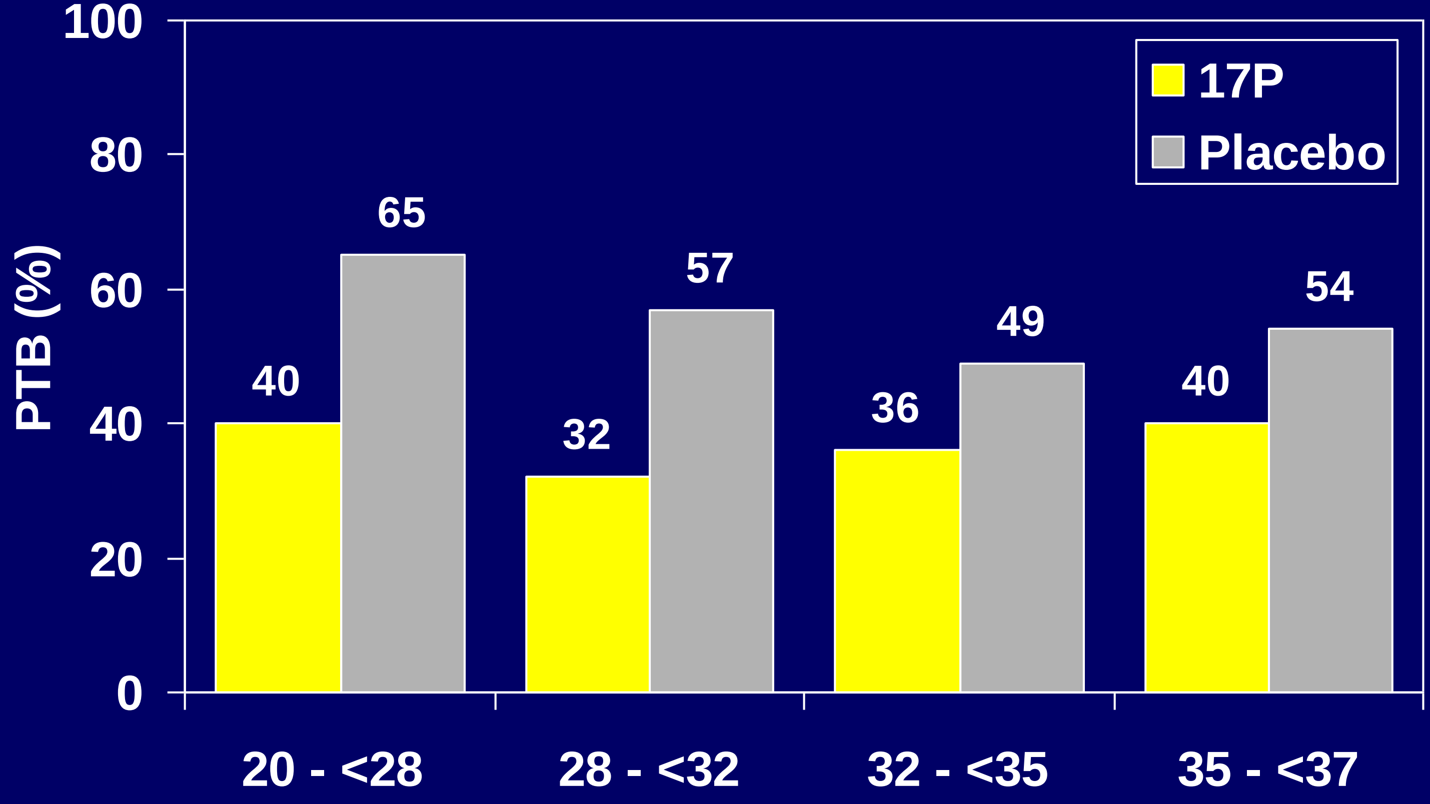
Bacterial Vaginosis



Breslow-Day P value >0.05

Preterm Birth <37 Weeks of Gestation

Gestational Age of Qualifying Preterm Birth



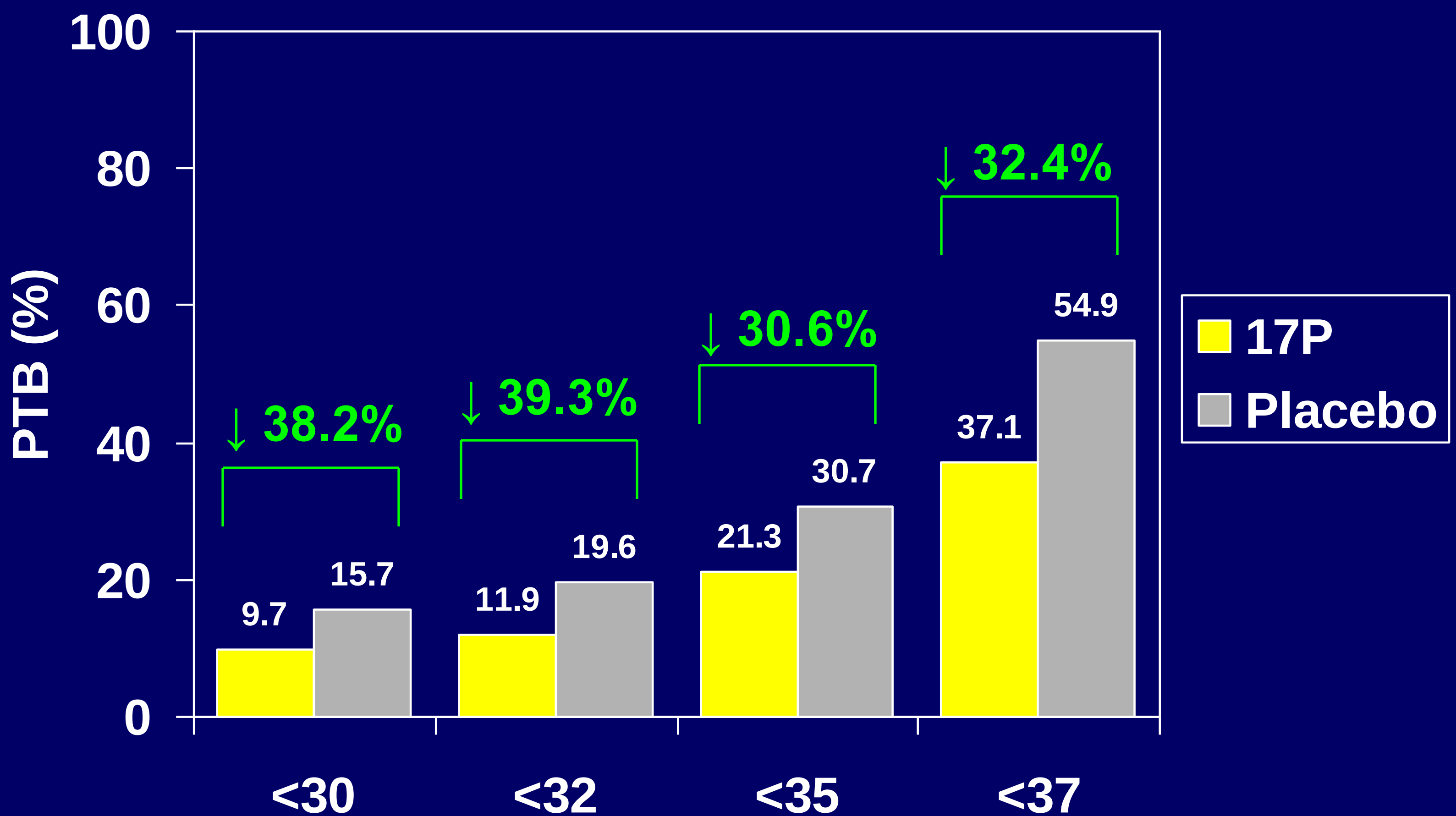
Breslow-Day P value >0.05

Secondary Maternal Efficacy Endpoint Results

Pregnancy Outcome	17P (N=310) %	Placebo (N=153) %	P value
Preterm birth $<35^0$ weeks	21.3	30.7	0.0263
Preterm birth $<32^0$ weeks	11.9	19.6	0.0273
Preterm birth $<30^0$ weeks	9.7	15.7	0.0581

Note: Data from the 4 patients lost to follow-up are included based upon last known date pregnant

Preterm Birth <37, <35, <32, and <30 Weeks



Note: Data from the 4 patients lost to follow-up are included based upon last known date pregnant

Gestational Ages at Birth

Gestational Age at Birth	17P (N=310) %	Placebo (N=153) %
Term (>37 weeks)	62.9	45.1
35^{0}-36^{6} weeks	15.8	24.2
32^{0}-34^{6} weeks	9.4	11.1
28^{0}-31^{6} weeks	2.6	9.2
24^{0}-27^{6} weeks	3.9	7.2
20^{0}-23^{6} weeks	3.6	3.3
16^{0}-19^{6} weeks	1.9	0
Total	100%	100%

Hazard Ratio for Delivery

Gestational Age at Delivery	Hazard Ratio	95% Confidence Interval
Term (>37 weeks)	1.00	–
35^{0}-36^{6} weeks	0.52	0.28 – 0.94
32^{0}-34^{6} weeks	0.73	0.31 – 1.70
28^{0}-31^{6} weeks	0.27	0.08 – 0.90
24^{0}-27^{6} weeks	0.54	0.17 – 1.72
20^{0}-23^{6} weeks	1.01	0.23 – 4.50
16^{0}-19^{6} weeks	NC	NC

NC=not calculable

Neonatal Outcomes

Neonatal Outcome	17P	Placebo	P value
Birthweight			
<2500 g	27.2%	41.1%	0.0029
<1500 g	8.6%	13.9%	0.0834
Birthweight (g), mean (SD)	2760 (859)	2582 (942)	0.0736
Admitted to NICU (live births)	27.8%	36.4%	0.0434
Days in NICU (median)	9.1	14.1	0.1283

Neonatal Morbidities

Neonatal Morbidity	17P	Placebo	P value
Necrotizing enterocolitis (NEC)	**0%**	**2.7%**	**0.0127**
Intraventricular hemorrhage (IVH)	**1.4%**	**5.3%**	**0.0258**
Supplemental oxygen	**15.4%**	**24.2%**	**0.0248**
Days respiratory therapy (mean)	**1.7**	**2.7**	**0.0438**
Ventilator support	8.9%	14.8%	0.0616
Transient tachypnea	3.7%	7.3%	0.0990
Respiratory distress syndrome (RDS)	9.9%	15.3%	0.0900
Bronchopulmonary dysplasia (BPD)	1.4%	3.3%	0.1730
Patent ductus arteriosis (PDA)	2.4%	5.4%	0.1004

Composite Neonatal Morbidity Index

- Conducted as post hoc analysis
- Defined as any liveborn infant who experienced one or more of the following:
  - Death
  - Respiratory distress syndrome (RDS)
  - Bronchopulmonary dysplasia (BPD)
  - Grade 3 or 4 intraventricular hemorrhage (IVH)
  - Proven sepsis
  - Necrotizing enterocolitis (NEC)
- Trend toward improvement with 17P
  - 11.9% in 17P group
  - 17.2% in Placebo group

Summary of NICHD Efficacy Results

Weekly administration of 17P

- Reduces rate of recurrent preterm birth at <37, <35, and <32 weeks
  - prolongs gestation
  - consistent with previous studies
- Improves neonatal outcomes
  - reduced percentage of infants born <2500 g
  - reduced admission rate to NICU
- Reduces specific neonatal morbidities
  - NEC, IVH, supplemental oxygen, mean days of respiratory therapy

Safety

Safety Database

- Study 002
- Study 001
- Follow-Up Study

Safety Database Exposure – Studies 002 and 001

- 613 Patients exposed to at least 1 injection
  - 17P 404 patients
  - Placebo 209 patients

Pregnancy Related Admissions/Procedures

	17P (N=399) %	Placebo (N=205) %	P value
Hospital or labor admission for preterm labor	14.8	15.6	0.7834
Cerclage placement	1.3	1.5	1.0000

Pregnancy Related Complications

Complication	17P (N=399) %	Placebo (N=205) %	P value
Preeclampsia or gestational hypertension	8.3	4.4	0.0795
Gestational diabetes	6.3	3.4	0.1792
Oligohydramnios	3.3	1.5	0.2851
Abruption	1.8	2.9	0.3565
Significant antepartum bleeding	2.5	3.4	0.5654
Clinical chorioamnionitis	3.3	2.4	0.8011
Other complication	2.6	3.0	0.7928

Most Frequently Reported Maternal Adverse Events

	17P (N=404) %	Placebo (N=209) %
Any adverse event (AE)	59.2	56.5
Preferred Term		
Injection site reactions	44.6	40.7
Urticaria	12.6	11.5
Pruritus	6.9	5.3
Contusion	6.4	9.6
Nausea	5.0	3.8

Note: Table presents those adverse events reported by at least 2% of patients in either treatment group

Discontinuations Due to Adverse Events

- Patients discontinued early due to AEs
  - 17P group – 2.2% patients
  - Placebo group – 3.3% patients

- Injection site reactions most common
  - 17P group – 1.0% patients
  - Placebo group – 1.4% patients

Serious Adverse Events

- SAEs collected according to NICHD standardized procedures
  - All deaths (maternal, neonatal, fetal)
  - Other serious and unexpected AEs
- Analysis also included congenital anomalies

Serious Adverse Events – Nonfatal

	17P (N=404) %	Placebo (N=209) %
Any SAEs (Total)	9.4	10.5
Nonfatal SAEs		
Congenital anomalies	2.2	1.9
Injection site reactions	1.0	1.0
Hypersensitivity/adverse drug reaction	0.2	0.5
Infection	0.5	0
Pulmonary embolism (maternal)	0.2	0
Uterine rupture	0.2	0
Pruritus	0	0.5
Arthralgia	0.2	0
Testicular infarction	0.2	0

Congenital Anomalies Assessed at Birth

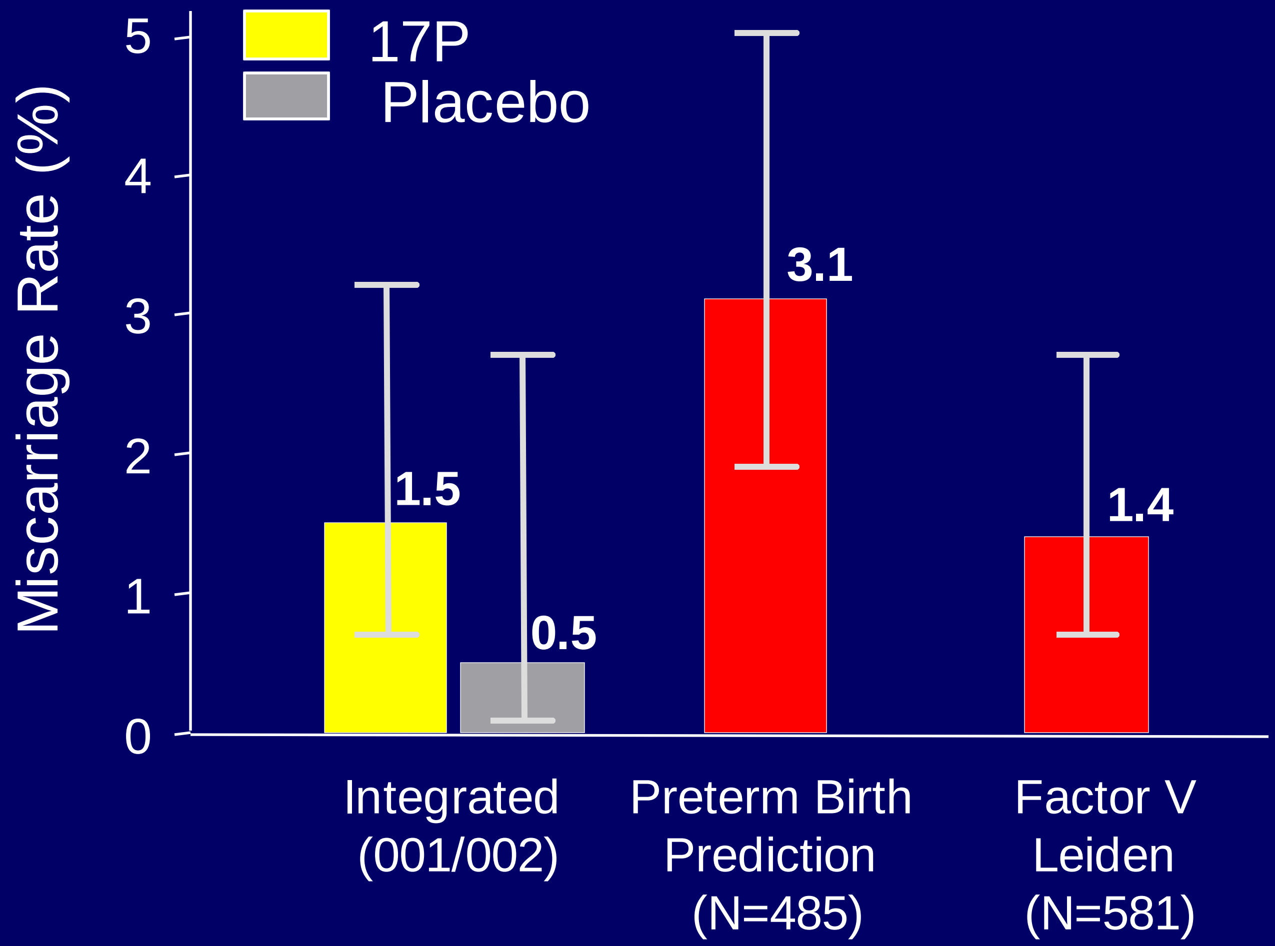
	17P (N=404) %	Placebo (N=209) %
Congenital anomalies	2.2	1.9
Musculoskeletal	0.7	1.0
Cardiovascular	0.5	0.5
Genitourinary	0.2	0.5
Male reproductive	0.5	0.5
Breast	0.2	0

Serious Adverse Events – Fetal/Neonatal Deaths

	17P (N=404) %	Placebo (N=209) %	P value
Miscarriages	1.5	0.5	0.2629
Stillbirths	1.7	1.9	0.8769
Neonatal deaths	2.5	4.3	0.1928

- No neonatal deaths, stillbirths, or miscarriages were considered related to study drug by investigators

Summary of Miscarriage Rates (16-20 Weeks) – NICHD Network Studies



17-HPC for Prevention of Miscarriage – Cochrane Database Review (2003)

- No difference between 17-HPC and Placebo
  - OR = 0.77 [0.36 – 1.68]
- Significant protective effect for progestins in women with ≥ 3 prior miscarriages
  - OR = 0.39 [0.17 - 0.91]
  - 3 studies, 1 of which used 17-HPC
- No difference for adverse effects on infant or mother

Oates-Whitehead RM et al. *Cochrane Database Syst Rev*. (4):CD003511; 2003

Safety Conclusions – Studies 002 and 001

The safety results demonstrate that weekly administration of 17P was

- Safe and well tolerated by pregnant women
- Safe for the developing fetus and neonate
  - Comparable rates of stillbirths, miscarriages, and neonatal deaths
  - Rates of congenital anomalies similar to general population rate of 2-3%

17P Follow-Up Study

- Assessed long-term impact of in utero exposure to 17P
  - Observational safety study
  - Based on surveys and physical examinations
- Enrolled 278 children born to women enrolled in Study 002
  - 17P Group – 194 infants (68% of births)
  - Placebo Group – 84 infants (59% of births)
- Age range from 30-64 months

Demographics
Follow-Up Study

	17P (N=194)	Placebo (N=84)
Age at enrollment (mo), mean (SD)	47.2 (8.6)	48.0 (8.3)
Gestational age at birth (wk), mean (SD)	37.3 (3.2)	36.2 (3.7)
Race/Ethnicity		
African American	54.1%	56.0%
Caucasian	28.4%	23.8%
Hispanic	14.9%	17.9%
Asian	1.0%	1.2%
Sex		
Male	58.2%	47.6%
Female	41.8%	52.4%

17P Follow-Up Study Components

- Based on surveys and physical examination
  - Ages and Stages Questionnaire
  - Survey Questionnaire
  - Physical Examination

Child Safety Assessments Follow-Up Study

- Ages and Stages Questionnaire (ASQ)
  - Widely used and validated screening tool
  - Identifies children at risk for developmental delay
    - Communication
    - Gross motor movement
    - Fine motor movement
    - Problem-solving
    - Personal-social

ASQ Sample Questions
3 Yr Old – Sample Questions

- Communication – 'Does your child make sentences that are three or four words long?'
- Gross motor – 'Does your child jump with both feet leaving the floor at the same time?'
- Fine motor – 'Does your child thread a shoelace through either a bead or an eyelet of a shoe?'
- Problem-solving – 'If your child wants something he cannot reach, does he find a chair or box to stand on to reach it?'
- Personal-social – 'Can your child put on a coat, jacket or shirt by himself?'
- Overall – 'Does anything about your child worry you?'
- Response options:
  - Yes
  - Sometimes
  - Not yet

ASQ Results

Area of Development	17P (N=193) %	Placebo (N=82) %	P value
Occurrence of score below cutoff on ≥1 area of development	27.5	28.0	0.9206
Communication	11.4	11.0	0.9191
Gross Motor	2.6	3.7	0.6989
Fine Motor	20.7	18.3	0.6445
Problem Solving	10.4	11.0	0.8797
Personal-Social	3.6	1.2	0.4427

- Conclusion: No differences observed between 17P and placebo

Child Safety Assessments Follow-Up Study

- Survey Questionnaire derived from
  - Preschool Activities Inventory
  - 2001 Child Health Supplement of the National Health Interview Survey
  - 1991 National Maternal and Infant Health Survey
  - Early Childhood Longitudinal Survey (Department of Education)
  - Avon Longitudinal Study of Parents and Children

Survey Questionnaire Sample Questions

- Communication/Problem Solving
  - ‘Does (name) pronounce words, communicate with and understand others?’
- Motor Skills/Activity Level
  - ‘Do you have any concerns about (name)’s overall activity level?’
- Overall Health
  - ‘Does (name) have an impairment or health problem that limits his/her ability to walk, run or play?’
- Personal-Social
  - ‘How often in the past month has he/she done the following?:
played house, played ball games, played at fighting, played at being a mother or father, etc.’

Survey Questionnaire

- Survey Questionnaire results revealed no significant differences in
  - Physical growth
  - Motor skills/activity levels
  - Communication and problem solving
  - Overall health
  - Reported diagnoses by health professionals
  - Hearing, vision, and use of special equipment
  - Gender-specific play

Physical Examination

- General examination of body systems
- Documentation of any major abnormalities
- Specific identification of genital anomalies

Physical Examination Findings

Abnormality or Location of Abnormality	17P (N=194) %	Placebo (N=84) %
Skin	12.3	7.5
Inguinal nodes palpable	10.9	8.8
Mouth	9.1	8.6
Neck	5.9	4.9
Heart	5.3	0
Ears	3.2	3.7
Supraclavicular nodes palpable	3.3	2.5
Other syndromes or stigmata	2.7	5.1

Safety – Literature Review

- Epidemiological studies
  - Michaelis, West Germany (1983)
    - n = 462
  - Resseguie, Mayo Clinic (1985)
    - n = 649, 11.5 year mean follow-up
  - Katz, Israel (1985)
    - n = 1,608
- No association between 17-HPC exposure and congenital anomalies

FDA Assessment on Progestogen Class

- Background to the 1999 ruling noted

"The reliable evidence, particularly from controlled studies, shows no increase in congenital anomalies, including genital abnormalities in male or female infants, from exposure during pregnancy to progesterone or hydroxyprogesterone."

From: FDA. 64 FR:17985 – 17988. April 13, 1999

Overall Safety Conclusions – NICHD Studies and Literature Review

17P considered safe based on:

- NICHD studies
  - Safe and well tolerated in pregnant women
  - Safe for the developing fetus and neonate based on
    - Comparable percentage of surviving offspring
    - Rates of congenital anomalies similar to general population rates of 2-3%
  - Safe for the child as evidenced by the lack of untoward effects on developmental milestones or physical health on follow-up safety assessments
- Literature review
- FDA assessment on progestogen class

Benefit / Risk

- Preterm birth is major unmet medical need
  - Leading cause of perinatal and neonatal mortality and morbidity
  - 33% increase in incidence of preterm birth since 1981
  - $26 billion annual cost associated with treating preterm infants
  - Staggering financial, social, and emotional costs associated with both early and late preterm birth

Benefit / Risk

- 17P has been shown to reduce the incidence of preterm birth
  - Significant efficacy demonstrated <37, <35, and <32 weeks of gestation
    - 32% reduction at <37 weeks
    - 31% reduction at <35 weeks
    - 39% reduction at <32 weeks
  - Results applicable irrespective of
    - Race of the mother
    - Number of previous preterm births
    - Gestational age of previous preterm birth

Benefit / Risk

- 17P treatment leads to healthier neonates
  - Lengthens mean gestational age at birth
  - Results in fewer infants under 2500 grams
    - 34% reduction
  - Reduces admissions to NICU
    - 24% reduction
  - Reduces important neonatal morbidities
    - Respiratory therapy
    - Necrotizing enterocolitis
    - Intraventricular hemorrhage

Benefit / Risk

- 17P administration was safe for pregnant women
  - Well tolerated
  - No increase in rates of complications or procedures
- No identified risk for fetus and neonate
  - Comparable rates of neonatal deaths, miscarriages, and stillbirths
  - No evidence of teratogenicity
    - Congenital anomalies at similar rates
    - Confirmed by 1999 FDA assessment
    - Second trimester administration
- No identified risk for the child
  - No association with developmental delays or other issues in children between 30 and 64 months of age

Proposed Indication

"Gestiva is indicated for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth."

All Back Up Slides Presented During Q&A

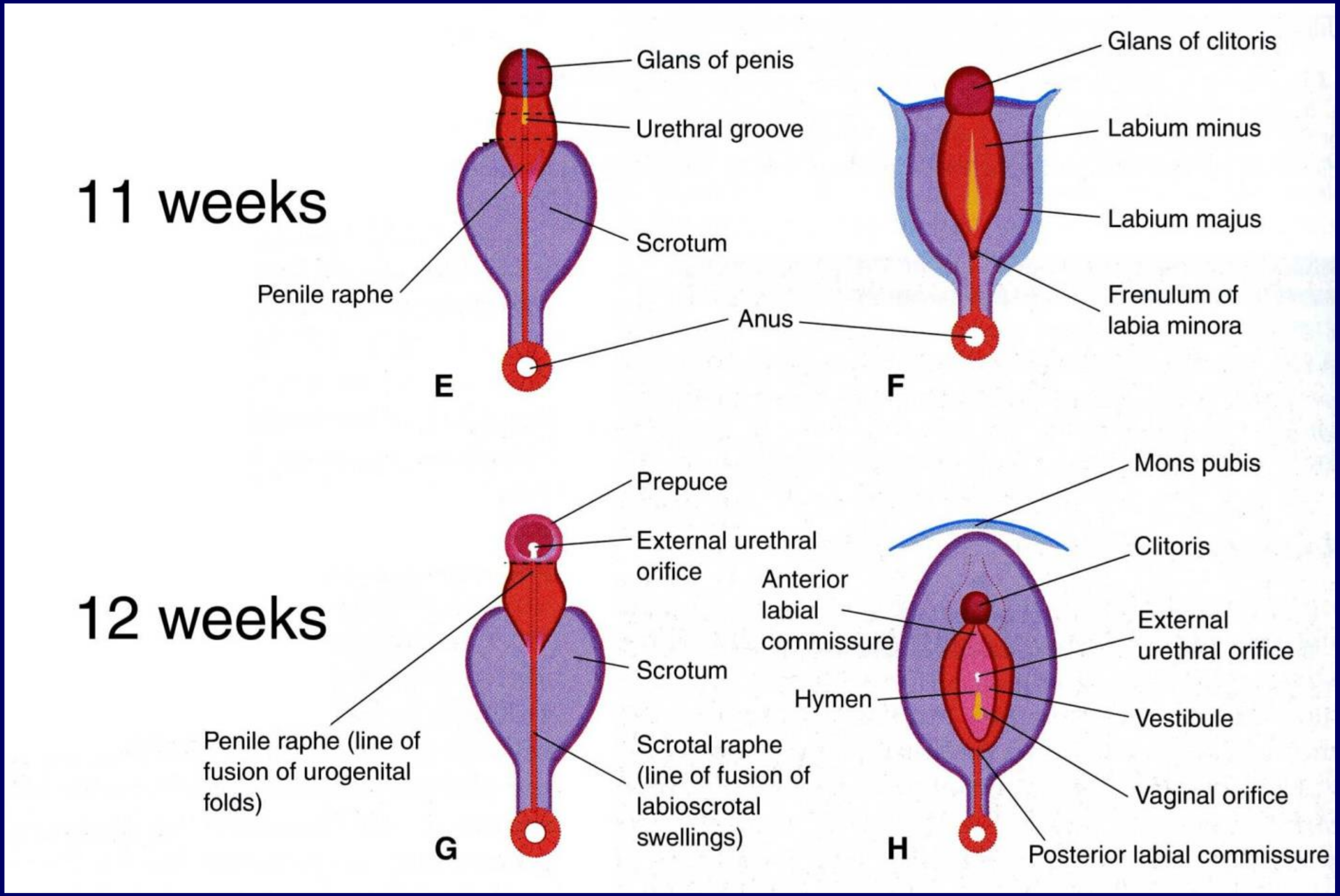
Not in any specific order

Hochberg* Adjustment for Multiple Comparisons

Outcome	P value	Rank	Statistically significant	Adjusted P value
PTD <32	0.027	1	Yes	0.027
PTD <35	0.026	2	Yes	0.027
PTD <37	0.0003	3	Yes	0.0009

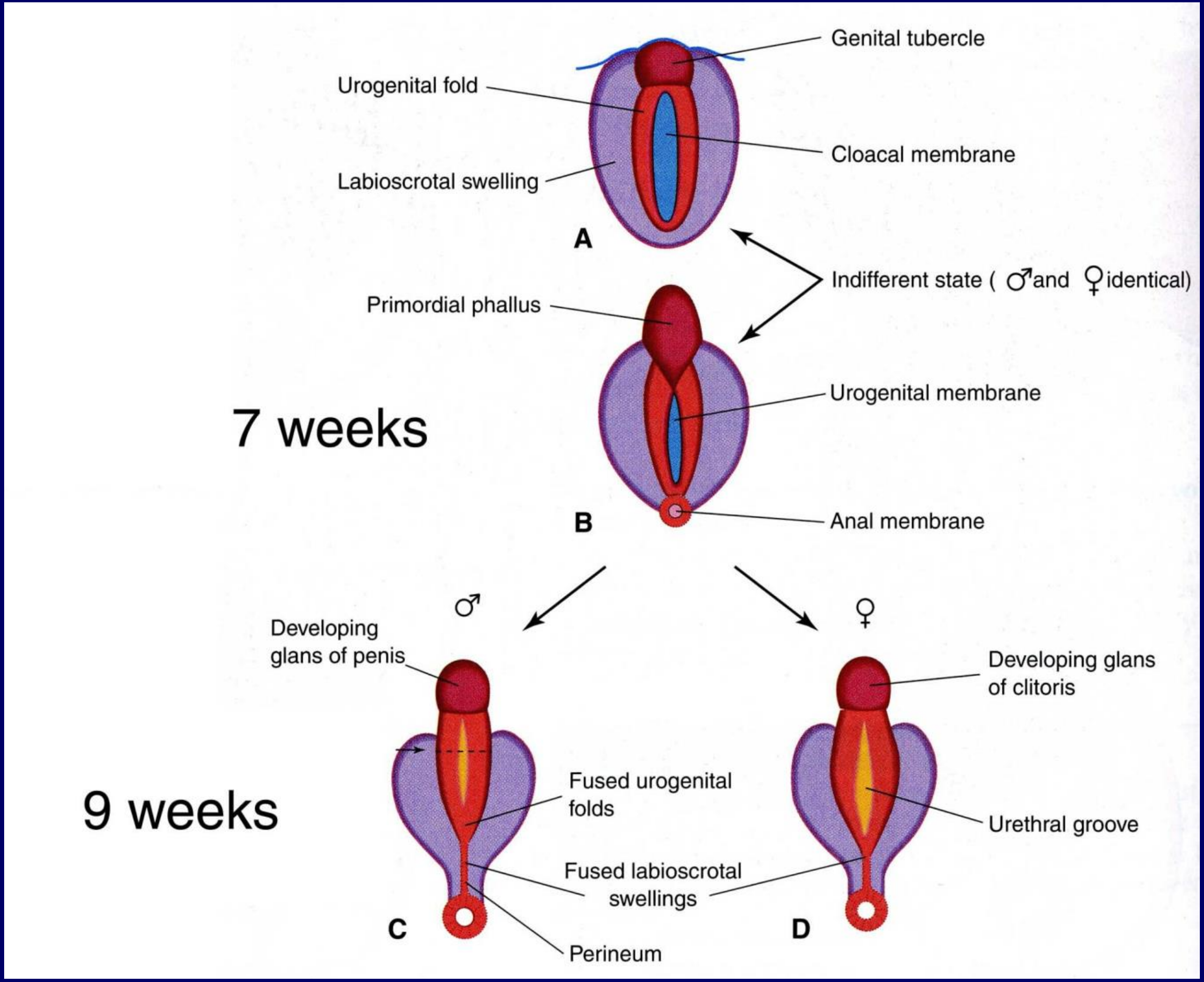
*Hochberg Y., Biometrica (1988)

Development of the External Genitalia (2 of 2)



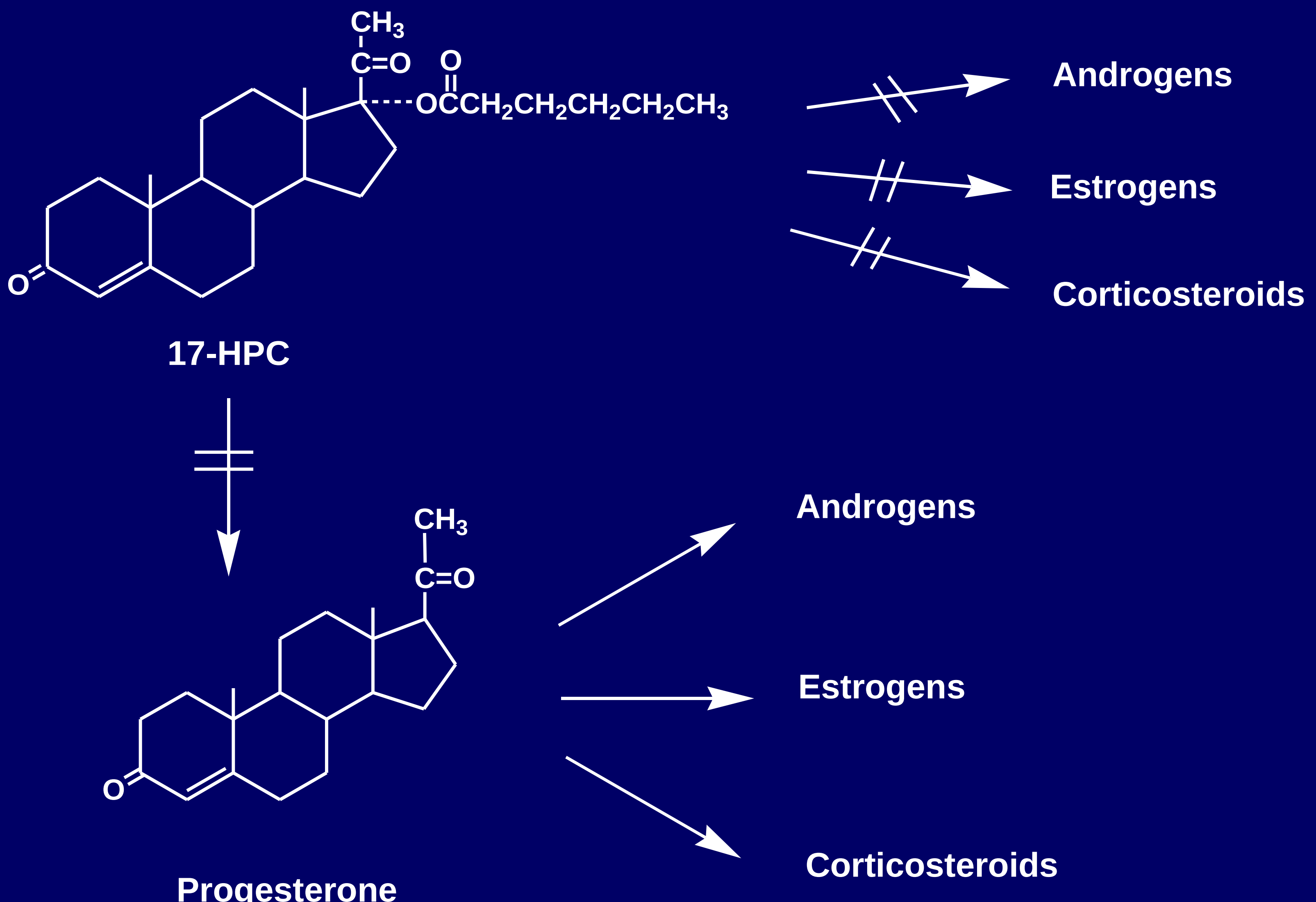
The Developing Human: Clinically Oriented Embryology, Moore, Persaud 2003

Development of the External Genitalia (1 of 2)



The Developing Human: Clinically Oriented Embryology, Moore, Persaud 2003

Unlike Progesterone, 17-HPC Is Not Converted to Androgens, Estrogens or Corticosteroids



Bacterial Vaginosis During Pregnancy vs Outcome

	17P N=64	Placebo N=24
Miscarriage	1 (1.6%)	0 (0%)
Stillborn	2 (3.1%)	1 (4.2%)
pPROM <37	6 (9.4%)	7 (29.2%)
Neonatal Sepsis[a]	2 (3.3%)	0 (0%)
Cerebral palsy[b]	0/46 (0)	0/16 (0)

[a] based on livebirths

[b] Based on 62 children enrolled in the Follow-up Study

Preterm Birth <37 in Patients with Bacterial Vaginosis

	17P n/N (%)	Placebo n/N (%)
Preterm birth <37 weeks		
No bacterial vaginosis	88/246 (35.8)	67/129 (51.9)
Bacterial vaginosis	27/64 (42.2)	17/24 (70.8)

Reasons for Oral Metronidazole Use

	17P (N=32) n %	Placebo (N=8) n %
Bacterial vaginosis	25 (78.1)	6 (75.0)
Trichomonas	10 (31.3)	2 (25.0)
Other vaginal/cervical infection	0 (0)	1 (12.5)

Note: 2 patients in the 17P group and 1 patient in the placebo group had both bacterial vaginosis and trichomonas

Use of Metronidazole

	17P (N=310) n %	Placebo (N=153) n %
Oral	32 (10.3)	8 (5.2)
Vaginal	1 (0.3)	1 (0.7)
Any use	33 (10.7)	9 (5.9)

Incidence of BV

	17P (N=310) n %	Placebo (N=153) n %
Prior to randomization	41 (13.2)	20 (13.1)
Randomization through delivery	27 (8.7)	8 (5.2)
At any time during pregnancy	64 (20.7)	24 (15.7)

Note: 4 patients in each group has BV prior to randomization and from randomization through delivery

Chorioamnionitis at Delivery

	17P N=399 n (%)	Placebo N=205 n (%)	P value
Confirmed clinical chorioamnionitis	13 (3.3)	5 (2.4)	0.8011

Infections – BV and Trichomonas

- Collected on CRF at 2 time points:
  - At baseline, patient report and record review
  - During study, the CRF for "Record of Antibiotic Use" included the reason for administration of antibiotic
- Clinical chorioamnionitis
  - Collected on the labor and delivery summary CRF
- Diagnosed by treating physician based on methods and criteria based at the local site

Gestational Diabetes – Summary

- Gestational diabetes following randomization was not statistically different (P=0.179)
  - 17P = 6.3%
  - Placebo = 3.4%
- Gestational diabetes rate reported by the American Diabetes Association ~ 7%
- Progestins may disturb glucose homeostasis
  - Rates of gestational diabetes in this study were similar to ADA

Gestational Diabetes – Integrated Studies

Rate of Gestational Diabetes

	17P n/N* (%)	Placebo n/N* (%)
No history of diabetes	25/382 (6.5)	7/200 (3.5)

***Number of women without a history of diabetes at baseline**

Diabetes – Study 001

Rate of Gestational Diabetes

	17P n/N* (%)	Placebo n/N* (%)
No history of diabetes	8/89 (9.0)	0/52 (0)

***Number of women without a history of diabetes at baseline**

Diabetes Study 002

Rate of Gestational Diabetes

	17P n/N* (%)	Placebo n/N* (%)
No history of diabetes	17/293 (5.8)	7/148 (4.7)

*Number of women without a history of diabetes at baseline

Prevention of Preterm Birth Integrated Results

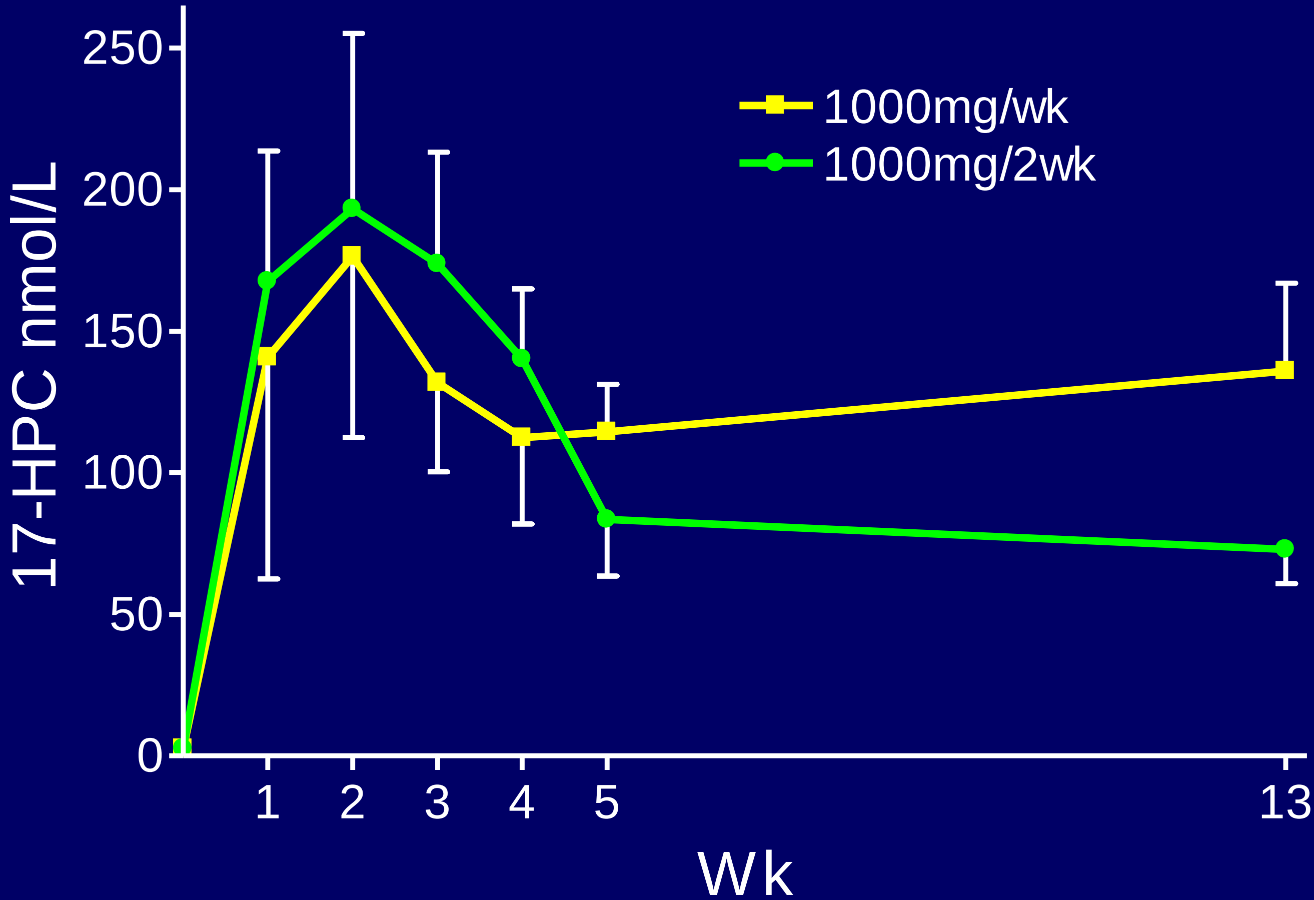
Pregnancy Outcome	17P (N=404) %	Placebo (N=209) %	P value
Birth <37^{0} weeks	38.1	49.8	0.0052 0.0155[a]
Birth <35^{0} weeks	22.0	30.6	0.0211
Birth <32^{0} weeks	12.4	18.7	0.0367

[a]P value from a logistic regression adjusting for the number of previous preterm deliveries

Composition of Injectable Formulations of 17-HPC

Component	Adeza Product	Study 17P-CT-002	Delalutin, 250 mg/mL
17-HPC	250 mg/mL	250 mg/mL	250 mg/mL
Benzyl benzoate	46%	46%	46%
Benzyl alcohol	2%	2%	2%
Castor oil	q.s. to volume	q.s. to volume	q.s. to volume

Multiple-Dose Pharmacokinetic Profile



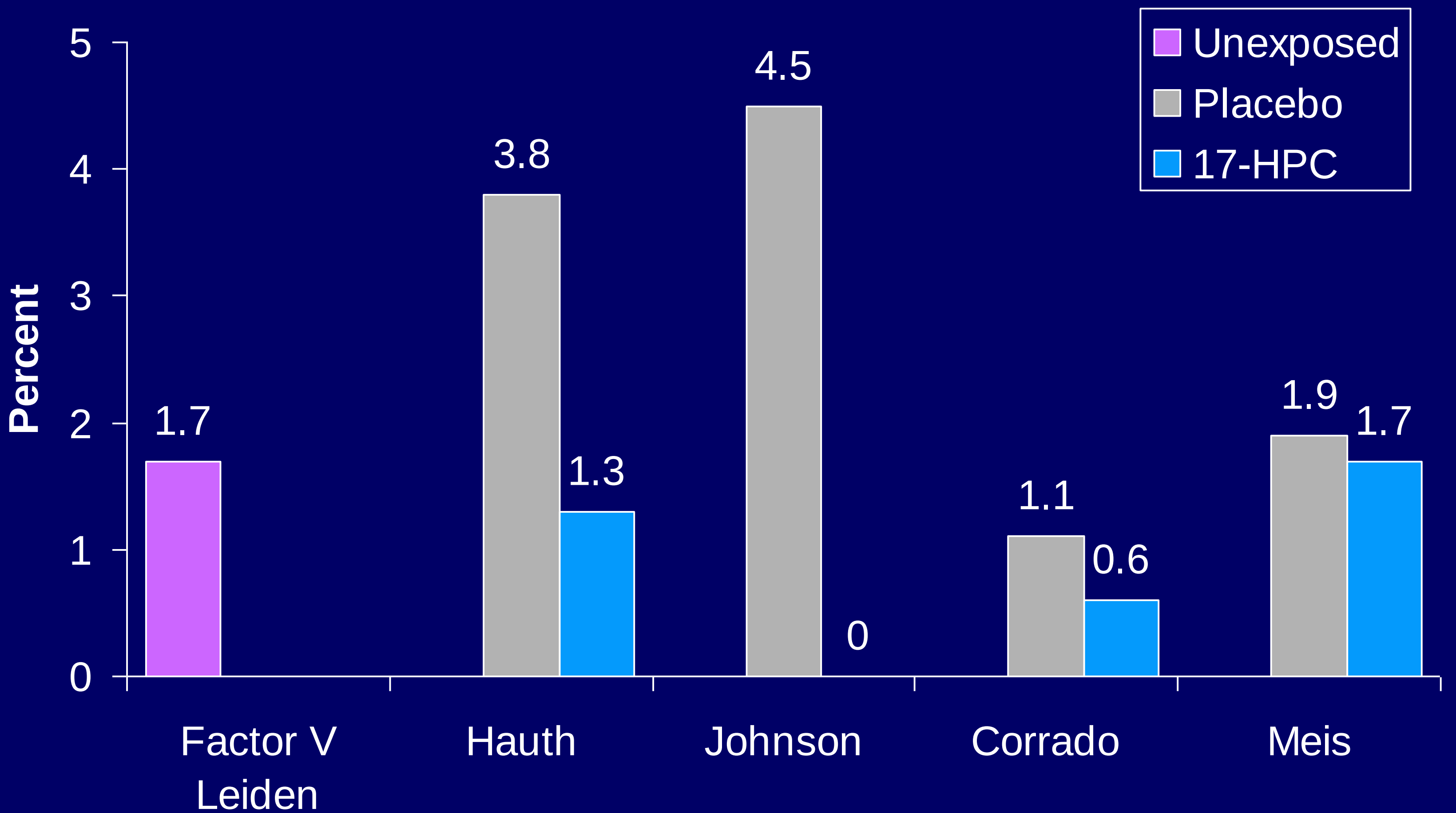
Serum concentrations of HPC in patients who after a loading dose of 1000 mg daily for 5 days were treated with either 1000 mg HPC every week or with 1000 mg every 2 weeks

From Onsrud, 1985

Tocolytic Use – Study 002

	17P (N=310) %	Placebo (N=153) %
Tocolytic use	12.9	11.8

Stillbirth Rates



Stillbirths – Study 001/002

	17P (N=404) n (%)	Placebo (N=209) n (%)	P value
Stillbirths	7 (1.7)	4 (1.9)	0.8769
Antepartum	6	2	
Intrapartum	1	2	

Cardiac Findings – Summary

- Low rate of cardiac anomalies observed at birth in both 17P and placebo groups (0.5% vs 0.5%)
- Patent ductus arteriosus observed in 2.4% of 17P cases and 5.4% of placebo cases
- At Follow-Up Study examination
  - Infants in the 17P
    - Murmurs – 4.6%
    - Irregular rhythm – 0.5%
  - No functional disabilities noted by history or physical exam

Corticosteroid Use At Baseline – Study 002

	17P (N=310) n (%)	Placebo (N=153) n (%)	P value
Any corticosteroid use (before randomization)	5 (1.6%)	8 (5.2%)	0.0324
Inhaled corticosteroid use	1 (0.3)	7 (4.6)	

Corticosteroids Use

- Time points for data collection
  - At baseline
  - Weekly during prenatal visits
  - Preterm labor admissions
- Corticosteroid use collected only prior to the birth hospitalization
- No specific guidelines were given to site investigators regarding use

Kester – Effects of Prenatal 17-HPC on Adolescent Males (1984)

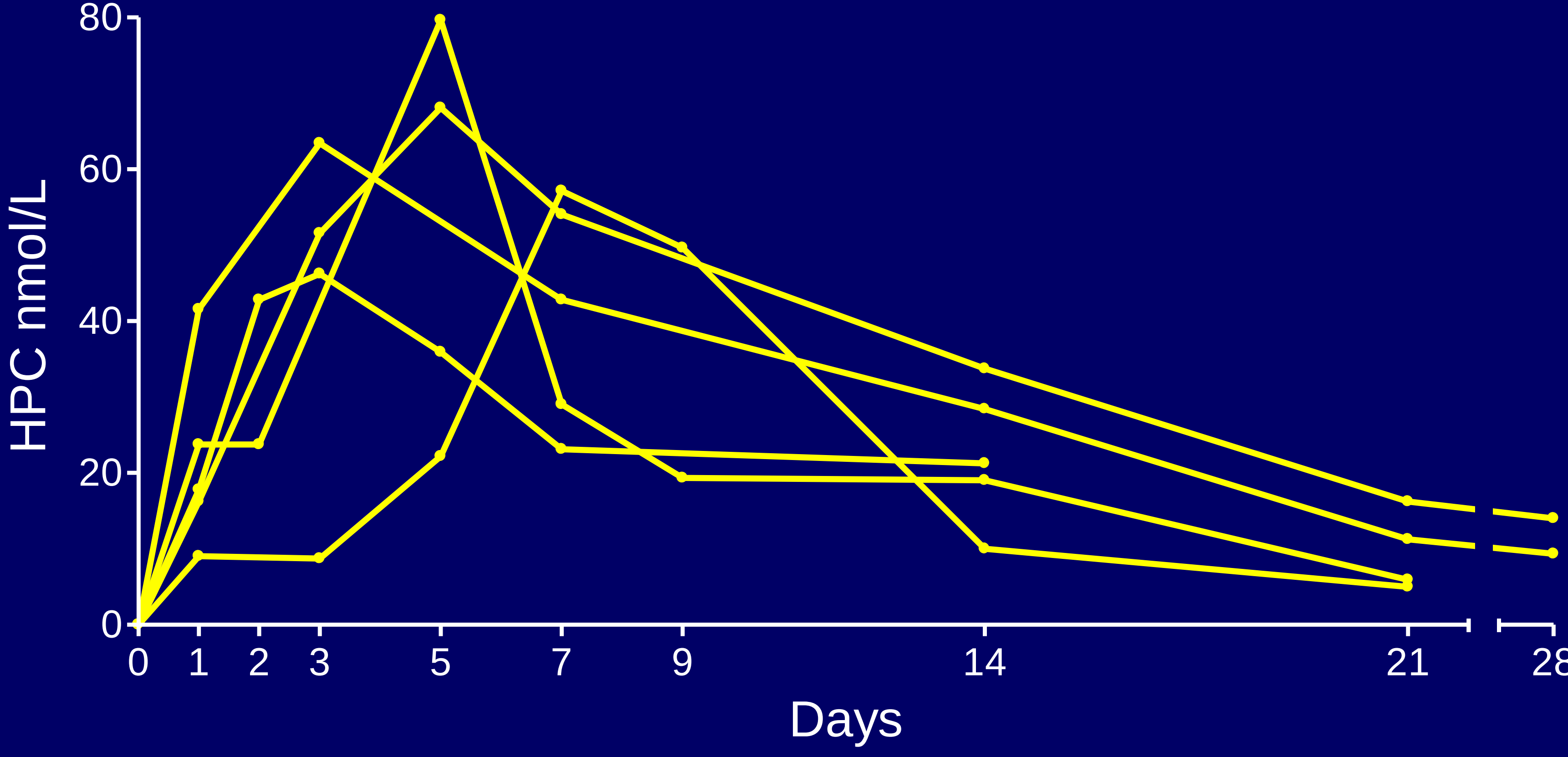
- Examined 25 adolescent males exposed to 17-HPC prenatally
- Assessed impact on recreational interests and psychosexual development in boyhood
- No difference in psychological testing noted between adolescents exposed to 17-HPC and unexposed controls
- No impact on results based on total dosage of 17-HPC, duration of exposure, or period of gestation

Kester PA. *Arch Sex Behav*. 1984;13(5):441-55

Table 4-10. Neonatal Morbidity and Mortality for Live Births (1 of 2)

Morbidity	17P N=295 n (%)	Placebo N=151 n (%)	P value
Transient tachypnea	11 (3.7)	11 (7.3)	0.0990
Respiratory distress syndrome (RDS)	29 (9.9)	23 (15.3)	0.0900
Bronchopulmonary dysplasia (BPD)	4 (1.4)	5 (3.3)	0.1730
Persistent pulmonary hypertension	2 (0.7)	1 (0.7)	1.0000
Ventilator support	26 (8.9)	22 (14.8)	0.0616
Supplemental oxygen	45 (15.4)	36 (24.2)	0.0248
Patent ductus arteriosus	7 (2.4)	8 (5.4)	0.1004
Seizures	3 (1.0)	0	0.5541
Any intraventricular hemorrhage (IVH)	4 (1.4)	8 (5.3)	0.0258
Grade 3 or 4 IVH	2 (0.7)	0	0.5511
Other intracranial hemorrhage	1 (0.3)	2 (1.3)	0.2628

Plasma Concentrations of 17-HPC over Time



Individual serum concentrations of HPC in 5 patients after intramuscular administration of a single dose of 1000 mg (arrow)

From Onsrud, 1985

Single Dose Pharmacokinetics of 17-HPC (1000 mg)

Parameter	Mean ± SD	n
C_{max} (ng/mL)	27.8 ± 5.3	5
T_{max} (days)	4.6 ± 1.7	5
$t_{1/2}$ (days)	7.8 ± 3.0	4
AUC_{0-7} (ng•day/mL)	118 ± 36	5
$AUC_{0-\infty}$ (ng•day/mL)	355 ± 136	4

From Onsrud, 1985

17-HPC Teratogenicity Data in Mice

- No teratogenicity or maternal toxicity observed
  - C57Bl/6J Mice exposed to 0.5, 5, and 50 mg/kg/d (0.1-10 X clinical dose) via subdermal pellets on gestation d 7-19 (n=8)[1]
- No teratogenicity observed
  - ARS Swiss Webster Mice exposed to 42, 416, and 833 mg/kg (~10-200 X clinical dose) on d 6-15; n=11-15[2]; SC

[1]Carbone 1993

[2]Seegmiller, 1983

17-HPC Teratogenicity Data in Rhesus and Cynomolgus Monkeys

- No drug related anomalies found in fetuses from either species of monkey
- Treatment initiated much earlier in gestation (first third) than what is indicated in humans (16-20 weeks)[1]
- No teratogenicity in Rhesus monkeys[2]

[1]Hendrickx *et al.* 1987

[2]Courtney and Valerio, 1968

17-HPC Mechanism of Action

- In vitro receptor binding studies show 17-HPC:
  - Better than either progesterone or 17-α-hydroxyprogesterone at inducing progesterone-responsive gene transcription[1]
  - Comparable to progesterone in binding affinity for progesterone receptor[2]
  - Displays greater selectivity for receptor isoform B (transcriptional activator) compared to isoform A (transcriptional repressor)

[1]Zeleznik et al. (abstract), 2006

[2]Attardi et al. (abstract), 2006

Proposed Genomic and Nongenomic Mechanisms of Progesterone

- Modulates progesterone receptor activity
- Reduces estrogen receptor activity
- Blocks oxytocin induced uterine contractility
- Enhances tocolytic response
- Promotes local antiinflammatory effects
- Inhibits myometrial gap junctions

Study 002 and HUAM Study: Sample Size Considerations

	Study 002	HUAM Study
1 previous PTD	314 (67.8%)	194 (76.4%)
>1 previous PTD	149 (32.2%)	57 (22.4%)
GA of worst previous PTB, mean (SD)	29.7 (4.9)	30.2 (4.9)
GA qualifying delivery (wk), mean (SD)	30.8 (4.5)	ND
Year completed	2002	1996
MFMU Sites	19	11
Design	Interventional	Observational

17-HPC Mechanism of Action

- Not known
  - Multiple pathways possible
- May be distinct from progesterone, though pharmacologically similar
- Progesterone inhibits myometrial contractility through
  - Non-genomic mechanisms
  - Genomic mechanisms

Study 002: Preterm Birth <37^0 by Site

Center	17P n/N (%)	Placebo n/N (%)
2 – Pittsburgh	5/24 (20.8)	11/12 (91.7)
4 – Tennessee	13/30 (43.3)	9/15 (60.0)
8 – Alabama	23/86 (26.7)	18/40 (45.0)
9 – Detroit	5/16 (31.3)	5/8 (62.5)
11 – Cincinnati	3/9 (33.3)	2/4 (50.0)
13 – Wake Forest	7/13 (53.9)	7/9 (77.8)
15 – Ohio State	11/20 (55.0)	4/8 (50.0)
18 – Dallas	12/28 (42.9)	8/11 (72.7)
20 – Utah	11/29 (37.9)	7/14 (50.0)
21 – Philadelphia	10/17 (58.8)	3/7 (42.9)
22 – Providence	1/3 (33.3)	1/2 (50.0)
23 – New York	2/6 (33.3)	1/5 (20.0)
25 – Cleveland	2/4 (50.0)	1/2 (50.0)
26 – Houston and 19 – San Antonio	3/10 (30.0)	4/7 (57.1)
27 – Chapel Hill and 17 – Miami	3/9 (33.3)	1/6 (16.7)
28 – Chicago and 14 – Chicago	4/6 (66.7)	2/3 (66.7)

Study 002: Secondary Pregnancy Outcomes

Pregnancy Outcome	17P N=310 n (%)	Placebo N=153 n (%)	P value
Delivery $<35^0$	67 (21.6)	47 (30.7)	0.0324
Delivery $<32^0$	39 (12.6)	30 (19.6)	0.0458
Spontaneous delivery $<37^0$	94 (30.3)	69 (45.1)	0.0017
SPTD $<37^0$ due to pPROM	26 (8.4)	16 (10.5)	0.4656
SPTD $<37^0$ due to PTL	67 (21.6)	53 (34.6)	0.0026
SPTD $<37^0$ due to PTL or pPROM	89 (28.7)	69 (45.1)	0.0005
Indicated delivery $<37^0$	25 (8.1)	15 (9.8)	0.5309

Genital/Reproductive Abnormalities

- Micropenis (17P)
  - Born at 38[1] weeks gestation
  - Aged 4.5 years at Follow-Up Study exam
  - Genital exam at birth – normal
- Micropenis (17P)
  - Born at 33[5] weeks gestation
  - Aged 3.5 years at Follow-Up Study exam
  - Infant with Down syndrome
  - Common associated finding

Genital/Reproductive Abnormalities

- Early puberty (17P)
  - Born at 39^{6} weeks gestation
  - Aged 3.6 years at Follow-Up Study exam
  - Breast buds observed at Follow-Up Study exam
  - Obese female child
    - 66 lbs (100^{th} percentile BMI)
- Sparse pubic hair (Placebo)
  - Born at 25^{1} weeks gestation
  - Aged 3.5 years at Follow-Up Study exam
  - “Four or five long pubic hairs” at Follow-Up Study exam
  - No other abnormalities noted

Reproductive & Genitourinary Anomalies

- Infant 020-023 (17P)
  - Born at 38^1 weeks gestation
  - Aged 5 years at Follow-Up Study exam
  - Labia “fused together” at Follow-Up Study exam
  - Genital exam at birth – normal
  - Multiple infant exams between 1 week and 3 years with normal exams
  - Urogenital sinus fuses at 12 weeks of gestation
  - Represents benign labial adhesions rather than labioscrotal fusion

Reproductive & Genitourinary Anomalies

- Infant 018-032
  - Born at 38[1] weeks gestation
  - Aged 4 years at Follow-Up Study exam
  - Genital exam at birth – normal
  - Infant was reexamined 4 months later
    - Same examiner
    - Reported to be normal
    - “Clitoris <5mm in transverse diameter”

Physical Examination – Genital Abnormalities

- Genital/reproductive abnormalities
  - 17P group – 1.5%
  - Placebo group – 1.2%
- Abnormalities identified were
  - Breast buds
    - 17P female, 100% BMI
  - Sparse pubic hair
    - Placebo female, no other abnormalities
  - Micropenis
    - 17P male, genital exam at birth, normal
    - 17P male, Down syndrome

17α-Alpha Hydroxyprogesterone Caproate for Prevention of Preterm Birth

Overview of FDA Background Document

Introduction

Adeza Biomedical has submitted New Drug Application (NDA) 21-945 for 17α-hydroxyprogesterone caproate (17OHP-C) injection for the proposed indication:

> "Prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth"

Preterm birth is defined as a birth prior to 37 weeks gestational age.

The proposed dosing regimen is a weekly intramuscular injection of 250 mg of 17OHP-C in 1 mL castor oil with 46% benzyl benzoate and 2% benzyl alcohol, beginning at 16 weeks 0 days (16^0) to 20 weeks 6 days (20^6) weeks gestation and used through 36^6 weeks gestation or birth.

Currently there is no drug product approved in the United States for prevention of preterm birth; however, 17OHP-C is being compounded by pharmacists and is being used widely for prevention of preterm birth in women at high risk. The medical need for an approved drug product for prevention of preterm birth is particularly acute because there also are no approved drug products currently marketed in the United States for the treatment of preterm labor. Although several drug products with tocolytic properties (i.e., stopping uterine contractions) are used off-label for treatment of preterm labor, randomized controlled trials have failed to demonstrate that these drugs improve perinatal outcomes.

In 2003, the findings from a multicenter, randomized, placebo-controlled, double-blind clinical trial of 17OHP-C in women at high risk for preterm birth were published. This trial was sponsored by the National Institute for Child Health and Human Development (NICHD) and was conducted by the Maternal-Fetal Medicine Units (MFMU) Network, which at that time consisted of approximately 19 university-based clinical centers in the U.S. This study (referred to as Study 17P-CT-002 in this document) showed a 34% reduction in preterm births prior to 37^0 weeks in women with a prior preterm birth (a population at high risk for a recurrent preterm birth).

NDA 21-945 is based largely on the clinical data from Study 17P-CT-002 and a follow-up study to support the safety and effectiveness of 17OHP-C for the prevention of preterm birth. The database submitted by the Applicant to support safety and effectiveness includes data from the following three studies:

- Initial Formulation Study (Study 17P-IF-001). This study began in February 1998, and 150 of the proposed 500 subjects were randomized. Treatment was terminated in March 1999 because the active study drug (17OHP-C) was recalled by its manufacturer, under the direction of the FDA, due to violations of manufacturing practices. Eighty-six subjects completed the treatment regimen before the study was stopped: 57 (61%) of the 17OHP-C subjects and 29 (52%) of the placebo subjects.
- Primary Clinical Trial for Safety and Efficacy (Study 17P-CT-002). This study, which was started in October 1999, randomized 463 subjects who had at least one documented prior spontaneous preterm birth of a singleton, non-anomalous fetus. Of these, 418 subjects (90.3%) completed dosing through 36^6 weeks or birth: 279 (90.0%) in the

17OHP-C group and 139 (90.8%) in the placebo group. This study was terminated prior to enrolling the planned 500 subjects because the pre-specified stopping criterion for efficacy was attained at an interim analysis.

- Follow-up Study of the Children from the 17P-CT-002 Trial (Study 17P-FU). This was a follow-up to Study 17P-CT-002. The follow-up study collected data with a validated child development instrument, the Ages and Stages Questionnaire (ASQ), a Survey Questionnaire concerning the health and development of the child, and a physical examination. The children were at least 2 years of age at the time of the follow-up assessments. The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received weekly intramuscular injections of 17OHP-C compared with placebo during the pregnancy in Study 17P-CT-002.

Points for the Advisory Committee to Consider

The major issues that the FDA would like the Advisory Committee for Reproductive Health Drugs to consider include:

Adequacy of Clinical Data to Support the Effectiveness of 17OHP-C

In general, the FDA requires an Applicant for a new drug product to submit two adequate and well-controlled clinical trials as substantial evidence of effectiveness. One of the circumstances in which a single clinical trial may be used as substantial evidence of effectiveness is a trial that has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome, and confirmation of the result in a second trial would be logistically impossible or ethically unacceptable.

The Applicant is seeking approval for 17OHP-C based primarily on (1) the findings from a single clinical trial and (2) a surrogate endpoint for neonatal/infant morbidity and mortality (i.e., reduction in the incidence of preterm births at less than 37 weeks gestation).

Although preterm birth is defined as a birth prior to 37 weeks gestation, the clinical significance of preterm birth is more pronounced prior to 32 weeks gestation. In the U.S., infants born after 32 weeks have very low mortality rates, and relatively low long-term morbidity. However, since a larger number of preterm births occur after 32 weeks gestation, the public health importance of preventing even these later gestational age preterm births may be noteworthy.

Study 17P-CT-002 demonstrated a statistically significant reduction in the primary endpoint of preterm births prior to 37^0 weeks gestation. However, the reduction in preterm births prior to 35^0 weeks and prior to 32^0 weeks gestation, better surrogates for significant neonatal morbidity or mortality, was not statistically persuasive. In addition, the primary clinical trial did not demonstrate a significant reduction in another secondary endpoint, a composite assessment of infant mortality and morbidity.

The FDA asks the Advisory Committee whether the primary endpoint, prevention of preterm birth prior to 37 weeks, is an adequate surrogate for infant mortality and morbidity. If so, does the available information provide sufficient evidence of effectiveness such that an additional confirmatory clinical trial is not warranted?

Generalizability of Efficacy Results

The results of Study 17P-CT-002 demonstrate a reduction in the rate of preterm birth prior to 37 weeks from the **55%** incidence seen in the placebo group to the 36% incidence observed in the 17OHP-C group. However, a previous large clinical trial sponsored by the NICHD (on which the sample size calculations for the current clinical trial were based) found the incidence of preterm birth prior to 37 weeks in an untreated, but similarly high risk population to be **37%**. The incidence of preterm births in the placebo arm of Study 17P-IF-001 (also conducted by the MFMU Network) was **36%**.

The FDA asks the Advisory Committee whether the difference in the incidence of preterm birth prior to 37 weeks observed in the placebo group of this trial as compared to another MFMU Network trial evaluating a similar untreated high risk population suggests the need to replicate the findings of Study 17P-CT-002 in a confirmatory study. Does the Committee believe that the efficacy findings of Study 17P-CT-002 would be applicable to women in the general U.S. population who have a history of one or more preterm births?

Potential Safety Signal

There was a trend toward an increase in second trimester miscarriage rate (pregnancy loss prior to 20 weeks' gestation) and a suggestion of an increase in stillbirth rate (death of the fetus prior to or during delivery) in the 17OHP-C group.

The FDA asks the Advisory Committee whether further studies are needed to evaluate the potential association of 17OHP-C with increased risk of second trimester miscarriage and stillbirth.

Gestiva

(17α-hydroxyprogesterone caproate)

NDA 21-945

Proposed Indication

"**GESTIVA** is indicated for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth"

Dosing Regimen

GESTIVA is to be administered intramuscularly at a dose of 250 mg (1 mL) once each week beginning at 16 weeks 0 days (16^0 weeks) to 20 weeks 6 days (20^6 weeks) of gestation to week 37 of gestation or until birth.

Drug Product

GESTIVA will be supplied as 5 mL of a sterile solution in a multiple dose glass vial. Each mL will contain 17α-hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), castor oil (28.6% v/v), benzyl benzoate (46% v/v), and benzyl alcohol (2% v/v) as preservative.

Review by the Division of Reproductive and Urologic Products
Food and Drug Administration
August 2, 2006

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1 BACKGROUND

1.1 Public Health Significance of Prematurity

Preterm birth (PTB), birth prior to 37 weeks of gestational age, is the leading cause of neonatal mortality (infant death <28 days of life) and is a major cause of early childhood mortality and morbidity in the United States.[1] As many as half of all pediatric neurodevelopmental problems can be attributed to preterm birth.[2] The U.S preterm birth rate increased by 29% over the previous 2 decades to a high of 12.1% in 2002.[3] Most of this increase occurred in preterm births of 32-36 weeks gestational age and is thought to be due to the increasing frequency of pregnancy in women older than 35 years and the use of infertility treatments.[4] The rate for very early preterm births (< 32 completed weeks gestation) has remained stable at about 2% of all births; however, most perinatal/neonatal and infant mortality/morbidity occurs in these infants.[3] Preterm births most often result from spontaneous preterm labor and preterm premature rupture of membranes (pPROM).[5,6,7] However, 20-30% of preterm births are considered "indicated" to avoid or minimize maternal/fetal complications.[8]

Rates of PTB in the United States differ profoundly among ethnic groups; the rate of PTB in non-Hispanic black births is twice as high as that of non-Hispanic white births. These disparities remain even after adjusting for confounders such as education and occupation, suggesting a combination of genetic, environmental, and social factors as the etiology.[9,10,11,12,13,14]

Accurate prediction and prevention of PTB remain elusive.[2,6-8,15-19] Most biomarkers to assess the risk of PTB have poor positive predictive value to guide clinical decisions.[2,8,15-20] Examples of risk factors include history of previous preterm birth; multifetal gestation; and cervical, uterine, and placental structural or physiologic abnormalities.

Prophylactic methods for prevention of preterm birth, including drugs, bed rest, or other interventions, have been shown in general to lack effectiveness. Tocolytic drugs may be given to reduce the frequency of uterine contractions. However, they have not been efficacious in preventing preterm birth nor have they resulted in improved newborn outcomes.

Preterm birth has been described as a "common, complex disorder, stemming from heterogeneous composites of multiple gene-environment interactions."[21] Evidence supporting this includes findings of familial aggregation, non-Mendelian heritability, high rates of recurrence, and the existence of ethnic/racial disparities.

1.2 Description and Causes of Prematurity

The "syndrome" of PTB is now understood as the clinical endpoint for a number of potential causes. Four major pathophysiologic pathways have been hypothesized:

(1) inflammation/infection with its associated maternal and fetal cytokine response

(2) maternal/fetal stress with generation of placental and fetal membrane-derived corticotropin-releasing hormone, which enhances placental estrogen and fetal adrenal cortisol production

(3) abruption or decidual hemorrhage with thrombin-induced protease expression and disturbances in uterine tone

(4) mechanical stretch due to multifetal pregnancy or polyhydramnios-induced abnormal uterine and cervical distension

Infection/inflammation is the only pathologic process for which a firm causal link with prematurity has been established and for which a defined molecular pathophysiology is known.[22] It has been estimated that 40% of all preterm births occur to mothers with intrauterine infection, which is usually subclinical. The lower the gestational age at delivery, the greater the frequency of intrauterine infection.[23] The most common pathway is ascending organisms from the lower genital tract, more commonly from an alteration in the normal vaginal flora.[24] The organisms enter the amniotic cavity and then, in some cases, will gain access to the fetus which may result in fetal sepsis or the Fetal Inflammatory Response Syndrome (FIRS).[25] The clinician managing preterm labor must balance the possibility of sub-clinical infection, against the sequelae of prematurity, both having the potential for causing death.

1.3 Clinical History and Background Data on 17α-hydroxyprogesterone Caproate

17α-hydroxyprogesterone caproate (17OHP-C) was approved by the Food and Drug Administration (FDA) in 1956 for use in pregnant women (NDA 10-347; Delalutin®). The approved indications included the treatment of habitual and recurrent abortion, threatened abortion, and post-partum “after pains.” This approval was based largely on safety consideration in that it occurred prior to the FDA Drug Amendment of 1962, which required that drugs must have substantial evidence of efficacy in addition to evidence of safety in adequate and well-controlled trials. In 2000, the FDA withdrew approval for Delalutin. This action was taken at the request of the holder of the NDA because the holder was no longer marketing the drug. The action was not taken because of safety concerns.

The published literature includes several studies evaluating the efficacy of 17OHP-C in preventing preterm birth (see Table 1). Not included in Table 1 is the publication by Meis PJ, Klebanoff M, et al. that was based on the finding from Study 17P-CT-002 (the primary study supporting the efficacy and safety of 17OHP-C in this NDA.)

Table 1 Studies of the Efficacy and Safety of 17OHP-C in Preventing Preterm Birth

Investigator	Drug:Dose	Entry Criteria	Design	Subjects	Start	Stop	Outcome % PTB[A]	No. of SAB[B]
LeVine 1964[1]	17P: 500 mg weekly vs. Placebo	3 SABs[B]	RCT, DB[C] Placebo 1:1	17P: 15 Placebo: 15	< 16 wks	36 wks	17P: 7/15 (46%) Placebo: 10/15 (66%)	17P: 3/15 Placebo: 7/15
Papiernik-Berkhauer 1970[2]	17P: 250 mg q 3 days vs. Placebo	High preterm risk score	RCT Placebo 1:1	17P: 50 Placebo: 49	28 – 30 wks	8 doses	17P: (4.1%) Placebo: (18.8%)	
Johnson et al 1975[3]	17P: 250 mg weekly vs. Placebo	2 SABs[B] or 1PTB[A] + 1 SAB[B] or hx 2 PTBs	RCT, DB[C] Placebo 1:1	17P: 18 (4 cerclage) Placebo: 22 (3 cerclage)	Booking < 24 wks	37 wks	17P: 0/18 (0%) Placebo: 9/22 (41%)	17P: 3/23 Placebo: 0/27
Yemini 1985[4]	17P: 250 mg weekly + cerclage vs. Placebo	Hx of 2 SABs[B] or 2 PTBs[A]	RCT, DB[C] Placebo 1:1	17P: 39 (39 cerclage) Placebo: 40 (40 cerclage)	Booking (12.2 wks av.)	37 wks	17P: 5/31 (16.1%) Placebo: 14/37 (37.8%)	17P: 8/39 Placebo: 3/40
Suvonnakote 1986[5]	17P: 250 mg weekly vs. no treatment	Hx of 1 PTB[A] or 2 late SABs[B]	Non-randomized	17P: 36 No Rx: 39	16 – 20 wks	37 wks	17P: 5/35 (14%) No Rx: 19/39 (49%)	
Hauth 983[6]	17P: 1000 mg weekly vs. Placebo	Active duty military	RCT, DB[C]	17P: 80 Placebo: 88	16 – 20 wks	36 wks	17P: (6.3%) Placebo: (5.7%)	

[A] PTB=Preterm Births

[B] SABs=Spontaneous Abortions

[C] RCT, DB=Randomized Controlled Trial, Double Blind

1 LeVine L. Habitual abortion. A controlled clinical study of progestational therapy. West J Surg Obstet Gynecol. 1964;72:30-6.

2 Papiernik-Berkhauer E. Double blind study of an agent to prevent pre-term delivery among women at increased risk. In: Edition Schering, Serie IV, fiche 3; 65-8; 1970.

3 Johnson JW, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17 α-hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med. 1975;293(14): 675-80.

4 Yemini M, Borenstein R, Dreazen E, Apelman Z, Mogilner BM, .Kessler I, et al. Prevention of premature labor by 17 a-hydroxyprogesterone caproate. Am J Obstet Gynecol. 1985;151(5):574-7.

5 Suvonnakote T. Prevention of pre-term labour with progesterone. J Med Assoc Thai.1986; 69(10):538-42.

6 Hauth JC, Oilstrap LC 3rd, Brekken AL, Hauth JM. The effect of 17 α-hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. Am J Obstet Gynecol. 1983;146(2):187-90.

The study previously conducted that is most comparable to the MFMU Network trial was the double-blind randomized controlled trial conducted by Johnson et al in 1975 at Johns Hopkins University.[26] This study enrolled women with ≥ 2 preterm births, ≥ 2 spontaneous abortions, or a combination of both. Exclusion criteria included: absence of a viable intrauterine pregnancy; failure to enter the study before 24 weeks gestation; and failure to receive a minimum of 3 doses of the assigned medication. Subjects were randomized to receive 17OHP-C 250 mg IM weekly from enrollment into prenatal care until 37 weeks gestation. Cervical suturing was performed on patients thought to have cervical incompetence (4 in the treatment arm; 3 in the placebo arm). Four patients received isoxsuprine: 2 in the treatment arm; 2 in the placebo arm. Premature birth did not occur in any of the 18 patients receiving 17OHP-C; 9 of 22 patients (41%) receiving placebo had premature birth. The perinatal mortality rate in the 17OHP-C arm was 0% compared to 27% in the placebo arm: of the 7 placebo deaths, 2 were neonatal deaths and 5 were intrauterine deaths.

Other published clinical studies with 17OHP-C have both supported and raised doubt about the effectiveness of 17OHP-C for the prevention of preterm birth. This disparity of opinion prompted the NICHD, via the MFMU Network, to conduct a multicenter placebo-controlled trial to assess the efficacy of 17OHP-C for the prevention of PTB. On June 12, 2003, data from the MFMU Network clinical trial was published in the New England Journal of Medicine, reporting a benefit of 17OHP-C by reducing preterm birth at < 37 weeks.[27] Data from the MFMU Network clinical trial (referred to as Study 17P-CT-002 in this application) provide the primary support for the safety and efficacy of 17OHP-C for the prevention of preterm birth.

2 REGULATORY CONSIDERATIONS AND ISSUES

2.1 Clinical Evidence of Effectiveness

2.1.1 General Considerations

The Division of Reproductive and Urologic Products (hereafter referred to as DRUP or the Division) would typically advise a sponsor developing a drug product for a condition for which there was no previously approved drug product, such as "prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth," to conduct 2 adequate and well-controlled clinical trials. The principal reason for such a recommendation is to provide independent substantiation of experimental results. It has been FDA's position that Congress generally intended to require at least 2 adequate and well-controlled studies, each convincing on its own, to establish effectiveness. However, in the 1997 Food and Drug Administration Modernization Act, Congress amended section 505(d) of the Food, Drug, and Cosmetic Act to clarify that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness.

In NDA 21-945 for Gestiva for prevention of preterm birth, the Applicant has submitted data from only one clinical trial that appears to be adequate and well-controlled (subject to the FDA's inspection of the clinical trial sites and ongoing review of the clinical data). The Division decided to accept this NDA for review in spite of there being only one adequate and well-controlled clinical trial, in part, because of the public health importance of reducing the incidence of preterm birth and its attendant morbidity and mortality and the absence of an approved drug product for this disorder. In addition, there have been examples where the FDA has approved a new drug product based on data from a single adequate and well-controlled clinical trial. In the following sections, the Division provides an overview of the quantity and quality of evidence that is required to approve a new drug product and examples of situations in which data from a single adequate and well-controlled clinical trial has formed the basis for demonstrating effectiveness. The following discussion is derived from the FDA's Guidance Document entitle *Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998).* The complete Guidance can be found in Appendix No. 1 of this background document.

2.1.2 Regulatory Background regarding the Quantity of Evidence Necessary to Support Effectiveness of a Drug Product

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies. The 1962 Amendments included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." Substantial evidence was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

With regard to quantity, it has been FDA's position that Congress generally intended to require at least 2 adequate and well-controlled studies, each convincing on its own, to establish effectiveness. FDA's position is based on the language in the statute and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence. Section 505(d) of the Act uses the plural form in defining "substantial evidence" as "adequate and well-controlled investigation**s**, including clinical investigation**s** [underlines added]." Section 505(b) of the Act also uses "investigations" in describing the contents of a new drug application.

Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and where a confirmatory study would have been difficult to conduct on ethical grounds

2.1.3 Scientific Basis for the Legal Standard

The usual requirement for more than one adequate and well-controlled investigation reflects the need for independent substantiation of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness. The reasons for this include:

- Any clinical trial may be subject to unanticipated, undetected, systematic biases.
- The inherent variability in biological systems may produce a positive trial result by chance alone. This possibility is acknowledged, and quantified to some extent, in the statistical evaluation of the result of a single efficacy trial. It should be noted, however, that hundreds of randomized clinical efficacy trials are conducted each year with the intent of submitting favorable results to FDA. Even if all drugs tested in such trials were ineffective, one would expect one in forty of those trials to "demonstrate" efficacy by chance alone at conventional levels of statistical significance. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.
- Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet). In such cases, the results, although correct, may not be generalizable to the intended population. This possibility is the primary basis for emphasizing the need for independence in substantiating studies.

Although there are statistical, methodological, and other safeguards to address the identified problems, they are often inadequate to address these problems in a single trial. Independent substantiation of experimental results addresses such problems by providing consistency across more than one study, thus greatly reducing the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a drug is effective.

2.1.4 The Quantity of Evidence to Support Effectiveness

There may be situations in which a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a use is effective.

In each of these situations, it is assumed that any studies relied on to support effectiveness meet the requirements for adequate and well-controlled studies as defined in 21 CFR 314.126. It should also be appreciated that reliance on a single study of a given use, whether alone or with substantiation from related trial data, leaves little room for study imperfections or contradictory (nonsupportive) information. In all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that the results reflect a clear prior hypothesis documented in the protocol. Moreover, a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use unless there were a strong argument for discounting the outcomes in the studies that failed to show effectiveness.

2.1.5 Evidence of Effectiveness from a Single Study

At present, major clinical efficacy studies are typically multicenter, with clear, prospectively determined clinical and statistical analytic criteria. These studies are less vulnerable to certain biases, are often more generalizable, may achieve very convincing statistical results, and can often be evaluated for internal consistency across subgroups, centers, and multiple endpoints. The added rigor and size of contemporary clinical trials have made it possible to rely, in certain circumstances, on a single adequate and well-controlled study, without independent substantiation from another controlled trial, as a sufficient scientific and legal basis for approval.

Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on 2 persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, *reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be logistically impossible or ethically unacceptable.* Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns.

The discussion that follows identifies the characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim. Although none of these characteristics is necessarily determinative, the presence of one or more in a study can contribute to a conclusion that the study would be adequate to support an effectiveness claim.

- **Large multicenter study**
  In a large multicenter study in which (1) no single study site provided an unusually large fraction of the subjects and (2) no single investigator or site was disproportionately responsible for the favorable effect seen, the study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator. If analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished.

- **Consistency across study subsets**
  Frequently, large trials have relatively broad entry criteria and the study populations may be diverse with regard to important covariates such as concomitant or prior therapy, disease stage, age, gender or race. Analysis of the results of such trials for consistency across key patient subsets addresses concerns about generalizability of findings to various populations in a manner that may not be possible with smaller trials or trials with more narrow entry criteria.

- **Multiple endpoints involving different events**
  In some cases, a single study will include several important, prospectively identified primary or secondary endpoints, each of which represents a beneficial, but different, effect. Where a study shows statistically persuasive evidence of an effect on more than one of such endpoints, the internal weight of evidence of the study is enhanced. For example, favorable effects on both death and nonfatal myocardial infarctions in a lipid-lowering, post angioplasty, or post infarction study would, in effect, represent different, but consistent, demonstrations of effectiveness, greatly reducing the possibility that a finding of reduced mortality was a chance occurrence.

  In contrast, a beneficial effect on multiple endpoints that evaluate essentially the same phenomenon and correlate strongly, such as mood change on 2 different depression scales, or SGOT and CPK levels post-infarction, does not significantly enhance the internal weight of the evidence from a single trial.

Although 2 consistent findings within a single study usually provide reassurance that a positive treatment effect is not due to chance, they do not protect against bias in study conduct or biased analyses. For example, a treatment assignment not well balanced for important prognostic variables could lead to an apparent effect on both endpoints. Thus, close scrutiny of study design and conduct are critical to evaluating this type of study.

- **Statistically very persuasive finding**
  In a multicenter study, a very low p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect. In some studies it is possible to detect nominally statistically significant results in data from several centers, but, even where that is not possible, an overall extreme result and significance level means that most study centers had similar findings. For example, preventive vaccines for infectious disease indications with a high efficacy rate (e.g., point estimate of efficacy of 80% or higher and a reasonably narrow 95% confidence interval) have been approved based on a single adequate and well-controlled trial.

2.1.6 Reliance on a Single, Multicenter Study — Caveats

While acknowledging the persuasiveness of a single, internally consistent, strong multicenter study, it must be appreciated that even a strong result can represent an isolated or biased result, especially if that study is the only study suggesting efficacy among similar studies. There are examples where the apparent highly favorable effect of drug, studied in what appeared to be a well-designed, placebo-controlled, multicenter trial, resulting in an extreme p-value, has proven to be unrepeatable.

When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single multicenter trial.

Inadequacies and inconsistencies in the data, such as lack of pharmacologic rationale and lack of expected other effects accompanying a critical outcome, can weaken the persuasiveness of a single trial. Although an unexplained failure to substantiate the results of a favorable study in a second controlled trial is not proof that the favorable study was in error — studies of effective agents can fail to show efficacy for a variety of reasons — it is often a reason not to rely on the single favorable study.

2.1.7 Documentation of the Quality of Evidence Supporting an Effectiveness Claim

When submitting the requisite quantity of data to support approval of a new product or new use of an approved product, sponsors must also document that the studies were adequately designed and conducted. To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the Agency, and detailed subject records are made available at the clinical sites.

From a scientific standpoint, however, it is recognized that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim. Therefore, the Agency is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured. The issues of prime importance in documenting the quality of the evidence are

(1) the completeness of the documentation and (2) the ability to access the primary study data and the original study-related records (e.g., subjects' medical records, drug accountability records) for the purposes of verifying the data submitted as evidence.

In practice, to achieve a high level of documentation, studies supporting claims are ordinarily conducted in accordance with good clinical practices (GCPs). Sponsors routinely monitor all clinical sites, and FDA routinely has access to the original clinical protocols, primary data, clinical site source documents for on-site audits, and complete study reports.

However, situations often arise in which studies that evaluate the efficacy of a drug product lack the full documentation described above (for example, full subject records may not be available) or in which the study was conducted with less monitoring than is ordinarily seen in commercially sponsored trials. Under certain circumstances, it is possible for sponsors to rely on such studies to support effectiveness claims, despite less than usual documentation or monitoring. Some of those circumstances are described below.

Reliance on Studies with Alternative, Less Intensive Quality Control/On-Site Monitoring

Industry-sponsored studies typically use extensive on-site and central monitoring and auditing procedures to assure data quality. Studies supported by other sponsors may employ less stringent procedures and may use no on-site monitoring at all. An International Conference on Harmonisation guideline on good clinical practices (*"International Conference on Harmonisation Guidance for Industry E6, Good Clinical Practice: Consolidated Guideline, April 1996"*) emphasizes that the extent of monitoring in a trial should be based on trial-specific factors (e.g., design, complexity, size, and type of study outcome measures) and that different degrees of on-site monitoring can be appropriate. In recent years, many credible and valuable studies conducted by government or independent study groups, often with important mortality outcomes, had very little on-site monitoring. These studies have addressed quality control in other ways, such as by close control and review of documentation and extensive guidance and planning efforts with investigators.

2.2 Discussions between Adeza and the Division

After data from Study 17P-CT-002 were published in the New England Journal of Medicine (Meis et al. 2003),[27] Adeza met with the Division to discuss the possibility of submitting an NDA for 17OHP-C for prevention of preterm birth.

The Division conveyed several recommendations and concerns to the Applicant during this and subsequent meetings. These included the following:

- A major concern was the lack of follow-up data, beyond the period of initial hospital assessment, of babies in which the mother received 17OHP-C for the prevention of preterm birth. The Division requested that the applicant obtain follow-up data on infants through at least 2 years of age.
- A second major concern related to the drug product(s) used during the trial. The Sponsor was informed that complete chemistry, manufacturing and control (CMC) information would need to be provided about the drug product, including its purity and potency. The applicant would need to provide information that the drug product used in the NIH sponsored clinical trial and the to-be-marketed formulation would be comparable.

- The Division had some concerns about outcomes of Study 17P-CT-002 and the adequacy of these outcomes to support approval of a new drug product for marketing in the U.S, particularly since the NDA supporting the safety and effectiveness of 17OHP-C would be based primarily on the outcome of a single clinical trial. These concerns included:
  - The lack of any suggestion of improvement in overall mortality in the 17OHP-C treated subjects compared to the placebo treated subjects.
  - Clinical Trial 17P-CT-002 did not show a statistically robust effect for reducing the number of births at gestational ages <32 weeks, when infant morbidity/mortality is a much greater problem in the U.S. The Division, however, recognized that the trial was not powered for this endpoint.
  - The primary endpoint of Clinical Trial 17P-CY-002 was a surrogate for pregnancy outcome (neonatal/infant morbidity and mortality). The Division indicated that its review would focus on what it believed to be the most important outcomes (overall survival of fetuses/infants and a significant reduction in serious morbidities from the time of enrollment rather than merely an increase in gestational age, without other accompanying clinical benefits).
  - Normally, either 2 adequate and well-controlled studies or a single study with a robust and compelling outcome and strong supporting data would be required to support approval of a new drug product. There was a possibility that the data from Trial 17P-CT-002 would not be sufficient to demonstrate that 17OHP-C is safe and effective for the prevention of preterm birth.

3 OVERVIEW OF CLINICAL DATA IN NDA 21-945

In support of their application for the use of 17OHP-C for the prevention of preterm birth the Applicant submitted data from 2 active treatment clinical trials and a follow-up safety study: Study 17P-IF -001; Study 17P-CT-002 and follow up study 17P-FU. An overview of these studies is presented in Table 2.

Table 2 Studies of 17OHP-C for Prevention of Recurrent Preterm Births

Protocol # /Status	Study Design	Study Population	Treatment Dose	Duration of Drug Treatment	Number of Subjects	Race: Black/Non-Black	Mean Age (Range)
17P-IF-001 Terminated [A] Mar 1999	Double-blind, Placebo-controlled, Randomized 2:1 active treatment to Placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 37^0 wks gestation or delivery	Total: 150 17P: 94 Placebo: 56	Total: 95/55 17P: 54/40 Placebo: 41/15	26.2 yr (17, 42)
17P-CT-002 Completed [B] Aug 2002	Double-blind, Placebo-controlled, Randomized 2:1 active treatment to Placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 37^0 wks gestation or delivery	Total: 463 17P: 310 Placebo: 153	Total: 273/190 17P: 183/127 Placebo: 90/63	26.2 yr (16, 43)
17P-FU Completed Nov 2005	Observational long-term safety follow-up for Study 17P-CT-002	Infants discharged live in Study 17P-CT-002	None	No study treatment was administered	Total: 278 17P: 194 Placebo: 84	Total: 152/126 17P: 105/89 Placebo: 47/37	47.4 mo (30, 64)

[A] Study 17P-IF-001 was terminated early by the Sponsor when the manufacturer recalled the study drug. The last subject visit was in August 1999. Of the 150 subjects, only 60.6% (57/94) of subjects randomized to 17OHP-C and 51.8% (29/56) of subjects randomized to placebo completed study treatment to 36^6 weeks of gestation or delivery.

[B] An independent Data and Safety Monitoring Committee (DSMC) reviewed the study data after 400 subjects had completed the study. Based on that interim dataset, the primary endpoint, birth <37^0 weeks of gestation, was significantly reduced and the p-value was below the p-value specified in predefined stopping rules. The DSMC recommended that enrollment in the study be stopped, so that no new subjects would be assigned placebo. By the time the study was stopped, 463 subjects had been enrolled, which was 92.5% of the proposed sample size of 500 subjects.

Initial Formulation Study (Study 17P-IF-001)

This study began in February 1998, but treatment was terminated in March 1999 because the active study drug (17OHP-C) was recalled by its manufacturer, under the direction of the FDA, due to violations of manufacturing practices potentially affecting the potency of the drug. At the time of termination, only 150 of the proposed 500 subjects had been randomized, and no data analysis had been done. Ninety subjects completed the treatment regimen before the study was stopped: 57 (61%) of the 17OHP-C subjects and 29 (52%) of the placebo subjects. The study drug used in this terminated study is referred to as the Initial Formulation (IF). The data collected from subjects enrolled in the terminated study were analyzed separately in the NDA and the results are also summarized separately.

Principal Clinical Trial (Study 17P-CT-002)

This study, which began in October 1999, randomized 463 subjects who had at least one documented prior spontaneous preterm birth of a singleton, non-anomalous fetus. Of these, 418 subjects (90.3%) completed dosing through 36^6 weeks or birth: 279 (90.0%) in the

17OHP-C group and 139 (90.8%) in the placebo group. This study was terminated prior to enrolling the proposed 500 subjects because the prespecified stopping criterion for efficacy was attained at an interim analysis.

Follow-up of Children from the 17P-CT-002 trial (Study 17P-FU)

This was a follow-up to Study 17P-CT-002. The follow-up study collected data with a validated child development instrument, the Ages and Stages Questionnaire (ASQ), a Survey Questionnaire concerning the health and development of the child, and a physical examination. The children were at least 2 years of age at the time of the follow-up assessments. The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received weekly intramuscular injections of 17OHP-C compared with placebo during the pregnancy in Study 17P-CT-002.

4 PRIMARY EFFICACY AND SAFETY CLINICAL TRIAL

Study 17P-CT-002: "A Randomized Trial of 17α-Hydroxyprogesterone Caproate for Prevention of Preterm Birth in High Risk Women"

4.1 Background Information

The National Institute of Child Health and Human Development (NICHD) created the Maternal-Fetal Medicine Units (MFMU) Network in 1986 to focus on clinical questions in maternal fetal medicine and obstetrics, particularly with respect to the continuing problem of preterm birth. Operating under cooperative agreements at the time this study was conducted, the MFMU Network comprised 19 university-based clinical centers and a data-coordinating center, the Biostatistical Coordinating Center (BCC) at George Washington University. The NICHD/MFMU Network was responsible for operational issues including site monitoring and project management for this study

The plan was to conduct one multicenter, randomized, placebo-controlled, double-blinded study on the efficacy and safety of 17OHP-C in pregnant women at high risk for preterm birth. Study 17P-IF-001 enrolled its first subject in February 1998, but had to be terminated early in March 1999 after only one-third of the proposed subjects were enrolled. None of the data had been analyzed at the time of termination. This termination occurred because the study drug (17OHP-C) was recalled by its manufacturer at the request of the FDA as described in Section 3.

The clinical trial was started afresh in October 1999 using study drug from a new manufacturer and is referred as Study 17P-CT-002. The data collected from subjects enrolled in the terminated Study 17P-IF-001 were not merged with data collected in Study 17P-CT-002 nor were they provided in the Report for Study 17P-CT-002.

4.2 Study Drugs

Active study drug consisted of 17α-hydroxyprogesterone caproate (250 mg/mL) in castor oil with 46% benzyl benzoate and 2% benzyl alcohol. Inactive (placebo) study drug was identical to the active drug product but did not contain 17OHP-C. Study drugs were administered once weekly by intramuscular injection.

4.3 Overview of Protocol for Study 17P-CT-002

Study 17P-CT-002 was conducted at 19 investigational sites in the United States. All principal investigators were members of the NICHD MFMU Network. Certification of each study center was required before recruitment of subjects.

The study was a randomized, placebo-controlled, efficacy and safety study of 17OHP-C in pregnant women, from 16^0 to 20^6 weeks gestation, who had a history of spontaneous preterm birth, defined as delivery from 20^0 to 36^6 weeks gestation following spontaneous preterm labor (PTL) or preterm premature rupture of membranes (pPROM). The requirement that the gestational age be at least 16^0 weeks and no more than 20^6 weeks was instituted in order to initiate treatment after the first trimester, but before the gestational age at which a preterm birth, by definition, could occur.

Prior to randomization into the clinical trial, an injection of the placebo drug product was administered to potential subjects from 15^0 to 20^3 weeks gestation, to assess the subject's tolerability to the injection. Qualifying subjects were randomized in a 2:1 ratio to 17OHP-C or placebo. Study drug was administered weekly by intramuscular injection through 36^6 weeks gestation or delivery, whichever occurred first.

4.3.1 Inclusion/Exclusion Criteria

<u>Inclusion Criteria</u>. Subjects had to meet all of the following criteria at screening to be eligible for enrollment into the study:

1. Gestational age between 16^0 weeks and 20^6 weeks at the time of randomization, based on clinical information and evaluation of the first ultrasound.
2. Documented history of a previous singleton spontaneous preterm birth. Spontaneous preterm birth was defined as delivery from 20^0 to 36^6 weeks gestation following spontaneous preterm labor or preterm premature rupture of membranes. Where possible, the gestational age of the previous preterm birth (referred to as the qualifying birth) was determined. If the gestational age at delivery was obtained directly from the medical record and more than one gestational age appeared, the latest was used. The qualifying delivery could not be an antepartum stillbirth.

<u>Exclusion Criteria.</u> If any of the following criteria applied, the subject was not eligible to enroll into the study:

1. Multifetal gestation.
2. Known major fetal anomaly or fetal demise. An ultrasound examination after 14 weeks gestation had to be performed to rule out fetal anomalies.
3. Progesterone treatment during current pregnancy.
4. Heparin therapy during current pregnancy or history of thromboembolic disease.
5. Maternal medical/obstetrical complications including:
    a. Current or planned cerclage;
    b. Hypertension requiring medication;
    c. Seizure disorder.

6. Prenatal follow-up or delivery planned elsewhere (unless the study visits could be made as scheduled and complete outcome information obtained).
7. A 14^0 to 20^6 week ultrasound could not be arranged before randomization.
8. Participation in an antenatal study in which the clinical status or intervention could have influenced gestational age at delivery. Subjects enrolled in any of the following MFMU Network studies during this period were ineligible for the trial: "Randomized Clinical Trials of the Effect of Metronidazole on Pregnancy Outcome in Women Infected with T. Vaginalis or Bacterial Vaginosis," "Randomized Trial of Metronidazole Plus Erythromycin to Prevent Preterm Birth in Women with Elevated Cervical/Vaginal Oncofetal Fibronectin," "Randomized Clinical Trial of Theophylline versus Inhaled Beclomethasone," and "The Effects of Asthma and Treatment Regimens on Perinatal Outcome."
9. Participation in this trial in a previous pregnancy. Subjects who were screened in a previous pregnancy, but not randomized, were not excluded.

4.3.2 Endpoints

Primary Objective. The primary per protocol objective of this study was to determine if, compared with placebo, 17OHP-C treatment initiated before 21^0 weeks gestation reduces the risk of preterm birth ($<37^0$ weeks gestation) in women who have previously experienced a spontaneous preterm birth.

All deliveries occurring from the time of randomization through 36^6 weeks gestation, including miscarriages (i.e., spontaneous abortions) and elective abortions, were counted in the primary outcome.

Secondary Objectives. The secondary objectives defined in the protocol were to determine the following in women with a previous spontaneous preterm birth:

- If treatment with 17OHP-C reduces the use of tocolytic therapy and/or cervical cerclage.
- If treatment with 17OHP-C reduces neonatal morbidity/mortality.

Neonatal outcomes considered secondary efficacy measures included: birthweight; score reflecting condition of neonate (Apgar score); admission to the neonatal intensive care unit (NICU); infant hospital days; number of days of neonatal respiratory therapy; stillbirths; neonatal deaths; neonates with respiratory distress syndrome (RDS); intraventricular hemorrhage (IVH); bronchopulmonary dysplasia (BPD); necrotizing enterocolitis (NEC); early onset of neonatal sepsis; seizures; retinopathy of prematurity; and transient tachypnea. In addition, the percentage of infants who received ventilator support, and the percentage of infants who received supplemental oxygen were provided.

Based on communications with the FDA, the following secondary endpoints were added to the analyses:

- If treatment with 17OHP-C, compared to placebo, reduces the risk of preterm birth of $<35^0$ weeks gestations.
- If treatment with 17OHP-C, compared to placebo, reduces the risk of preterm birth of $<32^0$ weeks gestations.

- If treatment with 17OHP-C, compared to placebo, reduces overall neonatal morbidity based on a composite measure of neonatal morbidity.

4.3.3 Statistical Methods/Sample Size Determination

Applicant's Analyses. All statistical comparisons were between 17OHP-C and placebo. Except where explicitly indicated, data were pooled across study centers for all statistical analyses. Subjects were analyzed based on the group to which they were randomized.

Summary statistics consisted of numbers and percentages of subjects for categorical measures and were compared for statistical significance between treatment groups using the chi-square test, Fisher's Exact test, or the Wilcoxon Rank Sum test for ordered categorical data. For categorical variables, percentages were calculated based on available data.

Summary statistics consisted of means, medians, standard deviations, and minimum and maximum values for continuous measures and were compared for statistical significance between the treatment groups using the Wilcoxon Rank Sum test.

All statistical tests were reported as 2-sided p-values. The final primary efficacy analysis utilized the Type 1 α=0.034 level of statistical significance as required by the O'Brien Fleming boundary. For all other analyses, no adjustments were made for multiple comparisons and a nominal α=0.05 level of statistical significance was used.

4.4 Demographics, Concomitant Medication Use, and Subject Disposition

4.4.1 Demographics and Obstetrical History

The subjects randomized to the 2 treatment groups (17OHP-C vs. placebo, respectively) were comparable in mean age, race or ethnic group, mean BMI prior to pregnancy, marital status, mean years of education, and substance use during pregnancy. The mean age of the subjects was 26.2 years (26.0 vs. 26.0 years) and their mean pre-pregnancy BMI was 26.6 kg/m^2 (26.9 vs. 26.0 kg/m^2). Half of the subjects were married or living with a partner (51% vs. 46%), while 39.5% had never been married (38% vs. 42%). More than half of the subjects were African American (59% in each group); and 4% had a history of diabetes (4% vs. 3%). During the study pregnancy but prior to randomization, 22% had smoked (23% vs. 20%), 8% had consumed alcoholic drinks (9% vs. 6%), and 3% had used street drugs (4% vs. 3%).

Obstetrical histories were comparable in the 17OHP-C and placebo groups for gestational age at randomization (18.9 vs. 18.8 weeks), gestational age of qualifying delivery (30.6 and 31.3 weeks), number of previous term deliveries (0.8 and 0.7); percentage with previous miscarriages (30.0% vs. 37.3%) and stillbirths (10.0% vs. 8.5%). (See Table 3.)

Division's Comment

- *The 17OHP-C subjects had statistically significantly fewer previous preterm births (1.4 vs. 1.6), fewer previous SPTB (1.3 vs. 1.5), and a lower percentage of subjects with >1 previous preterm birth (27.7% vs. 41.2%). They may therefore represent a lower-risk group as compared to the placebo subjects.*

One-third of the subjects in each treatment group had an infection during the study pregnancy prior to randomization (32% in 17OHP-C vs. 36% in placebo groups). The types of infections prior to randomization were similar across the treatment groups. The most common infections were bacterial vaginosis (13% in both treatment groups), urinary tract infections (12% vs. 13%), and Chlamydia infections (3.9% vs. 4.6%).

A smaller percentage of subjects randomized to 17OHP-C used corticosteroids during the study pregnancy prior to randomization (1.6% vs. 5.2%); the difference was due to a lower use of inhaled corticosteroids in the 17OHP-C group (0.3% vs. 4.6%).

Table 3 Obstetrical History

Obstetrical History	17OHP-C (N=310)	Placebo (N=153)	P-value[A]
Gestational age of qualifying birth, wk			
Mean (SD)	30.6 (4.6)	31.3 (4.2)	
Min, Max	20, 36	20, 36	
No. of previous preterm births (PTBs)			
Mean (SD)	1.4 (0.7)	1.6 (0.9)	<0.05
Min, Max	1, 5	1, 6	
>1 Previous preterm birth, n (%)	86 (27.7)	63 (41.2)	<0.05
No. of previous spontaneous PTBs			
Mean (SD)	1.3 (0.7)	1.5 (0.9)	<0.05
Min, Max	1, 5	1, 6	
No. of previous term deliveries			
Mean (SD)	0.8 (1.1)	0.7 (1.0)	
Min, Max	0, 7	0, 5	
Previous miscarriage, n (%)	93 (30.0)	57 (37.3)	
Previous stillbirth, n (%)	31 (10.0)	13 (8.5)	
Infection during pregnancy (before randomization), n (%)	98 (31.6)	55 (35.9)	
Corticosteroids during pregnancy (before randomization), n (%)	5 (1.6)	8 (5.2)	<0.05
Duration of gestation at randomization, wk			
Mean (SD)	18.9 (1.4)	18.8 (1.5)	
Min, Max	16, 21	16, 21	

[A] Only p-values ≤ 0.05 shown.

Source: Table 11-2, Final Report for Study 17-CT-002.

4.4.2 Concomitant Medication Use

No attempt was made to mandate clinical management of the subjects during the study. The percentages of subjects who received any type of corticosteroids (16.8% vs. 19.6%), antibiotic therapy (31.6% vs. 23.5%), or tocolytic therapy (12.9% vs. 11.8%) were not significantly different between the 17OHP-C and placebo groups. The most common (>5% of subjects) type of corticosteroid used after randomization was parenteral corticosteroids (14.2% in the 17OHP-C group vs. 13.7% in the placebo group). The most common types of antibiotics were penicillin (17.7% vs. 14.4%), oral metronidazole (10.3% vs. 5.2%), and erythromycin (8.7% vs. 8.5%).

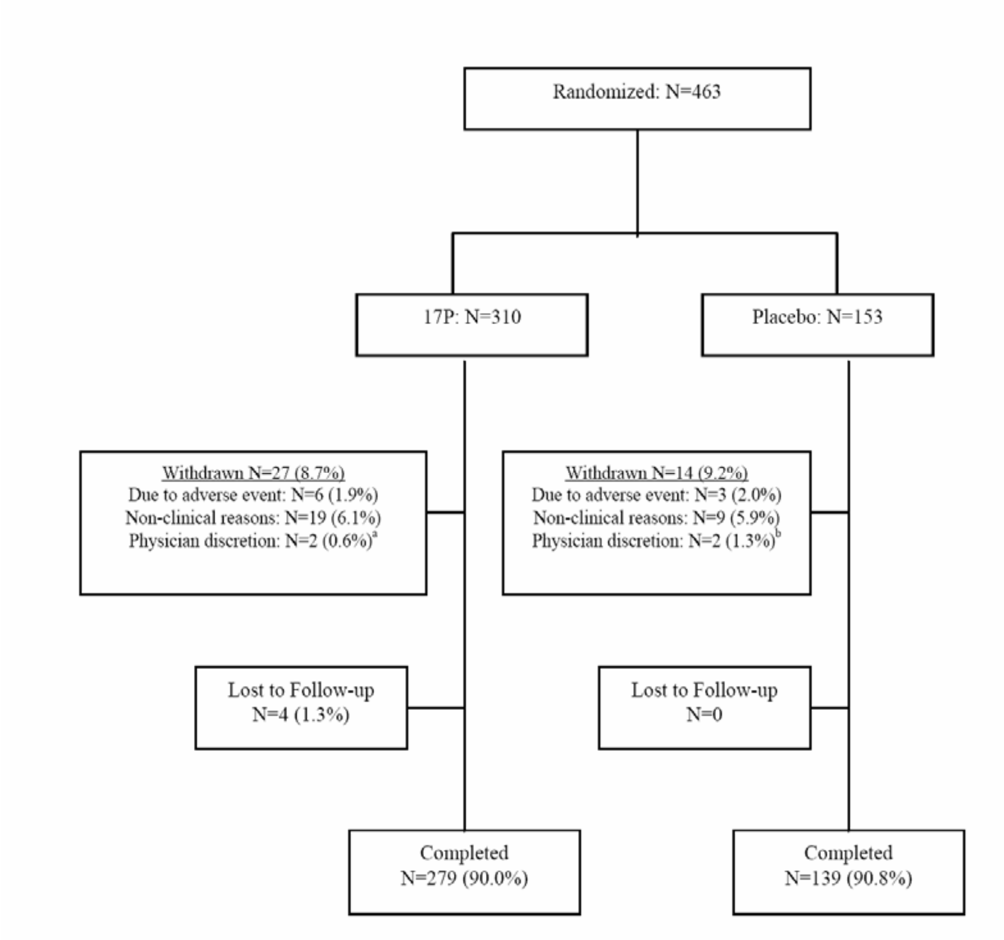
The percentage of subjects using the following concomitant medications differed between the 17OHP-C and placebo groups: inhaled corticosteroids (1.9% vs. 4.6%), oral metronidazole

(10.3% vs. 5.2%), and nitrofurantoin (4.2% vs. 1.3%). Oral metronidazole was administered for bacterial vaginosis or Trichomonas vaginalis and nitrofurantoin was administered for urinary tract infections, which suggests that a slightly higher rate of these infections occurred in the 17OHP-C group during the study pregnancy.

4.4.3 Subject Disposition

A total of 463 subjects were randomized at 19 study centers in the U.S (Figure 1). Four hundred eighteen (418; 90.3%) subjects completed injections through 36^6 weeks gestation or delivery, whichever occurred first: 279 (90.0%) in the 17OHP-C group and 139 (90.8%) in the placebo group. Early discontinuation of treatment with study drug occurred at a similar rate in both treatment groups (8.7% 17OHP-C vs. 9.2% placebo). Most of these subjects discontinued due to “non-clinical reasons,” which were not further defined by the Applicant (6.1% vs. 5.9%); those potentially due to adverse events (AEs) are discussed in Section 4.6.6. Four (<1.0%) subjects, all in the 17OHP-C group, were lost to follow-up.

Figure 1 Overview of Subject Disposition in Study 17P-CT-002



Note: "Withdrawn from the study" was defined as the patient no longer received study drug. "Lost to follow-up" was defined as the patient's delivery data could not be obtained. "Completed the study" was defined as the patient did not withdraw from the study and was not lost to follow-up.

[a] In the 17P group, Investigators stopped the participation of one patient due to injection site reactions and another patient due to pPROM, which was not considered an AE. Therefore, 7 (2.2%) patients in the 17P group discontinued due to AEs.

[b] In the placebo group, Investigators stopped the participation of one patient due to a potential allergic reaction and another patient due to pPROM, which was not considered an AE. Therefore, 4 (2.6%) patients in the placebo group discontinued due to AEs.

Source: Section 10.1, Figure 10-1, Final Report for Study 17-CT-002.

4.5 Efficacy Outcomes

4.5.1 Primary Endpoint (Applicant's Analyses)

The proportions of deliveries prior to 37^0 weeks gestation based on the ITT population and on all available data are summarized in Table 4. In the ITT population, 115 of 310 ((37.1%) had a delivery prior to 37^0 weeks gestation. In the placebo group, 84 of 153 subjects (54.9%) had a delivery prior to 37^0 weeks gestation. The difference was statistically significant.

Table 4 Percentages of Subjects with Delivery <37^0 Weeks Gestation (Sponsor's Analysis)

Data Source	17P N	17P n (%)	Placebo N	Placebo n (%)	Nominal P-value [A]	Treatment difference and 95% Confidence Interval [B]
ITT population	310	115 (37.1)	153	84 (54.9)	0.0003	-17.8% [-28%, -7%]
Only available data	306	111 (36.3)	153	84 (54.9)	0.0000	-18.6% [-29%, -8%]

ITT population was all randomized subjects. The 4 subjects with missing outcome data were classified as having a preterm birth of <37^0 weeks (i.e., treatment failure). "Only available data" does not include the 4 subjects with missing outcome data.

[A] Chi-square test. Adjusting for interim analyses, p-values should be compared to 0.035 rather than the usual 0.05.

[B] Confidence interval (CI) calculated by FDA, adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, a p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

Source: Modified from Table 11-3, Final Report for Study 17P-CT-002.

Subjects who delivered prior to 37^0 weeks gestation also were classified (1) by the gestational age of the previous qualifying SPTB using the intervals of 20^0-<28^0 weeks, 28^0-<32^0 weeks, 32^0-<35^0 weeks, and 35^0-<37^0 weeks), (2) by race (African American [non-Hispanic Black] and Non-Black), and (3) by number of previous preterm births (1, 2, and ≥3) (see Table 5)

Table 5 Percentages of Subjects with Delivery <37^0 Weeks by Gestational Age of Qualifying Birth, Race, and Number of Previous Preterm Deliveries

Characteristic	17OHP-C n/N (%)	Placebo n/N (%)
Previous SPTB (qualifying birth) by gestational age		
20^0 - <28^0 weeks	33/82 (40.2)	19/29 (65.5)
28^0 - <32^0 weeks	21/66 (31.8)	17/30 (56.7)
32^0 - <35^0 weeks	30/84 (35.7)	27/55 (49.1)
35^0 - <37^0 weeks	31/78 (39.7)	21/39 (53.8)
Race		
Black	66/183 (36.1)	47/90 (52.2)
Non-Black	49/127 (38.6)	37/63 (58.7)
Number of previous preterm births (PTBs)		
1 prior PTB	74/224 (33.0)	40/90 (44.4)
2 prior PTB	27/56 (48.2)	31/46 (67.4)
≥3 prior PTB	14/30 (46.7)	13/17 (76.5)

Data based on ITT Population (all randomized subjects). The 4 subjects with missing outcome data were classified as having a preterm birth <37^0 weeks (i.e., treatment failure).

Abbreviations:

SPTB = spontaneous preterm birth; PTB = preterm birth.

n = number of subjects in a specific category who delivered study pregnancy at <37^0 weeks gestation
N = total number of subjects overall in a specific category.

Source: Table 11-4, Final Report for Study 17-CT-002.

Rates of preterm birth at <37^0 weeks did not appear to differ significantly according to the gestational age of the qualifying delivery in either treatment group (with the possible exception of the category of 20^0 - <28^0 weeks in the placebo group). For all intervals of gestational age, the rates of preterm birth <37^0 weeks were numerically lower in the 17OHP-C treatment group.

The percentage of Black subjects in Study 17P-CT-002 was 59% in both groups. 17OHP-C reduced the rate of preterm birth of <37^0 weeks gestation compared to placebo for both the Black (36.1% vs. 52.2%) and the Non-Black (38.6% vs. 58.7%) populations.

Subjects with more than one previous preterm birth, regardless of treatment group, had numerically increased rates of preterm births for the study pregnancy compared to subjects with only one previous preterm birth. The rates of preterm births in the 17OHP-C treatment group, compared with placebo, were numerically lower for subjects with one previous preterm birth (33% vs. 44%), 2 previous preterm births (48% vs. 67%), and 3 or more previous preterm births (47% vs. 77%). If the last 2 categories were combined, the incidence of preterm birth in this study for subjects with >1 previous preterm birth was 48% in the 17OHP-C group compared with 70% in the placebo group.

Division's Comment

- *Treatment with 17OHP-C reduces preterm births < 37 weeks gestation.*
- *The reduction in preterm birth appeared independent of race, number of qualifying preterm deliveries, and gestational age of qualifying preterm birth.*

4.5.2 Secondary Endpoints

4.5.2.1 Proportion of Deliveries <35 and <32 Weeks Gestational Age (Applicant's Analysis)

At the request of the Division, the Applicant also calculated the proportion of deliveries <35^0 weeks gestation and <32^0 weeks gestation because of the increasing morbidity associated with earlier premature deliveries. The proportion of deliveries <35^0 weeks gestation (21.6% vs. 30.7%) and <32^0 weeks gestation (12.6% vs. 19.6%) were lower in the 17OHP-C group compared with the placebo group (see Table 6).

Table 6 Percentages of Subjects with Delivery <35^0 and <32^0 Weeks Gestation (Applicant's Analysis)

Pregnancy Outcome	17P N=310 n (%)	Placebo N=153 n (%)	Nominal P-value [A]
Delivery <35^0	67 (21.6)	47 (30.7)	0.0324
Delivery <32^0	39 (12.6)	30 (19.6)	0.0458

Data presented are from the ITT population (i.e., all randomized subjects). The 4 subjects with missing outcome data were classified as having a preterm birth <37^0 weeks (i.e., treatment failure).

[A] Adjusting for interim analyses, p-values should be compared to 0.035 rather than the usual 0.05.

Source: Table 11-5, Final Report for Study 17-CT-002.

Division's Comments

- *The p-values presented in Table 6 should be interpreted with caution for several reasons: (1) there were 2 interim analyses and a final analysis and (2) multiple endpoints, likely to be correlated with each other and with the primary endpoint, were analyzed. The adjustment to the p-value that should be used for analyses of multiple endpoints in this setting is not clear. To declare statistical significance, the p-value boundary is likely smaller than the 0.035 used for analysis of the primary endpoint.*
- *Thus, the difference in deliveries at $<35^0$ weeks may be suggestive of a treatment effect but not statistically significant.*

4.5.2.2 Proportion of Deliveries <35 and <32 Weeks Gestational Age (Division's Analysis)

The Division's analysis of the effects of treatment with 17OHP-C, as compared to placebo, on the percentage of deliveries at $<37^0$, $<35^0$, $<32^0$, and $<28^0$ weeks gestation is shown in Table 7. At each of weeks $<37^0$, $<35^0$, and $<32^0$, the percentage of deliveries was numerically lower in the 17OHP-C treatment arm. The point estimates of the differences between the percentage of births at each gestational age ranged from -17.8% (at $<37^0$) to -7.0% (at $<32^0$). However, the upper limits of the 95% confidence intervals (adjusted to preserve the overall Type I error rate of 0.05) of the differences between treatment groups suggest that the true rate of preterm deliveries could be as much as 0.3% and 0.8% higher in the 17OHP-C groups at $<35^0$ weeks and $<32^0$ weeks gestation, respectively.

There was no difference between treatment groups for the percentages of deliveries $<28^0$ weeks.

Table 7 Percentages of Subjects with Delivery $<37^0$, $<35^0$, $<32^0$, and $<28^0$ Weeks Gestation (ITT Population, Division's Analysis)

Time of Delivery (Gestational Age)	17OHP-C (N=310)	Placebo (N=153)	Treatment difference [A] and 95% Confidence Interval [B]
	%	%	
$<37^0$ weeks	37.1	54.9	-17.8% [-28%, -7.0%]
$<35^0$ weeks	21.6	30.7	-9.1% [-18%, 0.3%]
$<32^0$ weeks	12.6	19.6	-7.0% [-14%, 0.8%]
$<28^0$ weeks	10.0	10.5	-0.5% [-6.9%, 5.9%]

[A] Chi-square test.

[B] The confidence intervals, based on a t-test, are adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, the final p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

Source: FDA statistical analysis of Applicant's data from Study 17P-CT-002.

Division's Comment

- *The 95% confidence intervals for the difference between treatment groups for deliveries $<37^0$ weeks gestation suggest that the true rate of preterm deliveries in the 17OHP-C group could range from 7 to 28% lower than the rate in the placebo group. This finding* *supports the Applicant's claim that treatment with 17OHP-C, compared to placebo, had a statistically significantly effect in reducing the proportion of deliveries <37^0 weeks.*

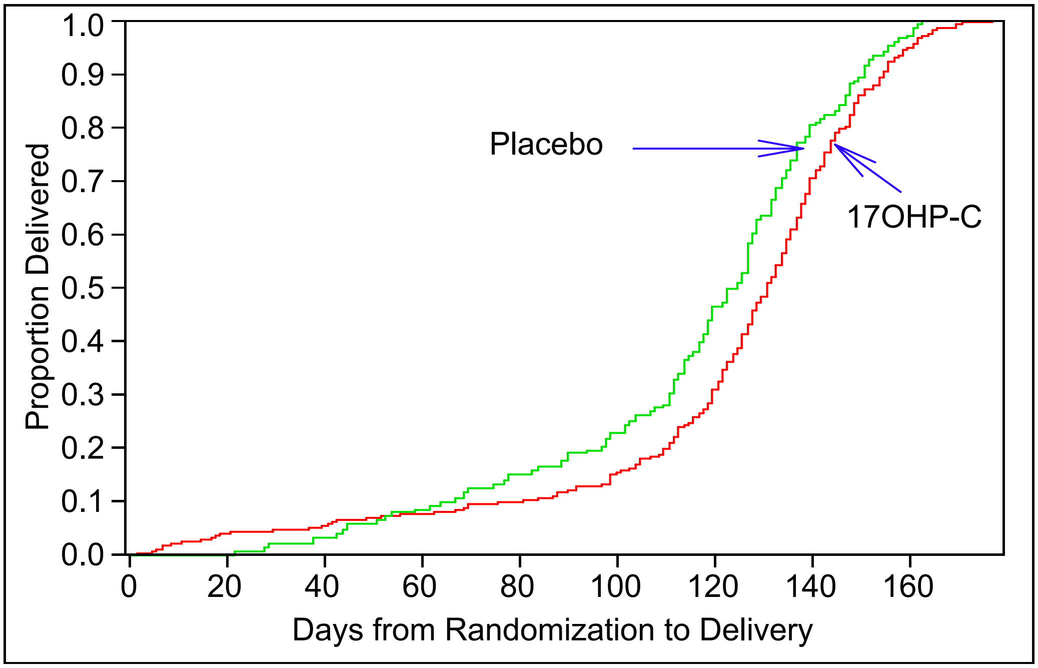
- *The upper limits of the 95% confidence intervals for the differences between treatment groups for deliveries at <35^0 weeks and <32^0 weeks gestation suggest the true rate of preterm deliveries in the 17OHP-C group could be as much as 0.3% and 0.8% higher, respectively, than that in the placebo group. This finding does not allow a conclusion as to whether there is a difference in the true rate of preterm delivery between the treatment groups at <35^0 weeks and <32^0 weeks gestation. If further adjustment of the 95% confidence interval were required (see Division's comment in Section 4.5.2.1), there would be greater doubt as to whether this clinical trial had demonstrated a true difference in the rates of deliveries between the treatment groups at <35^0 weeks and <32^0 weeks gestation.*
- *The Division recognizes that this clinical trial was not powered to demonstrate a difference in the rates of deliveries between the 2 treatment groups at either <35^0 weeks or <32^0 weeks gestation. However, because the Applicant is seeking approval for 17OHP-C based on (1) only a single clinical trial and (2) a surrogate endpoint of neonatal/infant morbidity and mortality, inability to demonstrate a robust effect at either <35^0 weeks or <32^0 weeks gestation is an important consideration in assessing the overall effectiveness of 17OHP-C for the proposed indication.*

4.5.2.3 Mean Gestational Age at Delivery and Duration of Pregnancies

The mean gestational age at delivery for subjects with available outcome data (306 in the 17OHP-C group and 153 in the placebo group) was one week greater in the 17OHP-C group (36.2 weeks vs. 35.2 weeks). The gestational ages at delivery ranged from 18.1 to 41.6 weeks. The median prolongation of pregnancy (defined as the time from randomization until delivery or date that the subject was last confirmed to be pregnant) was higher in the 17OHP-C group compared to the placebo group (131 days vs. 125 days).

A plot of the proportion of subjects delivered as a function of time (days) after randomization is provided in Figure 2. During the period from randomization through approximately 6-7 weeks post-randomization, the proportion of subjects who had delivered was numerically greater in the 17OHP-C treatment group. Thereafter, the proportion of subjects who had delivered was numerically greater in the placebo treatment group at all times through at least Day 150 post-randomization.

Figure 2 Proportion of Subjects Delivered after Onset of Treatment (Study 17P-CT-002)



Source: FDA statistical analysis of Applicant's data from Study 17P-CT-002.

Division's Comment

- *The increased proportion of delivered subjects in the 17OHP-C group, relative to the placebo group, during the first 6 weeks after randomization was due in part to the 5 miscarriages (spontaneous abortions) at <20 weeks gestation in the 17OHP-C group. No miscarriages (spontaneous abortions) at <20 weeks gestation were reported in the placebo group. Whether treatment with 17OHP-C contributed to these early pregnancy losses is not known.*
- *A second randomized clinical trial (or data from other sources) would be helpful in assessing whether treatment with 17OHP-C may be associated with an increase in early pregnancy loss at <20 weeks gestation.*

4.5.2.4 Other Secondary Efficacy Endpoints

The percentage of subjects who were given tocolytic agents during the study was similar in the 2 treatment groups (12.9% vs. 11.8%). The incidence of cerclage placement was also similar in both treatment groups (1.6% vs. 1.3%).

The incidence of caesarian section (C-section) in the 17OHP-C group was similar to that in the placebo group (25.2% vs. 26.8%). The most common reasons for a C-section in the 17OHP-C and placebo groups, respectively, were previous C-section (44.2% vs. 41.5%), abnormal presentation (23.4% vs. 29.3%), and fetal distress (14.3% vs. 19.5%).

4.5.3 Miscarriages, Stillbirths, and Neonatal Deaths

The incidences of miscarriages and stillbirths are summarized in Table 8 and discussed in more detail in Section 4.6.2. Five (1.6%) subjects, all in the 17OHP-C group, experienced miscarriages. No subject in the placebo group miscarried.

The incidence of stillbirths was slightly higher in the 17OHP-C group, but the difference was not statistically significant. Eight subjects had stillbirths: 6 (2.0%) subjects in the 17OHP-C group and 2 (1.3%) subjects in the placebo group. Six of the 8 stillbirths were antepartum stillbirths (fetal deaths in utero) and 2 occurred intrapartum.

The incidence of neonatal deaths was numerically twice as high in the placebo group (2.7% vs. 6.0%), but the difference was not statistically significant. If miscarriages and stillbirths are added to the neonatal deaths, the overall fetal and neonatal mortality was similar in the 2 treatment groups (6.2% in the 17OHP-C group vs. 7.2% in the placebo group).

Table 8 Miscarriages, Stillbirths, and Neonatal Deaths

Pregnancy Outcome	17OHP-C N=306 n (%)	Placebo N=153 n (%)	Nominal P-value[A]
Miscarriages <20 weeks gestation	5 (1.6)	0	0.1746
Stillbirth	6 (2.0)	2 (1.3)	0.7245
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.1159
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.6887**

[A] No adjustment for multiple comparisons.

Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

Division's Comments

- *The trend towards a benefit in the reduction of neonatal death is off-set by a trend toward an increase in the rates of miscarriage and possibly stillbirth associated with use of 17OHP-C, resulting in no net benefit regarding survival.*
- *Based on the data provided in Study 17P-CT-002, there is no indication that treatment with 17OHP-C will reduce overall fetal/neonatal mortality.*

4.5.4 Neonatal Outcomes

4.5.4.1 Neonatal Characteristics

Four hundred forty-six (446) live infants were delivered by 459 subjects with known delivery dates: 295 infants in the 17OHP-C group and 151 infants in the placebo group (Table 9).

Birthweight

The percentage of infants weighing <2500 g was significantly lower in the 17OHP-C group than in the placebo group (27.2% vs. 41.1%). The percentage of infants weighing <1500 g also was numerically (but not statistically) lower in the 17OHP-C group (8.6% vs. 13.9%). There were no differences between treatment groups in mean birthweight.

Apgar Scores
There were no differences between treatment groups in mean 1-minute and 5-minute Apgar scores.

Congenital Malformations
Nine (2.0%) infants overall had a major congenital malformation; the incidence rate was not different between treatment groups: 6 (2.0%) in the 17OHP-C group and 3 (2.0%) in the placebo group.

Admission to and Days in NICU
A smaller percentage of liveborn infants in the 17OHP-C group were admitted to the NICU compared with liveborn infants in the placebo group (27.8% vs. 36.4%). For live births, stay in the NICU ranged widely, from 0.1 - 194.8 days. The median stay in the NICU was numerically (but not statistically) shorter for the 17OHP-C group (9.1 vs. 14.1 days).

Hospital days were available for 285 infants in the 17OHP-C group and 140 infants in the placebo group. The difference in mean hospital days between treatment groups was not significant (8.7 vs. 13.3 days).

Table 9 Neonatal Outcomes in Study 17P-CT-002

Neonatal Outcome	17OHP-C	Placebo	Nominal P-value[A]
Number of subjects	310	153	--
Number of live births	295	151	--
Birthweight (g)			
Mean (SD)	2760 (859)	2582 (942)	0.0736
Min, Max	208, 4900	300, 4855	--
Birthweight <2500 g, n (%)	82 (27.2)	62 (41.1)	**0.0029**
Birthweight <1500 g, n (%)	26 (8.6)	21 (13.9)	0.0834
Head circumference			
Mean (SD)	32.5 (3.1)	32.0 (3.3)	0.0963
Min, Max	15.4, 37.5	21.5, 38.0	--
1 Minute Apgar			
Mean (SD)	7.5 (2.3)	7.3 (2.3)	0.2135
Min, Max	0, 9.0	0, 9.0	--
5 Minute Apgar			
Mean (SD)	8.3 (1.9)	8.3 (1.7)	0.1058
Min, Max	0, 10.0	0, 9.0	--
Major congenital malformation, n (%)	6 (2.0)	3 (2.0)	1.0000
Admitted to NICU or miscarriage/stillbirth/neonatal death, n (%)	93 (30.4)	57 (37.3)	0.1395
Admitted to NICU (live births), n (%)	82 (27.8)	55 (36.4)	**0.0434**
Days in NICU [B]			
Median	9.1	14.1	0.1283
Min, Max	0.1, 194.8	0.1, 147.0	--
Infant hospital days [C]			
Mean (SD)	8.7 (16.0)	13.3 (26.5)	0.3612
Min, Max	2, 123	2, 148	--

Birthweight and head circumference data were missing for some infants.

A: No adjustment for multiple comparisons

B: For neonatal deaths, days in the NICU were calculated until date of death. Days in NICU could not be determined for 3 patients in the 17OHP-C group and 2 patients in the placebo group.

C: Determined only for infants discharged alive.

Source: Table 11-7 Final Report for Study 17-CT-002.

4.5.4.2 Neonatal Morbidity other than Death for Live Births

The incidences of use of supplemental oxygen (15.4% vs. 24.2%), any type of intraventricular hemorrhage (IVH) (1.4% vs. 5.3%), and NEC (0% vs. 2.7%) were significantly lower in the 17OHP-C group than the placebo group (see Table 10). However, the incidence of severe IVH (Grades 3 or 4) was numerically higher in the 17OHP-C group (0.7% vs. 0.0%)

The incidences of the following neonatal morbidities, while not statistically different between treatment groups, were lower in the 17OHP-C group: BPD (1.4% vs. 3.3%); patent ductus arteriosus (PDA) (2.4% vs. 5.4%); other intracranial hemorrhages (0.3% vs. 1.3%); and confirmed pneumonia (1.0% vs. 2.7%).

Composite neonatal morbidity was based on the number of neonates who died or experienced RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC. The proportion of subjects who experienced the composite morbidity endpoint was numerically lower in the 17OHP-C group (11.9% vs. 17.2%), but the difference was not statistically significant.

Table 10 Neonatal Morbidity for Live Births

Morbidity	17P N=295 n (%)	Placebo N=151 n (%)	Nominal P-value [A]
Transient tachypnea	11 (3.7)	11 (7.3)	0.0990
Respiratory distress syndrome (RDS)	29 (9.9)	23 (15.3)	0.0900
Bronchopulmonary dysplasia (BPD)	4 (1.4)	5 (3.3)	0.1730
Persistent pulmonary hypertension	2 (0.7)	1 (0.7)	1.0000
Ventilator support	26 (8.9)	22 (14.8)	0.0616
Supplemental oxygen	***45 (15.4)***	***36 (24.2)***	***0.0248***
Patent ductus arteriosus	7 (2.4)	8 (5.4)	0.1004
Seizures	3 (1.0)	0	0.5541
Any intraventricular hemorrhage (IVH)	***4 (1.4)***	***8 (5.3)***	***0.0258***
Grade 3 or 4 IVH	2 (0.7)	0	0.5511
Other intracranial hemorrhage	1 (0.3)	2 (1.3)	0.2628
Retinopathy of prematurity	5 (1.7)	5 (3.3)	0.3164
Proven newborn sepsis	9 (3.1)	4 (2.6)	1.0000
Confirmed pneumonia	3 (1.0)	4 (2.7)	0.2330
Necrotizing enterocolitis (NEC)	***0***	***4 (2.7)***	***0.0127***
Composite Neonatal Morbidity Score [B]	*35 (11.9)*	*26 (17.2)*	*0.1194*

A: P-values have not been adjusted for multiple comparisons.

B: The composite neonatal morbidity measure counted any liveborn infant who experienced death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC.

Source: Table 11-8, Final Report for Study 17P-CT-002.

Division's Comments

- *The Applicant did not adjust for multiple comparisons. Had such a correction been performed, it is unlikely that any of the listed morbidities would have been statistically lower in the 17OHP-C treatment group in this clinical trial.*
- *The composite neonatal morbidity score included neonatal death and the major morbid conditions of the neonate. Although the composite neonatal morbidity score was numerically lower in the 17OHP-C treatment group (11.9% vs. 17.2%), the difference did not reach statistical significance.*

4.5.5 Summary of Division's Assessment of the Efficacy of 17OHP-C in Study 17P-CT-002

The results from this study of 463 pregnant women with a history of prior spontaneous preterm deliveries show the following:

- The frequency of preterm birth <37^0 weeks gestation was significantly decreased in the 17OHP-C treatment group compared to that in the placebo group (37.1% vs. 54.9%). The reduction in preterm birth < 37 weeks was independent of race, number of qualifying preterm births, and gestational age of the qualifying preterm birth.
- The prolongation of pregnancy, defined as the time from randomization to delivery or date last pregnant, was significantly longer, by a mean of 6 days, in the 17OHP-C group compared to the placebo group. The mean gestational age at delivery was one week greater in the 17OHP-C group compared to the placebo group (36.2 vs. 35.2 weeks).
- Use of tocolytic therapy and cerclage placement were not significantly different between the 17OHP-C and placebo groups.
- The percentage of infants weighing <2500 g was lower in the 17OHP-C group compared with the placebo group (27.2% vs. 41.1%). The percentage of infants weighing <1500 g was not statistically different between the treatment groups.
- A smaller percentage of live births in the 17OHP-C group were admitted to the NICU (27.8% vs. 36.4%).
- Neonatal mortality was numerically lower in the 17OHP-C group, but the between-group difference was not statistically significant (2.6% vs. 5.9%).
- Five miscarriages (1.6% of pregnancies) occurred in the 17OHP-C group compared to no miscarriages (0%) in the placebo group.
- The rate of stillbirths was slightly higher in the 17OHP-C (2.0% vs. 1.3%), but the difference was not statistically significant.
- Composite neonatal morbidity (neonates with death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC) was lower in the 17OHP-C group, but the between-group difference was not statistically significant (11.9 vs. 17.2).

4.6 Safety Outcomes

4.6.1 Collection of Safety Data

Studies 17P-IF-001 and 17P-CT-002 were conducted under an IND, but adverse events (AEs) were not captured in the typical manner used for studies designed to support a drug registration. Assessment of severity or relationship of AEs to study drug was not made for non-serious AEs. Adverse events that were considered serious and unexpected by the investigator were reported using the MFMU Network AE Form, which requested assessments of severity and relationship to study drug.

4.6.2 Deaths

4.6.2.1 *Maternal*

There were no maternal deaths in the trial.

4.6.2.2 Miscarriages, stillbirths, and neonatal deaths

There was a higher incidence of miscarriage and stillbirth in the 17OHP-C group (3.5% vs. 1.3%), but a lower incidence of neonatal deaths (2.6% vs. 5.9%). Neither of the between-group differences was statistically significant.

Miscarriages

Five (1.6%) subjects randomized to 17OHP-C had miscarriages, compared with no subjects randomized to placebo. Another 17OHP-C subject (Patient 004-035) had a spontaneous vaginal delivery of a nonviable fetus at 20^1 weeks gestation, which was classified as a neonatal death; the infant had 1- and 5-minute Apgar scores of 1 and died the day of delivery due to extreme prematurity.

Two of the five subjects who had miscarriages had a clinical diagnosis of chorioamnionitis at the time of the miscarriage. Patient 008-114 miscarried after her 3rd injection of 17P, at 19^1 weeks gestation. Patient 015-023 had a previous stillbirth, a previous miscarriage, and had a miscarriage on the day of her 2nd 17OHP-C injection, at 19^1 weeks gestation.

Patient 015-014 had a previous stillbirth and during this pregnancy had bacterial vaginosis prior to randomization. She received 3 injections of 17OHP-C before experiencing pPROM at 18^6 weeks gestation. She chose to terminate the pregnancy due to a poor prognosis for the infant. Although classified as an induced abortion on the AE form, the event was entered in the database as a miscarriage.

One subject, Patient 008-110, smoked a pack a day of cigarettes and used cocaine during the study pregnancy. After receiving a single injection of 17P, she experienced a miscarriage at 18^2 weeks gestation.

Only one of the five subjects who had a miscarriage had no identifiable factor that might have contributed to the miscarriage. However, prior to entering the study, this subject, Patient 004-048, had an emergency room visit for a threatened abortion at 9^4 weeks gestation. She was randomized to 17OHP-C at 17^3 weeks gestation and received her only injection of 17OHP-C on that day. Five days later, she experienced pPROM and had a spontaneous vaginal delivery of a nonviable infant.

Division's Comment

- *Although the Applicant notes that infection appears more likely to be contributory to miscarriage than does exposure to 17OHP-C, the rate of chorioamnionitis and vaginitis in placebo women (none of whom miscarried) was not significantly lower.*

Stillbirths

There were a total of 8 stillbirths, 6 occurring in the 17OHP-C group and 2 in the placebo group. The difference in incidence of stillbirths was not statistically significant (2.0% for 17OHP-C vs. 1.3% for placebo).

Two of the stillbirths, one in each treatment group, occurred intrapartum. Neither subject had a prior stillbirth. Subject 023-007 started 17OHP-C at 18^5 weeks gestation of her 4th pregnancy and received 3 injections with no AEs. She had nothing in her obstetrical history that could explain the stillbirth at 21^0 weeks gestation. Subject 008-060 started placebo at 18^4 weeks gestation. She had bacterial vaginosis prior to randomization. She received 5 injections of placebo with no AEs, and then developed preeclampsia at 23^6 weeks gestation with symptoms consistent with placental abruption and labor was induced; a stillborn fetus was delivered.

Six of the stillbirths occurred as fetal deaths in utero (5 in the 17OHP-C arm; one in the placebo arm). Three 17OHP-C subjects (008-102, 015-022, and 017-011) had bacterial vaginosis or Trichomonas vaginalis during the study pregnancy prior to randomization. Subject 014-012 in the 17OHP-C group had a clinical diagnosis of chorioamnionitis during the pregnancy. These infections may have played some role in causing the stillbirths. Subject 018-024 in the 17OHP-C group had no identifiable factor in her obstetrical history or study data that could have contributed to the stillbirth. The placebo subject, Subject 013-005, had a urinary tract infection before randomization and was a smoker (10 cigarettes/day).

Division's Comment

- *Data on second trimester miscarriage rates also are available from 4 studies reported in a meta-analysis of published studies.[28] Data in the meta-analysis publication showed a trend toward an increased risk of miscarriage in the 17OHP-C arms as compared to placebo (odds ratio of 1.30, with 95% confidence interval of 0.61 – 2.74).*
- *The results of the current clinical trial, along with the meta-analysis, demonstrated a trend toward increased second trimester miscarriage.*

Neonatal Deaths

The incidence of neonatal death was twice as high in the placebo group, with 9 deaths (5.9% of births) occurring in the placebo group, as compared to 8 in the 17OHP-C group (2.6%). This did not reach statistical significance. The gestational ages at delivery of these infants ranged from 20.3 to 28.1 weeks in the placebo group and from 20.1 to 35.1 weeks in the 17OHP-C group. The neonatal death in the 35-week delivery in the 17OHP-C group occurred in an infant delivered by emergency caesarian section following uterine rupture. Excluding this infant, the gestational age at the time of the delivery of the neonatal deaths was similar between groups.

Division's Comment

- *The similar gestational ages at delivery of the neonatal deaths in the 2 groups suggests that the gestational age-adjusted neonatal death rate would be similar for each group. This further suggests that the decreased neonatal death rate in the 17OHP-C group is attributable to a lower proportion of early preterm deliveries, rather than a difference in the condition of the delivered neonates.*

4.6.3 Congenital Anomalies

The incidence of congenital malformations was 2% in both treatment groups. The 6 cases in the 17OHP-C group included 2 congenital genitourinary anomalies (a male with obstructive defects of the renal pelvis and ureter and a female with a hydrocele of the tunica vaginalis), 2 infants with congenital cardiovascular anomalies (cardiomegaly/left ventricular diverticulum/ pericardial defect and one reported as "other anomalies of the circulatory system"), one infant with polydactyly and talipes calcaneovarus and one with congenital flat feet. The 3 cases in the placebo group were an infant with a congenital cardiovascular anomaly (stenosis and other anomalies of the circulatory system) and polydactyly, one with a congenital genitourinary anomaly (anomalies of the bladder and urethra), and one with talipes equinovarus.

Division's Comment

- *The number and type of congenital anomalies appear evenly distributed over the treatment arms. This rate of anomalies is consistent with the background rate for congenital anomalies in the general population of 2-3%.*

4.6.4 Non-Fatal Serious Adverse Event Reports

Four subjects, all of whom received 17OHP-C, had non-fatal AEs that triggered the submission of a serious unexpected adverse event report.

Patient 002-026 had a pulmonary embolus after delivery. The subject was randomized to 17OHP-C at 19^4 weeks gestation and received 17 injections of 17OHP-C before delivery. She had a labor visit between the 8^{th} and 9^{th} injections and again between the 15^{th} and 16^{th} injections of study drug. She experienced significant antepartum bleeding during the second labor visit and had a positive lupus anti-coagulant test, but continued in the study. She had no symptoms of thromboembolic events during the pregnancy. Eight days after delivery at 36^4 weeks, the subject experienced a pulmonary embolus, which was successfully treated and did not result in any sequelae.

Patient 013-021 reported a knot at the injection site on her right hip, which was very sore, after the 8th injection of 17P. She was diagnosed with cellulitis and started on penicillin. The subject requested to remain in the study and had a spontaneous PTD at 31^4 weeks gestation.

Patient 017-016 delivered a male infant at 37^5 weeks gestation with small penis and testes. An ultrasound of the scrotum revealed infarcted testicles secondary to intrauterine torsion. Human chorionic gonadotropin, congenital hypothyroidism, and follicle stimulating hormone, and chromosome testing were done and found to be normal. The infant was diagnosed as possibly having hypogonadism.

Patient 014-012 had a stillbirth at 21^1 weeks gestation, and developed postpartum hemorrhage and respiratory distress after delivery. The subject was intubated and given multiple transfusions of red blood cells before being discharged to specialty care. The subject continued on antibiotics for endometritis and excessive surgical manipulation.

Division's Comment:

- *A causal association of these 4 maternal serious AEs with exposure to 17OHP-C is unlikely.*

4.6.5 Common Adverse Events

The most common AEs in both treatment groups were injection site reactions, reported by 42.3% of 17OHP-C subjects and 38.6% of placebo subjects. The types of injection site reactions did not differ between the treatment groups, except for injection site swelling, which occurred with a significantly greater incidence in the 17OHP-C group compared with the placebo group (17.1% vs. 7.8%). Adverse events by preferred terms that occurred in >2% of subjects in either treatment group are shown in Table 11.

Table 11 Adverse Events that Occurred in >2% of Subjects in either Treatment Group

Preferred Term [A]	17P N=310 n (%)	Placebo N=153 n (%)
Injection site pain	108 (34.8)	50 (32.7)
Injection site swelling [B]	53 (17.1)	12 (7.8)
Urticaria	38 (12.3)	17 (11.1)
Pruritus	24 (7.7)	9 (5.9)
Injection site pruritus	18 (5.8)	5 (3.3)
Nausea	18 (5.8)	7 (4.6)
Contusion	17 (5.5)	14 (9.2)
Injection site nodule	14 (4.5)	3 (2.0)
Vomiting	10 (3.2)	5 (3.3)
Death [C, D]	8 (2.6)	9 (5.9)
Anorexia	5 (1.6)	6 (3.9)
Injection site irritation	4 (1.3)	5 (3.3)
Abdominal pain	3 (1.0)	4 (2.6)

[A] Patients reporting a particular AE more than once were counted only once for that AE. AEs were coded using MedDRA Version 8.0.

[B] Incidence in 17OHP-C group was significantly higher (p>0.05) than placebo group, based on a chi-square test.

[C] Death included only neonatal deaths.

[D] For safety assessments, the incidence of neonatal death was based on all randomized patients, so the percentages are slightly lower than those reported for the efficacy assessment based on liveborn infants.

Source: Table 12-2, Final Report for Study 17-CT-002.

Infections were not recorded as AEs during the study, but were captured indirectly if they resulted in antibiotic use. The incidence of any vaginal/cervical infection was greater in the 17OHP-C group (21.6%) as compared to the placebo group (15%). Incidences in the 17OHP-C and placebo groups, respectively, of bacterial vaginosis (8.7% vs. 5.2%) and trichomonas (3.9% vs. 1.3%) did not differ significantly.

4.6.6 Adverse Events That Led to Discontinuation of Study Drug

The rate of early discontinuations from treatment with study drug due to AEs was comparable in the 2 treatment groups and the AEs leading to discontinuation were not notably different. Seven (2.2%) subjects in the 17OHP-C group and four (2.6%) subjects in the placebo group either discontinued or were withdrawn by the investigator from study drug due to AEs.

The principal AEs that led to discontinuation from treatment in the 17OHP-C and placebo groups are listed by subject in Table 12:

Table 12 Adverse Events Leading to Treatment Discontinuation (Study 17P-CT-002)

Patient ID	Treatment Group	Adverse Event	Gestational Age at Discontinuation
002-024	17OHP-C	Urticaria	23.3 weeks
004-018	17OHP-C	Soreness at injection site	23.3 weeks
008-055	placebo	Pruritus (head to toe)	20.1 weeks
011-027	17OHP-C	Arthralgia/Severe Joint Pain	19.6 weeks
015-033	placebo	Swelling at injection site/Pruritus	30.6 weeks
018-018	placebo	Urticaria	26.1 weeks
019-015	17OHP-C	Urticaria	31.1 weeks
020-026	17OHP-C	Weight Gain	26.3 weeks
020-044	17OHP-C	Urticaria	24.3 weeks
020-060	17OHP-C	Red welt at injection site	20.5 weeks
025-001	placebo	Pruritus	34.3 weeks

Source: Section 16.2, Listing 7.5, Final Report for Study 17P-CT-002

Another subject in the 17OHP-C group was listed as being withdrawn early by the investigator due to pPROM, which was not considered an AE in this study. Four subjects in the 17OHP-C group were lost to follow up, and one of these 4 subjects reported swelling at the injection site at the last 2 visits before being lost to follow up. The other 3 subjects who were lost to follow up had no AEs reported.

A placebo subject was also withdrawn early by the investigator due to pPROM.

Twenty-eight other subjects discontinued study drug early due to non-clinical reasons: 19 in the 17OHP-C group and 9 in the placebo group. No other information was provided on the CRF as to why the subject discontinued. Of the 19 subjects in the 17OHP-C group, 12 had no recorded AEs. Of the remaining 7 subjects, 4 had AEs within 2 visits of discontinuation, and therefore, without additional information as to the reason for discontinuation, the role of an AE in the decision to discontinue can not be excluded. The AEs reported by these subjects prior to discontinuation were injection site reactions (n=3) and diarrhea, vomiting, and loss of appetite (n=1 for each).

Of the 9 subjects in the placebo group who discontinued for non-clinical reasons, 6 had no recorded AEs. Of the remaining 3 subjects, one subject reported itching (pruritus) at the time of discontinuation.

Division's Comment:

- *The Applicant computed a worst-case scenario by adding the five 17OHP-C subjects and the one placebo subject who experienced AEs shortly before discontinuation/loss to follow-up to the group of subjects who discontinued due to AEs. By this conservative estimate of the incidence of discontinuation due to AEs, the incidence is still similar between the treatment groups (3.9% vs. 3.3%).*
- *The majority of AEs that clearly or possibly led to early discontinuation were injection site reactions, which occurred with both 17OHP-C and placebo. Two subjects, one in each treatment group, had possible allergic reactions, which have been reported previously for 17OHP-C.*

4.6.7 Pregnancy Complications and Maternal Outcomes

The incidence of maternal pregnancy complications (gestational diabetes, oligohydramnios, significant antepartum bleeding, preeclampsia/gestational hypertension, abruption, confirmed clinical diagnosis of chorioamnionitis, or cerclage placement) did not differ between the treatment groups (Table 13). The most common pregnancy complications (>5% of subjects in either treatment group) were preeclampsia or gestational hypertension (8.8% vs. 4.6%) and gestational diabetes (5.6% vs. 4.6%).

Overall, 70 subjects were admitted for preterm labor (PTL), other than the delivery admission, with similar rates in the 2 treatment groups: 16.0% of 17OHP-C subjects and 13.8% of placebo subjects. The mean length of hospital stay for the mothers was not different between the treatment groups (3.1 vs. 3.7 days).

Table 13 Pregnancy Complications

Complication or Outcome	17P N=306 n (%)	Placebo N=152 n (%)
Hospital or labor/delivery admission for PTL (other than the delivery admission)	49 (16.0)	21 (13.8)
Gestational diabetes	17 (5.6)	7 (4.6)
Oligohydramnios	11 (3.6)	2 (1.3)
Significant antepartum bleeding	6 (2.0)	3 (2.0)
Preeclampsia or gestational hypertension	27 (8.8)	7 (4.6)
Abruption	5 (1.6)	4 (2.6)
Confirmed clinical chorioamnionitis	11 (3.6)	5 (3.3)
Cerclage placement	5 (1.6)	2 (1.3)
Other complication	8 (2.7)	5 (3.3)

Source: Table 12-3 Final Report for Study 17-CT-002.

4.6.8 Laboratory Findings

No blood samples for routine laboratory tests were collected.

4.6.9 Summary of Overall Safety

This study exposed 310 pregnant women to 17OHP-C, with an average of 14.1 injections, compared with 153 pregnant women who received an average of 13.7 injections of placebo. Comparing the safety profile in each group:

- No maternal deaths occurred in either treatment arm.
- The frequency of both miscarriage and stillbirth was higher in the 17OHP-C group, although not statistically significantly different.
- The incidence of neonatal death, also not statistically significantly different between the 2 treatment arms, occurred at more than twice the rate in the placebo group.
- The incidence of congenital malformations was consistent with the normal background rate of 2% in both treatment groups, and the types of anomalies were similar.

- Twenty-nine (9.4%) subjects or their infants in the 17OHP-C group and 15 (9.8%) subjects or their infants in the placebo group experienced at least one serious or unexpected AE. The most common serious AE was fetal or neonatal death (miscarriages, stillbirths, and neonatal deaths). Maternal serious AEs occurred in four 17OHP-C subjects, but were not clearly related to study drug exposure.
- The overall incidence of AEs, including the most common AE (injection site reaction) was similar in the 17OHP-C and the placebo groups. The incidence of injection site swelling was significantly higher in the 17OHP-C group than the placebo group. All other injection site reactions occurred at comparable rates in the treatment groups.
- Early discontinuations due to AEs occurred at a comparable rate in the 17OHP-C and placebo groups, and were most often associated with injection site reactions.
- The incidence of pregnancy complications and the mean length of hospital stay for mothers did not differ between the 2 treatment groups.

5 SUPPORTIVE CLINICAL TRIAL

Study 17P-IF-001: "A Randomized Trial of 17α-Hydroxyprogesterone Caproate (Initial Formulation) for Prevention of Preterm Birth in High Risk Women"

5.1 Background

This study was designed and initiated in 1998 by the NICHD MFMU Network to evaluate the use of 17OHP-C for the prevention of recurrent preterm births. In February 1999, the manufacturer of study drug issued a recall, at the request of the Food and Drug Administration (FDA), because of violations of manufacturing practices that may have jeopardized the validity and potency of the product. On March 15, 1999, the study was terminated. At the time of study termination, only 150 of the proposed 500 subjects had been enrolled into the study. Eighty-six subjects completed the treatment regimen before the study was stopped (57 [61%] of the 17OHP-C subjects and 29 [52%] of the placebo subjects). The study was freshly started at a later date as Study 17P-CT-002 (see Section 4) when a new manufacturer was identified.

5.2 Overall Study Design

The study design for Study 17P-IF-001 was identical to that of Study 17P-CT-002 and is described in detail in Section 4.3. Briefly, the study was a randomized, placebo-controlled, efficacy and safety study of 17OHP-C in pregnant women, beginning at 16^0 to 20^6 weeks gestation, who had a history of spontaneous preterm birth, defined as delivery from 20^0 to 36^6 weeks gestation following spontaneous PTL or pPROM.

Qualifying subjects were randomized in a 2:1 ratio to 17OHP-C or placebo (castor oil with 46% benzyl benzoate and 2% benzyl alcohol). Study drug was administered weekly by intramuscular injection through 36^6 weeks gestation or delivery, whichever occurred first. The primary efficacy outcome was birth prior to 37^0 weeks (as determined by the gestational age established during the study).

5.3 Findings

5.3.1 Subject disposition

A total of 150 subjects were randomized, 94 to 17OHP-C and 56 to placebo. Sixty-five subjects randomized to 17OHP-C and 39 subjects randomized to placebo either completed treatment with study drugs or were withdrawn prematurely because of reasons other than recall of study drugs. Fifty-seven (61%) of subjects in the 17OHP-C group and 29 (52%) in the placebo group completed treatment through 36^6 weeks or delivery.

Among the subjects not impacted by recall of study drug, the reasons for not completing treatment in the 17OHP-C group (other than for recall of study drug) were adverse event (n = 1), withdrawal for non-clinical reasons (n = 6), and lost to follow up (n = 1). The reasons for not completing treatment in the placebo group (other than for recall of study drug) were adverse event (n = 2), withdrawal for non-clinical reasons (n = 6), and lost to follow up (n = 2).

5.3.2 Efficacy Findings

5.3.2.1 Primary Efficacy Endpoint

The incidence of delivery $<37^0$ weeks gestation for the ITT population, the population for which data were available (all subjects other than those lost to follow up) and those subjects whose participation was not prematurely terminated because of recall of study drug are listed in Table 14. For each analysis population, the percentage of subjects with a delivery of $<37^0$ weeks gestation was numerically higher in the 17OHP-C treatment group. None of the differences were statistically different.

Table 14 Percentage of Subjects with Delivery $<37^0$ Weeks Gestation

Analysis Population	17P		Placebo	
	N	n (%)	N	n (%)
ITT population	94	39 (41.5)	56	20 (35.7)
All available data	93	38 (40.9)	54	18 (33.3)
Not withdrawn due to study termination	**65**	**28 (43.1)**	**39**	**15 (38.5)**

ITT population was all randomized subjects. Subjects with missing outcome data were classified as having a preterm birth $<37^0$ weeks (treatment failure).

Source: Table 9-3, pg 21, abbreviated Final Report for Study 17P-IF-001.

Division's Comment

- *The data obtained from the analysis population identified as "not withdrawn due to study termination" is of most value since all subjects in this population had the opportunity to complete a full course of treatment. However, because the potency and overall quality of the study drugs could not be assured, the efficacy data obtained from this prematurely terminated clinical trial is of limited value and must be interpreted with caution. The findings from this trial do not suggest any benefit of 17OHP-C (at the uncertain dose that was administered) in reducing the percentage of subjects with a delivery $<37^0$ weeks gestation.*

- *In the "not withdrawn due to study termination" analysis population, the percentage of subjects with a delivery <37^0 weeks gestation was 38.5% in the placebo group. This rate of premature birth is close to that which the NIH used in their sample size calculations for both this study and study 17P-CT-002. This rate also is close to rates for high risk subjects reported in the literature. The percentage of subjects with a delivery <37^0 weeks gestation in the placebo group of Study 17P-CT-002, however, was considerably higher — 54.9%. The difference in the rates of premature birth in the placebo arms of the 2 clinical trials (38.5% vs. 54.9%) is surprising since both studies were conducted at the same clinical sites in close temporal proximity.*

5.3.2.2 Secondary Efficacy Outcomes

Miscarriages, Stillbirths, and Neonatal Deaths

The number and percentages of miscarriages, stillbirths, and neonatal deaths in the ITT population are listed by treatment group in Table 15.

Table 15 Number of Miscarriages, Stillbirths, and Neonatal Deaths

Fetal/Neonatal Deaths	17P N=93	Placebo N=54
Miscarriages	1 (1.1)	1 (1.9)
Stillbirths	1 (1.1)	2 (3.7)
Neonatal deaths	2 (2.2)	0
Total	**4 (4.4)**	**3 (5.9)**

Source: Table 9-8, pg 28, abbreviated Final Report for Study 17P-IF-001.

Division's Comment

- *Although this study did not demonstrate any overall benefit for treatment with 17OHP-C in terms of reduction in overall mortality, there was no trend toward an increased rate of miscarriages in the 17OHP-C group as was seen in Study 17P-CT-002.*

5.3.3 Safety Findings

5.3.3.1 Deaths and Discontinuations because of Adverse Events

There were no maternal deaths. Four subjects, 2 in the 17OHP-C group and 2 in the placebo group, discontinued study drug early due to AEs. One 17OHP-C subject discontinued after the first injection due to an injection site rash, and the other 17OHP-C subject discontinued after the ninth 17OHP-C injection due to urticaria, swelling, and redness at the injection site. One placebo subject discontinued after the first injection due to vomiting, urticaria, and facial swelling and the other placebo subject discontinued after the seventh injection due to urticaria.

5.3.3.2 Common Adverse Events

Of the 150 subjects, 92 (61.3%) reported 368 AEs during the study; 60 (63.8%) subjects in the 17OHP-C group reported 237 AEs, and 32 (57.1%) subjects in the placebo group reported 131 AEs. The most commonly reported AEs were injection site reactions, which occurred at a comparable rate in the 2 treatment groups (52.1% in 17OHP-C vs. 46.4% in the placebo group). Adverse events that occurred in >2% of subjects in either treatment group are shown in Table 16 by preferred terms in descending order of incidence in the 17OHP-C group.

Table 16 Adverse Events that Occurred in >2% of Subjects in a Treatment Group

Preferred Term	17OHP-C N=94 n (%)	Placebo N=56 n (%)
Injection site pain	41 (43.6)	24 (42.9)
Injection site swelling	15 (16.0)	6 (10.7)
Urticaria	13 (13.8)	7 (12.5)
Contusion	9 (9.6)	6 (10.7)
Injection site pruritus	7 (7.4)	5 (8.9)
Pruritus	4 (4.3)	2 (3.6)
Injection site nodule	3 (3.2)	4 (7.1)
Abdominal pain	3 (3.2)	2 (3.6)
Nausea	2 (2.1)	1 (1.8)
Injections site erythema	2 (2.1)	0
Edema	2 (2.1)	0
Diarrhea	2 (2.1)	0
Death (neonatal)	2 (2.1)	0
Stillbirth	1 (1.1)	2 (3.6)
Dizziness	0	2 (3.6)

Source: Table 19-2, pg 34, abbreviated Final Report for Study 17P-IF-001.

5.3.3.3 Pregnancy Complications

The most common pregnancy complications in the 17OHP-C group (other than admission for preterm labor not related to the delivery admission) were gestational diabetes (8.6% 17OHP-C vs. 0% placebo) and preeclampsia or gestational hypertension (6.5% 17OHP-C vs. 3.8% placebo) (see Table 17). There was almost double the rate of hospitalization for preterm labor (other than the delivery admission) in the placebo group as compared to the 17OHP-C group.

Table 17 Pregnancy Complications

Complication	17OHP-C N=93 n (%)	Placebo N=53 n (%)
Hospital or labor/delivery admission for preterm labor (other than the delivery admission)	10 (10.8)	11 (20.8)
Gestational diabetes	8 (8.6)	0
Oligohydramnios	2 (2.2)	1 (1.9)
Significant antepartum bleeding	4 4.3)	4 (7.5)
Preeclampsia or gestational hypertension	6 (6.5)	2 (3.8)
Abruption	2 (2.2)	2 (3.8)
Confirmed clinical chorioamnionitis	2 (2.2)	0
Cerclage placement	0	1 (1.9)
Other complication	2 (2.2)	1 (2.0)

Source: Table 10-1, pg 38, abbreviated Final Report for Study 17P-IF-001.

Division's Comment

Comparing the safety profile in each group:

- No maternal deaths occurred in either treatment arm.
- The frequency of miscarriage, stillbirth, and neonatal death was not different in the 2 arms.
- The overall incidence of AEs, including the most common AE (injection site reaction) was similar in the 17OHP-C and the placebo groups. The incidence of injection site swelling was numerically higher in the 17OHP-C group than the placebo group. All other injection site reactions occurred at comparable rates in the treatment groups.
- Early discontinuations due to AEs occurred at a comparable rate in the 17OHP-C and placebo groups, and were most often associated with injection site reactions.
- The incidence of pregnancy complications was not different between the 2 treatment groups.
- The rate of admission for preterm labor, aside from the delivery hospitalization, was greater in the placebo group.

6 STUDY 17P-FU (FOLLOW-UP SAFETY STUDY)

6.1 Description of the Protocol

Infants born to women enrolled in Study 17P-CT-002, and who survived to be discharged from the nursery, were eligible for participation in the follow-up study, known as Study 17P-FU.

Instruments and Procedures

Assessment of the children's longer-term outcomes was performed using the following instruments and procedures:

- The primary endpoint was determined based upon the Ages and Stages Questionnaire (ASQ), completed by the parent or guardian
- Secondary endpoints were based upon items evaluated through use of
  - A Survey Questionnaire, administered by study personnel to the parent
  - Physical examination by a study pediatrician

The ASQ is composed of 19 questionnaires, each corresponding to a specific age window between 4 months and 5 years, and each containing 30 developmental items addressing five areas: communication, gross motor, fine motor, problem solving, and personal-social. The instrument was developed on a population including both children considered to be at risk for developmental problems and a normative sample of full term children with no health or developmental concerns. It has been validated against common professional assessment scales, including the Bayley Scales of Infant Development and the McCarthy Scales of Children's Abilities. The questionnaires are designed to identify young children who are in need of further evaluation and early intervention services. Cutoff points, generally corresponding to scores falling 2 standard deviations (SD) below the mean for the combined "at risk" and normal population, were generated for each of the five developmental domains assessed.

The Survey Questionnaire used in this study was derived from questions that were developed and reportedly validated by the following sources: the 2001 Child Health Supplement of the National Health Interview Survey, the 1991 National Maternal and Infant Health Survey, Early Childhood Longitudinal Survey (Department of Education), and the Avon Longitudinal Study of Parents and Children. This questionnaire was not formatted for self-administration; therefore it was administered by study personnel during the clinic visit. The Survey Questionnaire included evaluation of:

- Overall activity level and motor control, compared to age mates of the child, as measured by questions from the Early Childhood Longitudinal Study, Kindergarten (ECLSK), answered by the parent. If a perceived problem was reported by the parent, further questioning determined whether a professional evaluation and diagnosis had been made.
- Vision or hearing problems, assessed by questions from the National Health Interview Survey (NHIS), answered by the parent.
- Assessment of height, weight and head circumference, compared to reference curves generated by the Centers for Disease Control (CDC).
- Gender-specific behavior, assessed by the Pre-School Activities Inventory (PSAI).
- Diagnosis by a healthcare provider of cerebral palsy, asthma, allergic disorders, sensory disorders and neurodevelopmental disorders including attention deficit hyperactivity disorder (ADHD).

Division's Comment

- *Although the ECLSK was developed for use with children from kindergarten to fifth grade, the motor control and activity questions were reviewed by an NICHD* *developmental psychologist, who reportedly determined that they were appropriate for children as young as 2. The basis for this conclusion was not provided.*

A general physical examination was conducted by a pediatrician or nurse practitioner at the study center, and included measurements of the child's current weight, height, head circumference, and blood pressure, as well as the documentation of any major abnormality. In addition, a part of the examination was specifically directed toward the identification of genital abnormalities. If the child had a physical examination within the last year, and the parent/guardian was unable to bring the child in for a visit, the information from that previous physical examination was entered into the study database. In these cases, the medical record of the child was abstracted by an NICHD pediatrician.

Following IRB approval, MFMU Network study personnel attempted to locate the women who participated in Study 17P-CT-002. If the mother who was enrolled in Study 17P-CT-002 could not be found, but her child could be located, the child's father or guardian could enroll the child in this study.

The nurse used a standardized script to request consent to participate. If the parent was willing to allow the child to participate, the nurse obtained informed consent by mail. She also made arrangements for the child to visit the Network center accompanied by the parent. In addition, the ASQ was mailed to the parent with instructions to bring the completed form to the visit. If the parent was unable to attend a follow-up visit, the research nurse administered the Survey Questionnaire by telephone, and asked the parent to mail back the completed ASQ.

The following procedures were conducted at the study visit:

- Administration of the Survey Questionnaire
- Physical examination
- Completion of the ASQ, if not done prior to the study visit

Parents were instructed to complete the ASQ based on the age of the child at the follow-up visit. The ASQ recommends using gestational age-corrected age only until 24 months and since all children to be evaluated were at least 2 years of age, corrected age was not used in this study. The completed ASQ was scored by the Biostatistical Coordinating Center (BCC) and results were sent back to the study nurse. If a child fell below a pre-established cutoff (below 2 SD from the mean) in at least one of the five developmental domains on the ASQ, the study nurse was to inform the parent/guardian that the child might need additional evaluation in the particular developmental area.

At the time of enrollment in Study 17P-FU, some of the mothers had already been informed of their treatment assignment in Study 17P-CT-002. If they had not, the treatment group was not revealed before the follow-up assessments. Less than 10% of the mothers were informed of their treatment (8.3% in the 17OHP-C group and 7.1% in the placebo group). The physicians or nurse-practitioners who performed the physical examinations were blinded to the treatment group assignment of the mother.

6.2 Inclusion/Exclusion Criteria

Inclusion Criteria

1. Maternal enrollment in the Study 17P-CT-002 conducted at one of the 14 Network centers in the fourth MFMU Network cycle (2001-present). As the composition of the MFMU changes over time, only women initially enrolled at a site that remained in the Network were eligible for the follow-up study.
2. Infant discharged alive from birth hospitalization.

Exclusion Criteria
No exclusion criteria were defined in the protocol.

6.3 Primary and Secondary Endpoints

The primary objective of the study was to determine if there were differences in achievement of developmental milestones between children whose mothers received 17OHP-C and those who received placebo in Study 17P-CT-002, as measured by the ASQ. The primary endpoint was the proportion of children from each treatment arm who fell below a specified cut-off on <u>at least one</u> of the five developmental areas measured on the ASQ.

The secondary objectives of the study were to determine if differences existed between children whose mothers received 17OHP-C and those who received placebo in Study 17P-CT-002 in the following factors:

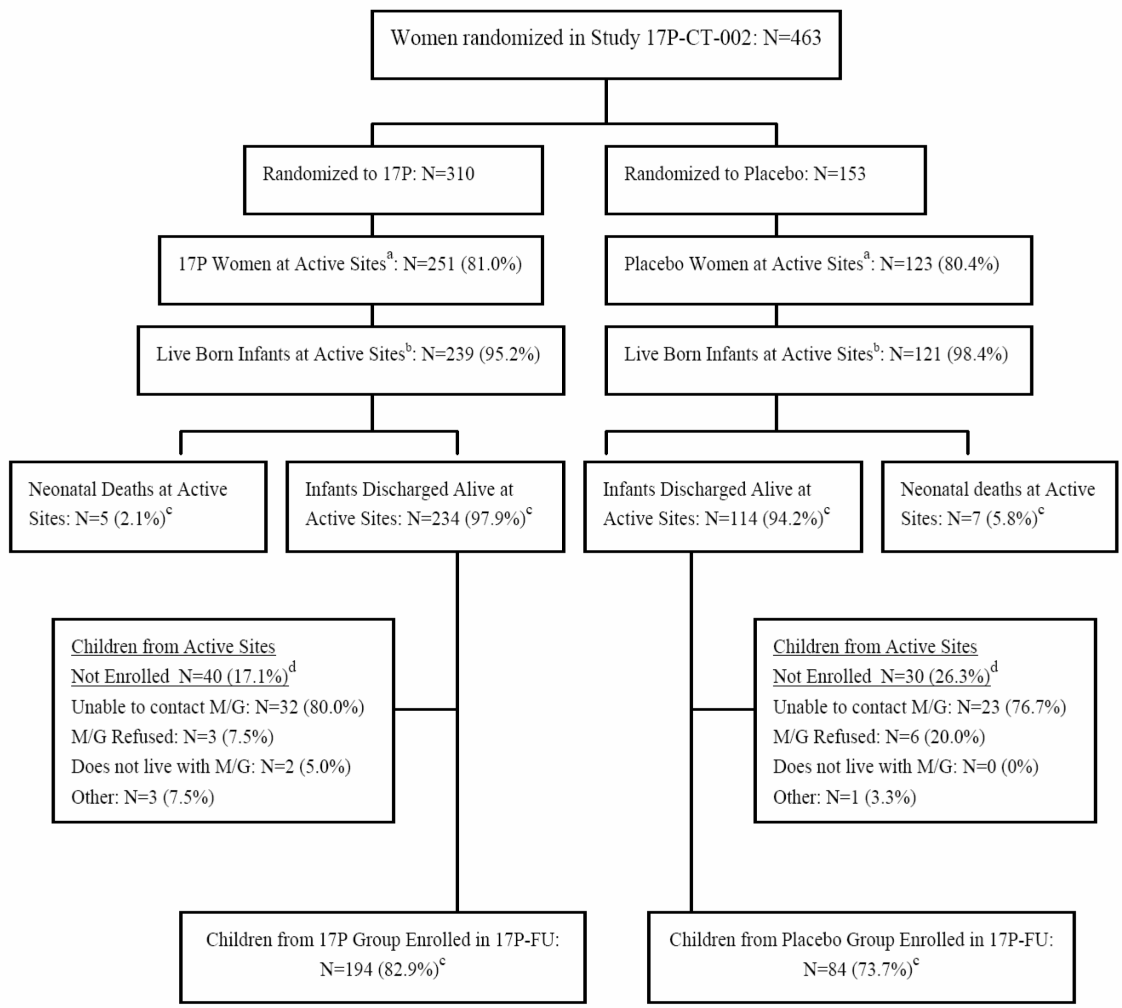
- Gender-specific play
- Physical growth (height and weight)
- Activity levels
- Motor control
- Vision or hearing difficulties
- Physician- or other health provider-diagnosed conditions, such as asthma, allergic disorders, sensory disorders, and neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD), as reported on the Survey Questionnaire

6.4 Subject Disposition

Figure 3 shows the disposition of infants born alive to mothers in Study 17P-CT-002. A total of 463 women were randomized to study drug; 310 women received 17OHP-C and 153 women received placebo. Of those women, a total of 374 women (251 [81.0%] of the 17OHP-C women and 123 [80.4%] of the placebo women) were enrolled at one of the 14 study sites still active in the MFMU Network at the start of this follow-up study. These women had a total of 360 live born infants, representing 74% of the 446 live births in Study 17P-CT-002. Twelve infants from the active sites died before discharge from the birth hospitalization, five (2.1%) of the 239 in the 17OHP-C group and seven (5.8%) of the 121 in the placebo group. There were no deaths following discharge from the nursery in children from the subset of mothers who were able to be located.

Of 348 eligible children, 278 (79.9%) were enrolled in Study 17P-FU. The percentage of eligible children who were enrolled in Study 17P-FU was greater in the 17OHP-C group (82.9% of the 17OHP-C-exposed vs. 73.7% of placebo-exposed). Inability to contact the parent was the primary reason children were not enrolled. A greater proportion of placebo-treated mothers refused to allow their child to participate (5% of eligible placebo mothers vs. 1% of 17OHP-C-treated mothers).

Figure 3 Disposition of Subjects in Follow Up Study 17P-FU



Abbreviations: M/G = mother/guardian

[a] An active study site was a clinical center participating in the MFMU Network at the time Study 17P-FU was conducted.

[b] Percentages were based on the number of patients from active study sites.

[c] Percentages were based on the number of live born infants in Study 17P-CT-002 from active study sites.

[d] Percentages were based on the number of live born infants in Study 17P-CT-002 discharged from birth hospitalization from active study sites.

Source: Section 10.1, Figure 10-1, Final Report for Study 17P-FU.

6.5 Demographics and Other Baseline Characteristics

6.5.1 Demographics

The children ranged in age from 30 to 64 months at the time of enrollment. The mean age was similar for the 2 treatment groups (47.2 months for 17OHP-C vs. 48.0 months for the placebo group), as was the distribution across the race/ethnic groups, which was assigned based on the mother's race or ethnicity. The majority of children were of African American descent (54.1% in the 17OHP-C group and 56.0% in the placebo), with children of Hispanic descent comprising 14.9% (17OHP-C) to 17.9% (placebo). Approximately one-fourth of the children were Caucasian. The 17OHP-C group had 58.3% male children compared with 47.6% in the placebo group.

6.5.2 Neonatal Outcomes of Enrolled Children

The neonatal outcomes of the enrolled children are listed in Table 18.

The gestational age at delivery ranged from 25.0 to 41.9 weeks, with a mean gestational age of 37.3 weeks in the 17OHP-C group and 36.2 weeks in the placebo group. This was slightly greater than the mean gestational ages observed in the total population in Study 17P-CT-002 (36.2 weeks for 17OHP-C vs. 35.2 for placebo).

Birthweight ranged from 714 - 4900 g in the 17OHP-C group and 615 - 4855 g in the placebo group. The 17OHP-C group had a lower percentage of infants with birthweight <2500 g (21.8% vs. 34.5%) and <1500 g (4.7% vs. 8.3%). The mean and range of APGAR scores were comparable between the 2 treatment groups.

Table 18 Neonatal Outcomes of Enrolled Children

Characteristic	17OHP-C	Placebo
Gestational age at delivery (wks)	N=194	N=84
Mean (SD)	37.3 (3.2)	36.2 (3.7)
Min, Max	25.0, 41.7	25.1, 41.9
Birthweight (g)	N=193	N=84
Mean (SD)	2,914 (707.8)	2,756.7 (813.7)
Min, Max	714, 4900	615, 4855
Birthweight <2500 g, n (%)	42 (21.8)	29 (34.5)
Birthweight <1500 g, n (%)	9 (4.7)	7 (8.3)
Head Circumference (cm)	N=188	N=82
Mean (SD)	32.8 (2.5)	32.2 (3.2)
Min, Max	23.0, 37.5	21.5, 38.0
1 Minute APGAR	N=191	N=84
Mean (SD)	7.8 (1.6)	7.6 (1.7)
Min, Max	1.0, 9.0	1.0, 9.0
APGAR <3, n (%)	5 (2.6%)	3 (3.6)
5 Minute APGAR	N=192	N=84
Mean (SD)	8.7 (0.8)	8.7 (0.9)
Min, Max	3.0, 10.0	3.0, 9.0
APGAR <3, n (%)	0	0

Source: Table 11-2 Final Report for Study 17P-FU.

The incidence of preterm births in the follow-up population is summarized in Table 19. At each of gestational ages <37^0, <35^0, and <32^0, the percentage of infants in the 17OHP-C treatment groups was numerically lower than that in the placebo group.

Table 19 Pregnancy Outcomes in the follow up Population

Pregnancy Outcome (Weeks Gestation)	17OHP-C N=194 Per cent	Placebo N=84 Per cent
Delivery <37^0	30.4%	52.4%
Delivery <35^0	14.9%	25.0%
Delivery <32^0	7.2%	13.1%

Source: Table 11-2 Final Report for Study 17P-FU.

Division's Comment

- *The 17OHP-C children in the follow-up study may represent a slightly lower risk subset of the total population, as their mean gestational age was one week greater than the total cohort of 17OHP-C children, and they were also more likely to have attained greater gestational age and birthweight than their placebo-exposed peers in the follow-up study.*

6.5.3 Neonatal Morbidity of Enrolled Children

The neonatal morbidities reported at birth for the children enrolled in this study are summarized in Table 20. All occurred with equal or greater frequency in the placebo group as compared to the 17OHP-C group. The differences between the 17OHP-C and placebo groups in the follow-up study were not analyzed statistically. The largest between-group differences (≥4 percentage points) were observed in the incidence of any IVH (1.6% vs. 6.0%) and use of supplemental oxygen (15.5% vs. 21.4%), which were neonatal morbidities that were also lower in the 17OHP-C group in the total population in Study 17P-CT-002.

Table 20 Percentage of Enrolled Neonates Experiencing Morbidities

Morbidity	17OHP-C N=193 (%)	Placebo N=84 (%)
Transient tachypnea	5.2	8.3
Respiratory distress syndrome	9.3	10.7
Bronchopulmonary dysplasia	1.6	3.6
Persistent pulmonary hypertension	0	0
Ventilator support	8.3	10.7
Supplemental oxygen	15.5	21.4
Patent ductus arteriosus	3.1	3.6
Seizures	0	0
Any intraventricular hemorrhage (IVH)	1.6	6.0
Grade 3 or 4 IVH	0.5	0
Other intracranial hemorrhage	0	1.2
Retinopathy of prematurity	2.1	3.6
Proven newborn sepsis	2.1	2.4
Confirmed pneumonia	1.0	2.4
Necrotizing enterocolitis	0	1.2

Source: Table 11-3, Final Report for Study 17P-FU.

The mean and median duration of respiratory therapy for the infants enrolled in the follow-up study were 1.5 and 0.0 days (range: 0.0, 74.0 days) for infants in the 17OHP-C group and 1.9 and 0.0 days (range: 0.0, 44.0 days) for infants in the placebo group.

6.6 Safety Outcomes

Safety assessments were collected via the ASQ, the Survey Questionnaire, and the physical examination. On the Survey Questionnaire, the parent was asked to report any medical diagnosis or operations that occurred between discharge from the birth hospitalization and the time the questionnaire was completed. During the physical examination, the physician was to document any medical abnormality.

Missing data on the ASQ were imputed with the mean of the scores for other items in the same developmental area, as long as ≤ 2 items were missing. If > 2 items were missing, that developmental area was considered missing, and the primary outcome was determined based on the remaining areas. On the PSAI, missing items were imputed with the mean score for that item from the entire sample of same-gender children. If >2 items were missing, the questionnaire was not used. No imputation of missing data was done for other items.

6.6.1 Primary Outcome: Findings from Age and Stages Questionnaire (ASQ)

The ASQ was completed for 275 children, 193 from the 17OHP-C group and 82 from the placebo group. The age of the children at the time of completion of the ASQ ranged from 30 to 64 months; mean age at time of completion did not differ between the 17OHP-C and placebo groups (47.2 vs. 48.0 months). (See Table 21)

Table 21 ASQ – Age of Child at Completion, Source of Information, and Where Completed

	17P N=193[A] n (%)	Placebo N=82[A] n (%)
Age ASQ Completed (months)		
30	1 (0.5)	0
33	9 (4.7)	3 (3.7)
36	30 (15.5)	8 (9.8)
42	49 (25.4)	25 (30.5)
48	32 (16.6)	12 (14.6)
54	38 (19.7)	17 (20.7)
60	34 (17.6)	17 (20.7)
Mean (SD)	47.2 (8.6)	48.0 (8.4)
Median	47.1	48.2
Min, Max	30.2, 63.9	33.5, 64.3
Who Completed Majority of ASQ		
Mother	114 (59.1)	53 (64.6)
Father	2 (1.0)	4 (4.9)
Grandparent	2 (1.0)	0
Foster Parent	1 (0.5)	0
Guardian	2 (1.0)	0
Study Nurse	72 (37.3)	25 (30.5)
Where ASQ Completed		
Home	84 (43.5)	40 (48.8)
Clinical Center	94 (48.7)	34 (41.5)
Home and Clinical Center	15 (7.8)	8 (9.8)

[A] Number of children with ASQ data.
Source: Section 12.3.1, Table 12-1 Final Study 17P-FU-Report

Division Comment

- *At the time that the ASQ was completed, the children in 17OHP-C group tended to be slightly younger, with 21% ≤ 3 years of age, as compared to 14% of placebo children. This might have affected the ability to diagnosis certain developmental problems that may present more noticeably in older children.*

The ASQ was completed predominately by the mother (59.1% 17OHP-C vs. 64.6% placebo) or the study nurse (37.3% vs. 30.5%), and was equally likely to be completed in the home as in the clinical center.

The ASQ responses were categorized to assess communication, gross motor, fine motor, problem solving, and personal-social. Using threshold scores (cutoffs) for normal development, the percentages of children who had scores below the cutoffs for the five areas of development were determined.

Table 22 shows the percentage of children in each treatment group whose ASQ scores suggested developmental problems in at least one of each of the five areas. As the cutoff for identifying a child as needing further developmental evaluation is based, according to the Applicant, on the mean for a normal population, the ASQ would be expected to identify about 20% of "at risk" children evaluated as possibly delayed. The percentage of children who scored below the cutoff in at least one developmental domain was comparable (27.5% in the 17OHP-C group and 28.0% in the placebo group [p=0.9206]).

The proportion of children below the cutoff in each developmental domain was similar for each treatment group. The area with the highest percentage of children with low scores was fine motor skills, with approximately one in five children scoring below the cutoff (20.7% in the 17OHP-C group vs. 18.3% in the control group). Approximately one in ten children had scores below the cutoff in communication and/or problem solving. Few children had low scores for gross motor and personal-social skills.

Table 22 Percentages of Children in Each Treatment Group Whose ASQ Scores Suggested Developmental Problems

	17OHP-C N=193		Placebo N=82	
	n	%	n	%
Occurrence of score <cutoff on at least one developmental area	53	27.5	23	28.0
Area of Development				
Communication	22	11.4	9	11.0
Gross Motor	5	2.6	3	3.7
Fine Motor	40	20.7	15	18.3
Problem Solving	20	10.4	9	11.0
Personal-Social	7	3.6	1	1.2

Source: Table 12-2, Final Report for Study 17P-FU.

Division's Comment

- *The placebo-exposed children had a greater frequency of very low birthweight (<1500 gm) and delivery prior to 32 weeks (see Table 18 and Table 19). It would be expected that a higher proportion of placebo treated children would be at risk for developmental delays on the basis of these perinatal risk factors. The classification of equal proportions (about 28%) of children in each group as possibly delayed suggests that the 17OHP-C group also resembled an "at risk" group, albeit not as strongly attributable to low birthweight and gestational age. The Applicant did not conduct an analysis adjusting for these risk factors in assessing the proportion of possibly delayed children in each treatment group.*

6.6.2 Secondary Outcomes from Survey Questionnaire

A similar proportion of the children in the 17OHP-C group (99%) and the placebo group (98%) had a completed Survey Questionnaire. Results of the various developmental areas assessed as secondary endpoints are shown in Table 23. There were no marked differences between the groups. A slightly higher proportion of the placebo group had diagnosed problems with motor skills, activity level, communication problems or inability to attend or learn. The most common reported diagnosis was inability to pay attention/learn. When this category is broken down further (not shown in Table 23) the most frequent causes included "developmental delay," (reported for 2.6% of the 17OHP-C children and 3.7% of the placebo children), and ADHD/ADD, (0.5% in the 17OHP-C group and 2.4% in the placebo group). A child in the 17OHP-C group had a reported diagnosis of mental retardation (Down syndrome) and another child in the 17OHP-C group had a reported diagnosis of autism.

Sensory impairments and need for special equipment were uncommon, but minimally more frequent in placebo children. More than 90% of the children in both treatment groups were reported to have height and weight within the normal range, according to CDC reference growth curves. Almost all of the children in both treatment groups were either in excellent, very good, or good health (98% vs. 95%). No differences in gender-specific roles were noted.

Table 23 Developmental Assessment Based on the Survey Questionnaire

Developmental Area (Scale included in Questionnaire)	Evaluation	17OHP-C N=193		Placebo N=82	
		n	%	n	%
Motor Skills (ECLSK)	% with diagnosis	1[A]	0.5	1[B]	1.2
Activity Level (ECLSK)	% with diagnosis	2	1.0	1	1.2
Communication problems	% with diagnosis	9	4.7	7	8.5
Inability to pay attention/learn	% with diagnosis	8	4.2	5	6.1
Hearing Impairment (NHIS)	% with problem	4	2.1	5	6.1
Vision impairment (NHIS)	% with problem	4	2.1	2	2.4
Need for special equipment	% with problem	1	0.5	1[b]	1.2
Impairment in ability to walk/run/play	% with problem	5	2.6	5	6.1
Overall health	% with "fair health"	4	2.1	4	4.9
	% with "poor health"	0		0	
Height	% below normal	7	3.8	4	5.2
Weight	% below normal	11	5.8	6	7.5
		Mean		Mean	
Gender specific roles (PSAI)	Male score	66.5		67.3	
	Female score	31.8		33.1	

[A] Upper body weakness
[B] Cerebral palsy
Source: Tables 12-5, 12-6, 12-7, 12-8, Final report for Study 17P-FU.

6.6.3 Reported Diagnoses by Health Professionals

Parents/guardians were asked to report for the child any diagnoses made by a health professional at any time between discharge from birth hospitalization and enrollment in the follow-up study. The reported diagnoses are summarized in Table 24. The incidence of each type of reported diagnosis was not meaningfully different (i.e., not > 4 percentage points) between the 2 treatment groups.

Table 24 Reported Diagnoses by Health Professionals

Reported Diagnosis	17OHP-C N=192[A] n (%)	Placebo N=82[A] n (%)
Asthma	39 (20.3)	20 (24.4)
Asthma attack in past 12 months	20 (10.4)	8 (9.8)
Visit to ER or Urgent Care due to asthma in past 12 months	18 (9.4)	7 (8.5)
Eczema or skin allergy	35 (18.2)	12 (14.6)
Ear infections (3 or more)	20 (10.4)	7 (8.5)
Hay fever	19 (9.9)	5 (6.1)
Respiratory allergy	16 (8.3)	9 (11.0)
Developmental delay [B]	14 (7.3)	7 (8.5)
Stuttering or stammering [C]	11 (6.4)	5 (6.6)
Frequent repeated diarrhea or colitis	5 (2.6)	1 (1.2)
Anemia	5 (2.6)	4 (4.9)
Food or digestive allergy	3 (1.6)	3 (3.7)
Seizures or convulsions with fever	3 (1.6)	1 (1.2)
Frequent or severe headaches or migraines [C]	1 (0.6)	2 (2.6)
Diabetes	1 (0.5)	0
Arthritis	1 (0.5)	0
Seizures or convulsions without fever	0	1 (1.2)
Cerebral palsy	0	1 (1.2)
Sickle cell	0	1 (1.2)
Cystic fibrosis	0	0

[A] The number of children for whom the Survey Questionnaire was completed; two children in each treatment group did not have a completed Survey Questionnaire.

[B] Parent/guardian answered “yes” to the question “Has a doctor or other health professional EVER told you that (the child) had any developmental delay?” Per help text provided with the Survey Questionnaire, the parent/guardian was to say “yes” if the health professional diagnosed the child as falling significantly behind age mates in physical, mental, social/emotional, or speech development.

[C] Question answered only for children 3 years or older. Percentages were based on N=171 in 17OHP-C group and N=76 in placebo group.

Source: Table 12-10, Final Report for Study 17P-FU.

6.6.4 Medical Events of Interest

Medical events of interest were potential adverse events that might be attributable to the study drug or to sequelae of prematurity and low birthweight. They were evaluated by integrating data obtained on the ASQ, from the parent on the Survey Questionnaire and from study pediatricians who performed physical exams on the children.

Genital and Reproductive Anomalies

As the study drug involved fetal exposure to a progestin, the occurrence of genital and reproductive anomalies was of particular interest. These were identified by parental reports on the Survey Questionnaire and by physician findings on the physical examination.

Six (3.2%) children in the 17OHP-C group and one (1.2%) child in the placebo group were initially reported by either parent or physician as having genital or reproductive abnormalities. After review of all available data, 2 findings were determined to be misclassified resulting in genital or reproductive abnormalities in 2.1% (n=4) of the children in the 17OHP-C group and 1.2% (n=1) in the placebo group. The four abnormalities in the 17OHP-C group included:

- micropenis and small scrotal sac noted on study physical examination of a child exposed to 17OHP-C from 19-38 weeks of gestation
- microphallus and Down Syndrome noted on study physical examination of a child exposed from 18-34 weeks of gestation
- surgical correction of undescended testes at an unspecified age in a child exposed from 19-41 weeks of gestation
- early puberty, described by mother as the cause of joint pain that limited the child's ability to walk/run/play, and noted on physical examination (including 4-5 cm breast buds) in a girl exposed from 20-40 weeks of gestation; she was also at the 100^{th} centile for body mass index.

The single genital/reproductive anomaly in the placebo group was described as "sparse public hair" in a 42 month old girl.

Developmental Delays

A second integrated evaluation concerned identification of the "true positives" among those children tagged as potentially at risk for developmental delay based on their ASQ scores. As the purpose of the ASQ is to identify children who may require further evaluation, only some will have confirmation of a developmental delay upon evaluation by a professional. Those children with at least one below-cutoff ASQ score <u>and</u> who also had a parental report of a diagnosis of developmental delay made independently by a professional were reviewed in more detail.

Thirteen (6.7%) of the 193 children in the 17OHP-C group and 8 (9.8%) of the 82 children in the placebo group had an ASQ score below cutoff for at least one developmental area <u>and</u> a reported diagnosis of developmental delay (either in a specific area or overall). The percentages of children evaluated on the ASQ who scored below the cutoff in a specific ASQ developmental area <u>and</u> had at least one reported diagnosis of developmental delay were as follows:

	17OHP-C	Placebo
Communication:	4.7%	8.5%
Gross motor:	1.6%	2.4%
Fine motor:	5.2%	3.6%
Problem solving:	2.6%	6.1%
Personal-social:	2.6%	1.2%

Of the 21 children meeting both criteria, the most common ASQ domains falling below the cutoff were fine-motor and communication for the 17OHP-C group and communication and problem-solving for the placebo children.

Developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age mates in physical, mental, social/emotional, or speech development, was reported for a similar percentage of children in the 17OHP-C and placebo groups (7.3% vs. 8.5%).

6.6.5 Physical Examination

Physical exams were performed by study physicians on 93% of children in the 17OHP-C group and 87% of the placebo children. Physical examination findings were abstracted from medical records of recent exams for 4% of the 17OHP-C group and 10% of the placebo children; in the remaining cases, no physical findings were available.

Physical findings occurring with disparate distribution over the 2 groups included heart murmurs and irregular rhythm (in ten 17OHP-C and no placebo children), and palpable kidneys (in four 17OHP-C and no placebo children).

6.7 Summary

Study 17P-FU assessed the health status of the children born to women who received weekly intramuscular injections of study drug (17OHP-C or placebo) during Study 17P-CT-002. Only study centers still active in the MFMU Network at the start of Study 17P-FU in the fall of 2004 could participate. Of the 348 infants who were discharged from birth hospitalization at active study sites, 83% (194/234) of the eligible infants in the 17OHP-C group and 74% (84/114) in the placebo group were enrolled in Study 17P-FU. As noted previously, the 17OHP-C children in the follow-up study may represent a slightly lower risk subset of the total population, given their greater mean gestational age as compared to the total cohort of 17OHP-C children, and their greater gestational age and birthweight as compared to their placebo-exposed peers in the follow-up study.

There was no difference between the 17OHP-C and placebo groups in the percentage of children who scored below the cutoff for at least one developmental area of the ASQ. The percentages of children who scored below the ASQ cutoff in each of the individual 5 developmental areas were similar in the 17OHP-C and placebo groups.

Developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age mates in physical, mental, social/emotional, or speech development, was reported for a comparable percentage of children in the 17OHP-C and placebo groups.

Appendix 1

FDA Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
Clinical 6

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products

Additional copies are available from:
the Drug Information Branch (HFD-210),
Center for Drug Evaluation and Research (CDER),
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573
Internet at http://www.fda.gov/cder/guidance/index.htm
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1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
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GUIDANCE FOR INDUSTRY[1]

Providing Clinical Evidence of Effectiveness[2] for Human Drug and Biological Products

I. INTRODUCTION

This document is intended to provide guidance to applicants planning to file new drug applications (NDAs), biologics license applications (BLAs), or applications for supplemental indications on the evidence to be provided to demonstrate effectiveness.

This document is also intended to meet the requirements of subsections 403(b)(1) and (2) of the Food and Drug Administration Modernization Act (the Modernization Act) of 1997 for human drug and biological products (P.L. 105-115).[3] Subsection 403(b)(1) directs FDA to provide guidance on the circumstances in which published matter may be the basis for approval of a supplemental application for a new indication. Section III of this guidance satisfies this requirement by describing circumstances in which published matter may partially or entirely support approval of a supplemental application. Subsection 403(b)(2) directs FDA to provide guidance on data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application to support approval of a supplemental application. Section II of this guidance satisfies this requirement by describing a range of circumstances in which related existing data, whether from an original application or other sources, may be used to support approval of a supplemental application.

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies. Since then, the issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others. Sound evidence of effectiveness is a crucial component of the Agency's benefit-risk assessment of a new product or use. At the same time, the demonstration of effectiveness represents a major component of drug development time and cost; the amount

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[1] This guidance document represents the agency's current thinking on providing clinical evidence of effectiveness for human drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] As used in this guidance, the term efficacy refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data.

[3] The Modernization Act requirements in Section 403 also apply to animal drugs and medical devices. These products will be addressed in separate guidances.

and nature of the evidence needed can therefore be an important determinant of when and whether new therapies become available to the public. The public health is best served by the development of sound evidence of effectiveness in an efficient manner.

The science and practice of drug development and clinical evaluation have evolved significantly since the effectiveness requirement for drugs was established, and this evolution has implications for the amount and type of data needed to support effectiveness in certain cases. As a result of medical advances in the understanding of pathogenesis and disease staging, it is increasingly likely that clinical studies of drugs will be more narrowly defined to focus, for example, on a more specific disease stage or clinically distinct subpopulation. As a consequence, product indications are often narrower, the universe of possible indications is larger, and data may be available from a number of studies of a drug in closely related indications that bear on a determination of its effectiveness for a new use. Similarly, there may be studies of a drug in different populations, studies of a drug alone or in combination, and studies of different doses and dosage forms, all of which may support a particular new use of a drug. At the same time, progress in clinical evaluation and clinical pharmacology have resulted in more rigorously designed and conducted clinical efficacy trials, which are ordinarily conducted at more than one clinical site. This added rigor and scope has implications for a study's reliability, generalizability, and capacity to substantiate effectiveness.

Given this evolution, the Agency has determined that it would be appropriate to articulate its current thinking concerning the quantitative and qualitative standards for demonstrating effectiveness of drugs and biologics. FDA hopes that this guidance will enable sponsors to plan drug development programs that are sufficient to establish effectiveness without being excessive in scope. The guidance should also bring greater consistency and predictability to FDA's assessment of the clinical trial data needed to support drug effectiveness.

Another major goal of this guidance is to encourage the submission of supplemental applications to add new uses to the labeling of approved drugs. By articulating how it currently views the quantity and quality of evidence necessary to support approval of a new use of a drug, FDA hopes to illustrate that the submission of supplements for new uses need not be unduly burdensome.

II. QUANTITY OF EVIDENCE NECESSARY TO SUPPORT EFFECTIVENESS

A. Legal Standards for Drug and Biological Products

Drugs: The effectiveness requirement for drug approval was added to the Federal Food, Drug, and Cosmetic Act (the Act or the FDC Act) in 1962. Between passage of the Act in 1938 and the 1962 amendments, drug manufacturers were required to show only that their drugs were safe. The original impetus for the effectiveness requirement was Congress's growing concern about the misleading and unsupported claims being made by pharmaceutical companies about their drug products coupled with high drug prices. After two years of hearings on these issues, Congress adopted the 1962 Drug Amendments, which included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." *Substantial evidence* was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Since the 1962 Amendments added this provision to the statute, discussions have ensued regarding the quantity and quality of the evidence needed to establish effectiveness. With regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. (See e.g., Final Decision on Benylin, 44 FR 51512, 518 (August 31, 1979); *Warner-Lambert Co. V. Heckler,* 787 F. 2d 147 (3d Cir. 1986)). FDA's position is based on the language in the statute[4] and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence. (S. Rep. No. 1744, Part 2, 87th Cong. 2d Sess. 6 (1962))

Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

In section 115(a) of the Modernization Act, Congress amended section 505(d) of the Act to make it clear that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial

[4] Section 505(d) of the Act uses the plural form in defining "substantial evidence" as "adequate and well-controlled investigation<u>s</u>, including clinical investigation<u>s</u>." See also use of "investigations" in section 505(b) of the Act, which lists the contents of a new drug application.

evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. In making this clarification, Congress confirmed FDA's interpretation of the statutory requirements for approval and acknowledged the Agency's position that there has been substantial progress in the science of drug development resulting in higher quality clinical trial data.

Biologics. Biological products are approved under authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C.§ 262). Under section 351, as in effect since 1944, licenses for biologics have been issued only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. *Potency* has long been interpreted to include effectiveness (21 CFR 600.3(s)). In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)). One such adequate alternative was identified to be serological response data where a previously accepted correlation with clinical effectiveness exists. As with nonbiological drug products, FDA has approved biological products based on single, multicenter studies with strong results.

Although section 123(a) of the Modernization Act amended section 351 of the PHS Act to make it clear that separate licenses are not required for biological products and the establishments at which the products are made, the evidentiary standard for a biological product was not changed: the product must be shown to be "safe, pure, and potent" (section 351 (a)(2) of the PHS Act as amended). In the Modernization Act (section 123(f)) Congress also directed the agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FDC Act.

B. Scientific Basis for the Legal Standard

The usual requirement for more than one adequate and well-controlled investigation reflects the need for *independent substantiation* of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness. The reasons for this include the following.

- Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions. In addition, some investigators may bring conscious biases to evaluations.

- The inherent variability in biological systems may produce a positive trial result by chance alone. This possibility is acknowledged, and quantified to some extent, in the statistical evaluation of the result of a single efficacy trial. It should be noted, however, that hundreds of randomized clinical efficacy trials are conducted each year with the intent of submitting favorable results to FDA. Even if all drugs tested in such trials were ineffective, one would expect one in forty of those trials to "demonstrate" efficacy by chance alone at conventional levels of statistical significance.[5] It is probable, therefore, that false positive findings (i.e., the chance appearance of efficacy with an ineffective drug) will occur and be submitted to FDA as evidence of effectiveness. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.

- Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet). In such cases, the results, although correct, may not be generalizable to the intended population. This possibility is the primary basis for emphasizing the need for independence in substantiating studies.

- Rarely, favorable efficacy results are the product of scientific fraud.

Although there are statistical, methodologic, and other safeguards to address the identified problems, they are often inadequate to address these problems in a single trial. Independent substantiation of experimental results addresses such problems by providing consistency across more than one study, thus greatly reducing the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a drug is effective.

The need for independent substantiation has often been referred to as the need for replication of the finding. Replication may not be the best term, however, as it may imply that precise repetition of the same experiment in other patients by other investigators is the only means to substantiate a conclusion. Precise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design. Results that are obtained from studies that are of different design and independent in execution, perhaps evaluating different populations, endpoints, or dosage forms, may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study.

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[5] p-value = 0.05, two-tailed, which implies an error rate in the efficacy (false positive) tail of 0.025 or one in forty.

C. The Quantity of Evidence to Support Effectiveness

The following three sections provide guidance on the quantity of evidence needed in particular circumstances to establish substantial evidence of effectiveness. Section 1 addresses situations in which effectiveness of a new use may be extrapolated entirely from existing efficacy studies. Section 2 addresses situations in which a single adequate and well-controlled study of a specific new use can be supported by information from other related adequate and well-controlled studies, such as studies in other phases of a disease, in closely related diseases, of other conditions of use (different dose, duration of use, regimen), of different dosage forms, or of different endpoints. Section 3 addresses situations in which a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a use is effective.

In each of these situations, it is assumed that any studies relied on to support effectiveness meet the requirements for adequate and well-controlled studies in 21 CFR 314.126. It should also be appreciated that reliance on a single study of a given use, whether alone or with substantiation from related trial data, leaves little room for study imperfections or contradictory (nonsupportive) information. In all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that the results reflect a clear prior hypothesis documented in the protocol. Moreover, a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use unless there were a strong argument for discounting the outcomes in the studies that failed to show effectiveness (e.g., study obviously inadequately powered or lack of assay sensitivity as demonstrated in a three-arm study by failure of the study to show efficacy of a known active agent).

Whether to rely on a single study to support an effectiveness determination is not often an issue in contemporary drug development. In most drug development situations, the need to find an appropriate dose, to study patients of greater and lesser complexity or severity of disease, to compare the drug to other therapy, to study an adequate number of patients for safety purposes, and to otherwise know what needs to be known about a drug before it is marketed will result in more than one adequate and well-controlled study upon which to base an effectiveness determination.

This guidance is not intended to provide a complete listing of the circumstances in which existing efficacy data may provide independent substantiation of related claims; rather, it provides examples of the reasoning that may be employed. The examples are applicable whether the claim arises in the original filing of an NDA or BLA, or in a supplemental application.

1. Extrapolation from Existing Studies

In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form. The following are examples of situations in which effectiveness might be extrapolated from efficacy data for another claim or product.

a. Pediatric uses

The rule revising the Pediatric Use section of product labeling (21 CFR 201.57(f)(9)(iv)) makes allowance for inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions. Examples in which pediatric use labeling information has been extrapolated from adult efficacy data include ibuprofen for pain and loratidine for seasonal allergic rhinitis.

b. Bioequivalence

The effectiveness of alternative formulations and new dosage strengths may be assessed on the basis of evidence of bioequivalence.

c. Modified-release dosage forms

In some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to a previously studied immediate-release dosage form. Because the pharmacokinetic patterns of modified-release and immediate-release dosage forms are not identical, it is generally important to have some understanding of the relationship of blood concentration to response, including an understanding of the time course of that relationship, to extrapolate the immediate-release data to the modified-release dosage form.

d. Different doses, regimens, or dosage forms

Dose-response relationships are generally continuous such that information about the effectiveness of one dose, dosage regimen, or dosage form is relevant to the effectiveness of other doses, regimens, or dosage forms. Where blood levels and exposure are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone. Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial. In this situation, pharmacokinetic data, together with the well-defined pharmacokinetic/pharmacodynamic (PK/PD) relationship, are used to translate the controlled trial results from one dose, regimen, or dosage form to a new dose, regimen, or dosage form (See also section II.C.2.a).

2. Demonstration of Effectiveness by a Single Study of a New Use, with Independent Substantiation From Related Study Data

The discussion that follows describes specific examples in which a single study of a new use, with independent substantiation from study data in related uses, could provide evidence of effectiveness. In these cases, the study in the new use and the related studies support the conclusion that the drug has the effect it is purported to have. Whether related studies are capable of substantiating a single study of a new use is a matter of judgment and depends on the quality and outcomes of the studies and the degree of relatedness to the new use.

a. Different doses, regimens, or dosage forms

As discussed in Sections II.C.1.d, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial where blood levels and exposure are not very different or, even if quite different, there is a well-understood relationship between blood concentration and response. Where the relationship between blood concentration and response is not so well understood and the pharmacokinetics of the new dose, regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness of a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient. For example, a single controlled trial was needed to support the recent approval of a once daily dose of risperidone because the once daily and twice daily regimens had different pharmacokinetics and risperidone's PK/PD relationship was not well understood.

b. Studies in other phases of the disease

In many cases, therapies that are effective in one phase of a disease are effective in other disease phases, although the magnitude of the benefit and benefit-to-risk relationship may differ in these other phases. For example, if a drug is known to be effective in patients with a refractory stage of a particular cancer, a single adequate and well-controlled study of the drug in an earlier stage of the same tumor will generally be sufficient evidence of effectiveness to support the new use.

c. Studies in other populations

Often, responses in subsets of a particular patient population are qualitatively similar to those in the whole population. In most cases, separate studies of effectiveness in demographic subsets are not needed (see also discussion of the pediatric population in section II.C.1.a) However, where further studies are needed, a single study would ordinarily suffice to support effectiveness in age, race, gender, concomitant disease, or other subsets for a drug already shown to be generally effective in a condition or to be effective in one population. For example, a single study was sufficient to support tamoxifen use in breast cancer in males.

d. Studies in combination or as monotherapy

For a drug known to be effective as monotherapy, a single adequate and well-controlled study is usually sufficient to support effectiveness of the drug when combined with other therapy (as part of a multidrug regimen or in a fixed-dose combination). Similarly, known effectiveness of a drug as part of a combination (i.e., its contribution to the effect of the combination is known) would usually permit reliance on a single study of appropriate design to support its use as monotherapy, or as part of a different combination, for the same use. For example, a single study of a new combination vaccine designed to demonstrate adequate immune response will ordinarily provide sufficient evidence of effectiveness if the new combination contains products or antigens already proven to be effective alone or in other combinations. These situations are common for oncologic and antihypertensive drugs, but occur elsewhere as well.

e. Studies in a closely related disease

Studies in etiologically or pathophysiologically related conditions, or studies of a symptom common to several diseases (e.g., pain) can support each other, allowing initial approval of several uses or allowing additional claims based on a single adequate and well-controlled study. For example, certain anti-coagulant or anti-platelet therapies could be approved for use in two different settings based on individual studies in unstable angina/acute coronary syndrome and in the postangioplasty state. Because the endpoints studied and the theoretical basis for use of an anti-coagulant or anti-platelet drug are similar, each study supports the other for each claim. Similarly, single analgesic studies in several painful conditions would ordinarily be sufficient to support either a general analgesic indication or multiple specific indications. The recent approval of lamotrigine for treatment of Lennox-Gastaut Syndrome (a rare, largely pediatric, generalized seizure disorder) was based on a single adequate and well-controlled trial, due in part to related data showing efficacy of the drug in partial-onset seizures in adults.

f. Studies in less closely related diseases, but where the general purpose of therapy is similar

Certain classes of drug therapy, such as antimicrobials and antineoplastics, are appropriate interventions across a range of different diseases. For therapies of this type, evidence of effectiveness in one disease could provide independent substantiation of effectiveness in a quite different disease. For example, it is possible to argue that evidence of effectiveness of an antimicrobial in one infectious disease setting may support reliance on a single study showing effectiveness in other settings where the causative pathogens, characteristics of the site of infection that affect the disease process (e.g., structure and immunology) and patient population are similar.[6] Similarly, for an oncologic drug, evidence of effectiveness in one or more tumor types may support reliance on a single study showing effectiveness against a different kind of tumor, especially if the tumor types have a common biological origin.

g. Studies of different clinical endpoints

Demonstration of a beneficial effect in different studies on two different clinically meaningful endpoints could cross-substantiate a claim for

[6] See Division of Anti-Infective Drug Products: Points to Consider in the Clinical Development and Labeling of Anti-Infective Drug Products, October 1992.

effectiveness for each outcome. For example, the initial claim for effectiveness of enalapril for heart failure was supported by one study showing symptom improvement over several months and a second study showing improved survival in a more severely ill population. The two different findings, each from an adequate and well-controlled study, led to the conclusion that enalapril was effective in both treating symptoms and improving survival.

h. Pharmacologic/pathophysiologic endpoints

When the pathophysiology of a disease and the mechanism of action of a therapy are very well understood, it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness. A pharmacologic effect that is accepted as a validated surrogate endpoint can support ordinary approval (e.g., blood pressure effects, cholesterol-lowering effects) and a pharmacologic effect that is considered reasonably likely to predict clinical benefit can support accelerated approval under the conditions described in 21 CFR 314 Subpart H and 21 CFR 601 Subpart E (e.g., CD4 count and viral load effects to support effectiveness of anti-viral drugs for HIV infection). When the pharmacologic effect is not considered an acceptable effectiveness endpoint, but the linkage between it and the clinical outcome is strong, not merely on theoretical grounds but based on prior therapeutic experience or well-understood pathophysiology, a single adequate and well-controlled study showing clinical efficacy can sometimes be substantiated by persuasive data from a well-controlled study or studies showing the related pharmacologic effect.

For example, a single clearly positive trial can be sufficient to support approval of a replacement therapy such as a coagulation factor, when it is combined with clear evidence that the condition being treated is caused by a deficiency of that factor. Demonstration of physical replacement of the deficient factor or restoration of the missing physiologic activity provides strong substantiation of the clinical effect. The corrective treatment of an inborn error of metabolism could be viewed similarly. In the case of preventive vaccines, one adequate and well-controlled clinical trial may be supported by compelling animal challenge/protection models, human serological data, passive antibody data, or pathogenesis information. The more evidence there is linking effects on the pharmacologic endpoint to improvement or prevention of the disease, the more persuasive the argument for reliance on a single clinical efficacy study.

Note, however, that plausible beneficial pharmacologic effects have often not correlated with clinical benefit, and, therefore, caution must be observed in relying on a pharmacologic effect as contributing to evidence of effectiveness. For example, pharmacologic effects such as arrhythmia suppression by Type 1 antiarrhythmics and increased cardiac output by phosphodiesterase inhibitors or beta adrenergic inotropes resulted in increased mortality, rather than, as was expected, decreased sudden death and improved outcome in heart failure. The reasons for the absence of an expected correlation between pharmacologic and clinical effects are diverse and can include an incompletely understood relationship between the pharmacologic effect and the clinical benefit and the presence of other pharmacologic effects attributable to a drug in addition to the effect being measured and thought to be beneficial. Generally, the utility of pharmacologic outcomes in providing independent substantiation will be greatest where there is prior experience with the pharmacologic class. Even in this case, however, it is difficult to be certain that a pharmacologic effect that correlates with a clinical benefit accounts for all the clinical benefit or that other effects are not present and relevant.

3. Evidence of Effectiveness from a Single Study

When the effectiveness requirement was originally implemented in 1962, the prevailing efficacy study model was a single institution, single investigator, relatively small trial with relatively loose blinding procedures, and little attention to prospective study design and identification of outcomes and analyses. At present, major clinical efficacy studies are typically multicentered, with clear, prospectively determined clinical and statistical analytic criteria. These studies are less vulnerable to certain biases, are often more generalizable, may achieve very convincing statistical results, and can often be evaluated for internal consistency across subgroups, centers, and multiple endpoints.

The added rigor and size of contemporary clinical trials have made it possible to rely, in certain circumstances, on a single adequate and well-controlled study, without independent substantiation from another controlled trial, as a sufficient scientific and legal basis for approval. For example, the approval of timolol for reduction of post-infarction mortality was based on a single, particularly persuasive (low p-value), internally consistent, multicenter study that demonstrated a major effect on mortality and reinfarction rate. For ethical reasons, the study was considered unrepeatable. The Center for Biologics Evaluation and Research has also approved a number of products based upon a single persuasive study. The Agency provided a general statement in 1995 describing when a single, multicenter study may suffice (60 FR 39181; August 1, 1995), but the Agency has not comprehensively described the situations in which a single adequate and well-controlled study might be considered adequate support for an effectiveness claim, or the characteristics of a single study that could make it adequate support for an effectiveness claim.

Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. For example, sequential repetition of strongly positive trials that demonstrated a decrease in post-infarction mortality, prevention of osteoporotic fractures, or prevention of pertussis would present significant ethical concerns. Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns.

The discussion that follows identifies the characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim. Although no one of these characteristics is necessarily determinative, the presence of one or more in a study can contribute to a conclusion that the study would be adequate to support an effectiveness claim.

a. Large multicenter study

In a large multicenter study in which (1) no single study site provided an unusually large fraction of the patients and (2) no single investigator or site was disproportionately responsible for the favorable effect seen, the study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator. If analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished.

b. Consistency across study subsets

Frequently, large trials have relatively broad entry criteria and the study populations may be diverse with regard to important covariates such as concomitant or prior therapy, disease stage, age, gender or race. Analysis of the results of such trials for consistency across key patient subsets addresses concerns about generalizability of findings to various populations in a manner that may not be possible with smaller trials or trials with more narrow entry criteria. For example, the timolol postinfarction study randomized patients separately within three severity strata. The study showed positive effects on survival in each stratum supporting a conclusion that the drug's utility was not limited to a particular disease stage (e.g., relatively low or high severity).

c. Multiple *studies* in a single study

Properly designed factorial studies may be analyzed as a series of pairwise comparisons, representing, within a single study, separate demonstrations of activity of a drug as monotherapy and in combination with another drug. This model was successfully used in ISIS II, which showed that for patients with a myocardial infarction both aspirin and streptokinase had favorable effects on survival when used alone and when combined (aspirin alone and streptokinase alone were each superior to placebo; aspirin and streptokinase in combination were superior to aspirin alone and to streptokinase alone). This represented two separate (but not completely independent) demonstrations of the effectiveness of aspirin and streptokinase.

d. Multiple endpoints involving different events

In some cases, a single study will include several important, prospectively identified primary or secondary endpoints, each of which represents a beneficial, but different, effect. Where a study shows statistically persuasive evidence of an effect on more than one of such endpoints, the internal weight of evidence of the study is enhanced. For example, the approval of beta-interferon (Betaseron) for prevention of exacerbations in multiple sclerosis was based on a single multicenter study, at least partly because there were both a decreased rate of exacerbations and a decrease in MRI-demonstrated disease activity — two entirely different, but logically related, endpoints.

Similarly, favorable effects on both death and nonfatal myocardial infarctions in a lipid-lowering, postangioplasty, or postinfarction study would, in effect, represent different, but consistent, demonstrations of effectiveness, greatly reducing the possibility that a finding of reduced mortality was a chance occurrence. For example, approval of abciximab as adjunctive treatment for patients undergoing complicated angioplasty or atherectomy was supported by a single study with a strong overall result on the combined endpoint (decreased the combined total of deaths, new infarctions, and need for urgent interventions) and statistically significant effects in separate evaluations of two components of the combined endpoint (decreased new infarctions and decreased need for urgent interventions). In contrast, a beneficial effect on multiple endpoints that evaluate essentially the same phenomenon and correlate strongly, such as mood change on two different depression scales or SGOT and CPK levels postinfarction, does not significantly enhance the internal weight of the evidence from a single trial.

Although two consistent findings within a single study usually provide reassurance that a positive treatment effect is not due to chance, they do not protect against bias in study conduct or biased analyses. For example, a treatment assignment not well balanced for important prognostic variables could lead to an apparent effect on both endpoints. Thus, close scrutiny of study design and conduct are critical to evaluating this type of study.

e. Statistically very persuasive finding

In a multicenter study, a very low p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect. In some studies it is possible to detect nominally statistically significant results in data from several centers, but, even where that is not possible, an overall extreme result and significance level means that most study centers had similar findings. For example, the thrombolysis trials of streptokinase (ISIS II, GISSI) had very sizable treatment effects and very low p-values, greatly adding to their persuasiveness. Preventive vaccines for infectious disease indications with a high efficacy rate (e.g., point estimate of efficacy of 80% or higher and a reasonably narrow 95% confidence interval) have been approved based on a single adequate and well-controlled trial.

4. Reliance on a Single, Multicenter Study — Caveats

While acknowledging the persuasiveness of a single, internally consistent, strong multicenter study, it must be appreciated that even a strong result can represent an isolated or biased result, especially if that study is the only study suggesting efficacy among similar studies. Recently, the apparent highly favorable effect of vesnarinone, an inotropic agent, in heart failure (60% reduction of mortality in what appeared to be a well-designed, placebo-controlled, multicenter trial with an extreme p-value) has proven to be unrepeatable. In an attempt to substantiate the finding, the same dose of the drug that seemed lifesaving in the earlier study significantly increased mortality (by 26%), and a lower dose also appeared to have a detrimental effect on survival. Although the population in the second study was, on the whole, a sicker population than in the first, the outcomes in similarly sick patients in each study were inconsistent so this factor does not explain the contradictory results.

When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single multicenter trial. In the case of vesnarinone, there were other data that were not consistent with the dramatically favorable outcome in the multicenter study. These data seemed to show an inverse dose-response relationship, showed no suggestion of symptomatic benefit, and showed no effect on hemodynamic endpoints. These inconsistencies led the Agency, with the advice of its Cardio-Renal Advisory Committee, to refuse approval — a decision borne out by the results of the subsequent study.

This example illustrates how inadequacies and inconsistencies in the data, such as lack of pharmacologic rationale and lack of expected other effects accompanying a critical outcome, can weaken the persuasiveness of a single trial. Although an unexplained failure to substantiate the results of a favorable study in a second controlled trial is not proof that the favorable study was in error — studies of effective agents can fail to show efficacy for a variety of reasons — it is often reason not to rely on the single favorable study.

III. DOCUMENTATION OF THE QUALITY OF EVIDENCE SUPPORTING AN EFFECTIVENESS CLAIM

When submitting the requisite quantity of data to support approval of a new product or new use of an approved product, sponsors must also document that the studies were adequately designed and conducted. Essential characteristics of adequate and well-controlled trials are described in 21 CFR 314.126. To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the Agency, and detailed patient records are made available at the clinical sites.

From a scientific standpoint, however, it is recognized that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim. Therefore, the Agency is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured. This section discusses the factors that influence the extent of documentation needed, with particular emphasis on studies evaluating new uses of approved drugs.

For the purposes of this section, the phrase *documentation of the quality of evidence* refers to (1) the completeness of the documentation and (2) the ability to access the primary study data and the original study-related records (e.g., subjects' medical records, drug accountability records) for the purposes of verifying the data submitted as evidence. These interrelated elements bear on a determination of whether a study is adequate and well-controlled.

In practice, to achieve a high level of documentation, studies supporting claims are ordinarily conducted in accordance with good clinical practices (GCPs). Sponsors routinely monitor all clinical sites, and FDA routinely has access to the original clinical protocols, primary data, clinical site source documents for on-site audits, and complete study reports.

However, situations often arise in which studies that evaluate the efficacy of a drug product lack the full documentation described above (for example, full patient records may not be available) or in which the study was conducted with less monitoring than is ordinarily seen in commercially sponsored trials. Such situations are more common for supplemental indications because postapproval studies are more likely to be conducted by parties other than the drug sponsor and those parties may employ less extensive monitoring and data-gathering procedures than a sponsor. Under certain circumstances, it is possible for sponsors to rely on such studies to support effectiveness claims, despite less than usual documentation or monitoring. Some of those circumstances are described below.

A. Reliance on Less Than Usual Access to Clinical Data or Detailed Study Reports

FDA's access to primary data has proven to be important in many regulatory decisions. There are also reasons to be skeptical of the conclusions of published reports of studies. Experience has shown that such study reports do not always contain a complete, or entirely accurate, representation of study plans, conduct and outcomes. Outright fraud (i.e., deliberate deception) is unusual. However, incompleteness, lack of clarity, unmentioned deviation from prospectively planned analyses, or an inadequate description of how critical endpoint judgments or assessments were made are common flaws. Typically, journal article peer reviewers only have access to a limited data set and analyses, do not see the original protocol and amendments, may not know what happened to study subjects that investigators determined to be non-evaluable, and thus may lack sufficient information to detect critical omissions and problems. The utility of peer review can also be affected by variability in the relevant experience and expertise of peer reviewers. FDA's experiences with the Anturane Reinfarction Trial, as well as literature reports of the efficacy of tacrine and the anti-sepsis HA-1A antibody, illustrate its concerns with reliance on the published medical literature.

Notwithstanding these concerns, the presence of some of the factors discussed below can make it possible for FDA to rely on studies for which it has less than usual access to data or detailed study reports to partially or entirely (the so-called *paper* filing) support an effectiveness claim. FDA's reliance on a literature report to support an effectiveness claim is more likely if FDA can obtain additional critical study details. Section 1 below describes additional information that, if available, would increase the likelihood that a study could be relied on to support an effectiveness claim. Section 2 describes factors that may make efficacy findings sufficiently persuasive to permit reliance on the published literature alone. Note that the factors outlined in Section 2 are relevant to an assessment of the reliability of literature reports generally, whether alone, or accompanied by other important information as discussed in Section 1.

1. Submission of Published Literature or Other Reports in Conjunction with Other Important Information that Enhances the Reliability of the Data

If a sponsor wishes to rely on a study conducted by another party and cannot obtain the primary data from the study, for most well-conducted studies it is possible to obtain other important information, such as a protocol documenting the prospective plans for the trial, records of trial conduct and procedures, patient data listings for important variables, and documentation of the statistical analysis. FDA has considerable experience evaluating large multicenter outcome studies sponsored by U.S. and European government agencies (NIH, British Medical Research Council) and private organizations (the ISIS studies, the SAVE study) for which there was limited access to primary study data, but for which other critical information was available. Providing as many as possible of the following important pieces of information about a study, in conjunction with the published report, can increase the likelihood that the study can be relied on to support an effectiveness claim:

a. The protocol used for the study, as well as any important protocol amendments that were implemented during the study and their relation to study accrual or randomization.

b. The prospective statistical analysis plan and any changes from the original plan that occurred during or after the study, with particular note of which analyses were performed pre- and post-unblinding.

c. Randomization codes and documented study entry dates for the subjects.

d. Full accounting of all study subjects, including identification of any subjects with on-treatment data who have been omitted from analysis and the reasons for omissions, and an analysis of results using all subjects with on-study data.

e. Electronic or paper record of each subject's data for critical variables and pertinent baseline characteristics. Where individual subject responses are a critical variable (e.g., objective responses in cancer patients, clinical cures and microbial eradications in infectious disease patients, death from a particular cause), detailed bases for the assessment, such as the case report, hospital records, and narratives, should be provided when possible.

f. Where safety is a major issue, complete information for all deaths and drop-outs due to toxicity. For postapproval supplemental uses, however, there is generally less need for the results of lab tests or for details of adverse event reports and, consequently, much more limited documentation may be sufficient (e.g., only for unexpected deaths and previously undescribed serious adverse effects). Exceptions to this approach would include situations in which the population for the supplemental use is so different that existing safety information has limited application (e.g., thrombolysis in stroke patients versus myocardial infarction patients) or where the new population presents serious safety concerns (e.g., extension of a preventive vaccine indication from young children to infants).

2. Submission of Published Literature Reports Alone

The following factors increase the possibility of reliance on published reports alone to support approval of a new product or new use:

a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.

b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.

c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.

d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or “evaluable” subset).

e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

There have been approvals based primarily or exclusively on published reports. Examples include the initial approval of secretin for evaluation of pancreatic function and recent approvals of bleomycin and talc for malignant pleural effusion and doxycycline for malaria.

B. Reliance on Studies with Alternative, Less Intensive Quality Control/On-Site Monitoring

Industry-sponsored studies typically use extensive on-site and central monitoring and auditing procedures to assure data quality. Studies supported by other sponsors may employ less stringent procedures and may use no on-site monitoring at all. An International Conference on Harmonisation guideline on good clinical practices,[7] recently accepted internationally, emphasizes that the extent of monitoring in a trial should be based on trial-specific factors (e.g., design, complexity, size, and type of study outcome measures) and that different degrees of on-site monitoring can be appropriate. In recent years, many credible and valuable studies conducted by government or independent study groups, often with important mortality outcomes, had very little on-site monitoring. These studies have addressed quality control in other ways, such as by close control and review of documentation and extensive guidance and planning efforts with investigators. There is a long history of reliance on such studies for initial approval of drugs as well as for additional indications. Factors that influence whether studies with limited or no monitoring may be relied on include the following:

1. The existence of a prospective plan to assure data quality.

2. Studies that have features that make them inherently less susceptible to bias, such as those with relatively simple procedures, noncritical entry criteria, and readily assessed outcomes.

3. The ability to sample critical data and make comparisons to supporting records (e.g., hospital records).

4. Conduct of the study by a group with established operating procedures and a history of implementing such procedures effectively.

[7] International Conference on Harmonisation Guidance for Industry E6, *Good Clinical Practice: Consolidated Guideline*, April 1996.

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[24] Romero R, Mazor M. Infection and preterm labor. Clin Obstet Gynecol 1988;31:553-584.

[25] Romero R, Espinoza J, Chaiworapongsa T, Kalache K. Infection and prematurity and the role of preventive strategies. Semin Neonatol 2002; 7:259-274.

[26] Johnson JW, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17 α-hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med. 1975; 293 (14):675-80.

[27] Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003; 348 (24):2379-85.

[28] Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Brit J Obstet Gynaecol. 1990;97(2):149-54.

Thoughts on the presented statistical analysis

Daniel Gillen, PhD
Consultant to the Committee
Department of Statistics, UC Irvine

Typical criteria for approval

- Submission of two independent well-controlled clinical trials as substantial evidence for effectiveness

- Goal of statistics is to quantify uncertainty in samples in order to make inference or generalize to the larger population

Typical criteria for approval

- A primary reason for requiring consistent results on two independent trials is to broaden the generalizability of observed results
  - Clinical centers
  - Training
  - Patient pools / cohort effects

Current reference standard for statistical evidence

- P-value - Probability of observing results as or more extreme than those actually observed if the null hypothesis were true
  - In the current setting null hypothesis is equal rates of preterm births in each treatment arm

- Reference standard for a single trial is a one-sided P-value of 0.025 or less

Statistical evidence from a single confirmatory trial

- In order to provide sufficient statistical evidence from a single confirmatory trial it has been suggested that one require a P-value of $0.025^2 = 0.000625$

(the threshold corresponding to 2 independent level .025 tests)

Results reported by the study sponsor (ITT)

- 37 week endpoint
    - Obs proportions: 0.371 vs. 0.549
    - Obs difference: -0.178
    - 95% CI: -0.28, -0.07
    - Corresponding P-value: 0.0003

Results reported by the FDA

- FDA notes the use of an interim monitoring plan
  - 2-sided level .05 O'Brien-Fleming rule
  - 2 interim analyses one final analysis

- Adjusted results
  - Obs difference: -0.178
  - 95% CI: -0.28, -0.07

Results adjusted for interim analyses

- Assumptions:
  - 2-sided level .05 O'Brien-Fleming boundary
  - Three equally spaced analyses (actually took place at 15.2% and 70.2% of maximal sample size)
  - Final analysis sample sizes: 310 vs. 153
  - Baseline event rate of 0.549

Results adjusted for interim analyses

- Adjusted results (based upon sample mean ordering)
  - Obs difference: -0.178
  - Bias adjusted diff: -0.165
  - Adjusted P-value: 0.0035

Results adjusted for interim analyses

- Adjusted results for other endpoints

Endpoint	Obs Diff	Adj Diff	Adj P-value
35 week	-0.091	-0.086	0.068
32 week	-0.070	-0.066	0.156
28 week	-0.005	-0.005	0.919

Final note

- P-values only represent one criteria of evidence
- Also need to consider clinical significance of observed point estimates
  - Observed rate of pre-term births in placebo arm
  - Mean time to birth
- Generalizability of findings
- Safety profile
- Urgency of clinical need

Meeting of the Advisory Committee for Reproductive Health Drugs

August 29, 2006

Scott Monroe, MD
Acting Director, Division of Reproductive and Urologic Products

17-Hydroxyprogesterone Caproate (Gestiva)

Proposed Indication

Prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth

The Problem and Impact of Preterm Birth

- ~12% of all live births in U.S. are preterm
- Preterm birth (PTB) is
  - Leading cause of neonatal death
  - Major cause of early childhood morbidity and mortality including pediatric neurodevelopmental problems
- No approved drug product for *prevention* of PTB
- No approved drug for *treatment* of preterm labor currently marketed in the U.S.
- Drugs used off-label for Tx of preterm labor not been shown to improve perinatal outcomes in controlled trials

Prevention of Preterm Birth
A New Indication for an “Old Drug”?

- 17OHP approved in 1956 largely on safety considerations
  - Suggested uses of 17OHP (tradename Delalutin) included Tx of habitual, recurrent, or threatened abortion
  - Withdrawn from marketing in 2000 at request of NDA holder
  - Presently available only from compounding pharmacies
- In 2003, findings from a multicenter randomized, double-blind, controlled trial of 17OHP for prevention of PTB sponsored by NICHD were published in NEJM
  - Showed reduction in rate of PTB < 37 weeks gestation
  - Application to be discussed today based largely on this trial and a follow-up safety study of the children from the trial

Clinical Issues that Committee Will Be Asked to Consider

- Adequacy of the clinical data to support a claim of effectiveness of 17-hydroxyprogesterone caproate for prevention of preterm birth
- Percentage of preterm births in vehicle (control) arm of principal study (55%) was considerably higher than expected rate of ~36%
- Possible safety concern based the relative increase in the percentage of second trimester miscarriages and stillbirths in the 17-hydroxyprogesterone caproate group

Adequacy of Data to Support Effectiveness

- FDA generally requires 2 adequate and well controlled studies for substantial evidence of effectiveness
- Circumstance in which a single trial may be adequate
  - Trial has shown meaningful effect on mortality, irreversible morbidity, or prevented a disease with a potentially serious outcome, and
  - Confirmation of result in a second trial would be logistically impossible or ethically unacceptable
- Applicant is seeking approval based on
  - Findings from a single clinical trial
  - Surrogate endpoint for neonatal/infant morbidity and mortality
    - Reduction in rate of preterm births prior to 37 weeks

Questions for the Committee

- Is the primary endpoint — prevention of PTB prior to 37 weeks gestation — an adequate surrogate for a reduction in fetal and neonatal morbidity or mortality?
  - If not, would prevention of PTB prior to 35 or 32 weeks gestation be adequate?
- Does the high percentage of PTBs (55%) in the vehicle arm of the principal trial indicate the need to replicate the findings in a confirmatory trial?
- Do the data provide substantial evidence that 17OHP
  - prevents PTB prior to 35 or 32 weeks gestation or
  - reduces fetal and neonatal morbidity or mortality ?

Questions for the Committee

- Is further study needed to evaluate the potential association of 17OHP with increased risk of second trimester miscarriage and stillbirth?
  - If so, should this information be obtained prior to approval for marketing or post-approval?
- Are the overall safety data obtained in Studies 17P-CT-002 and 17P-IF-001 and Study 17P-FU (long-term follow-up) adequate and sufficiently reassuring to support marketing approval of 17OHP without the need for additional preapproval safety data?

Agenda

8:20	Roberto Romero, MD — Causes of Premature Birth: The Premature Parturition Syndrome
9:00	Applicant (Adeza Biomedical) Presentation
10:30	Break
10:45	FDA Presentation
11:45	Questions from the Committee
12:00	Lunch
1:00	Open Public Forum
2:00	Discussion and Questions by the Committee
4:00	Committee Voting
5:30	Adjournment

Causes of Preterm Birth: “The Preterm Parturition Syndrome”

Roberto Romero,M.D.
Chief Perinatology Research Branch
Division of Intramural Research
NICHD/NIH/DHHS

Conflict of Interest Statement

- Official capacity (NICHD/NIH/DHHS)
- Division of Intramural Research
- Trial conducted by the Extramural Program of NICHD/NIH (17P-CT-002)
- Independent of PRB/NICHD
- No financial conflict of interest with sponsor

Preterm birth: crisis and opportunity

The health of much of the developed world has improved in recent years, thanks to social and medical advances, including improved diagnostics and therapeutics. But in the USA, at least one important public-health problem, preterm birth, has worsened in the past decade.

The US Institute of Medicine (IOM), in a report released on July 18, said that 9·4% of births occurred before 37 weeks of gestation in 1981. But since then, the rate has risen by more than 30%, and now preterm births account for 12·5% of all births. This proportion, which is unacceptably high, looks even worse when broken down by race, ethnic group, and socioeconomic status. The highest rates of preterm birth occur among racial and ethnic minorities, especially African-Americans (17·8% vs 11·5% for white women). Preterm birth rates are also higher for Hispanic women (11·9%), and American Indians and native Alaskans (13·5%), than for white women.

Advances in perinatal and neonatal care have reduced the mortality due to preterm birth, but morbidity remains a serious problem. Infants born early are at high risk for developmental problems, birth defects, cerebral palsy, mental retardation, visual impairment, hearing loss, and other, sometimes less obvious, central nervous system disorders, including language and learning disabilities, attention-deficit hyperactivity disorder, and behavioural problems. The cost to society of these complications was more than US$26·2 billion in 2005, or $51 600 for each infant born early, with the cost of medical care accounting for two-thirds of this amount. The rest of the price tag is mainly an estimate because little is known about the actual costs of preterm birth beyond inpatient care and first hospitalisation. A good deal of money is thought to be spent on early intervention programmes, special education, and lost productivity by parents and other caregivers. And, of course, the cost of preterm birth is not merely economic. Preterm birth also exacts an enormous physical, emotional, and psychological toll on families.

Why has preterm birth increased, and what can be done about it? The IOM report notes a paucity of published work on the prevention, diagnosis, and treatment of preterm birth. It suggests that the causes are complex and multifactorial, and that solutions must be equally wide-ranging. Some contributing factors are social and economic (lack of access to prenatal care, stress, major life events); some are biological (inflammation and infection, maternal stress, uteroplacental thrombosis, and intrauterine vascular lesions); some are behavioural (use of tobacco, alcohol, and illicit drugs, particularly cocaine); and some reflect genetic susceptibility and interactions between genes and the environment. Environmental exposures (especially to lead, tobacco smoke, sulphur dioxide, and particulate matter) may increase the risk of preterm birth. In addition, the huge rise in assisted reproductive technologies over the past two decades has resulted in delayed childbearing by older mothers and multiple gestations, which increase the risk of preterm delivery.

This dismayingly long and far from definitive list has one quirky advantage. It provides many opportunities for multidisciplinary research, particularly clinical research, which is currently severely underfunded, given the severity of the problem. Urgent research priorities fall into several categories: better definition of the problem, through national data collection; health-services research, designed to investigate and improve and quality of care for women and infants at risk; and documentation of the causes and epidemiology of preterm birth. Better and more accurate data on gestational age are needed, which, the IOM report notes, can often be provided by early prenatal (at less than 20 weeks of gestation) ultrasound. Also needed are the development of a scheme that would classify preterm birth according to its aetiology, documentation of fertility treatments (with a view towards the development of guidelines to reduce the number of multiple gestations), comprehensive economic evaluation of the consequences of preterm birth, and early identification of and treatment for women at risk. At present, treatment of symptomatic preterm labour, rather than prediction and prevention, is the primary method of dealing with preterm birth.

In part because preterm birth is a complex issue that frequently involves populations at the margins of mainstream society, research into its causes and solutions has up until now fallen short. The IOM report lays out a clear roadmap for the questions that must be answered to decrease the incidence of preterm birth. Such research should be given priority, funded, and undertaken without delay. The health of future generations depends on it. ■ *The Lancet*


Science Photo Library

For the **IOM report on preterm birth** see http://newton.nap.edu/catalog/11622.html#toc

But in the USA, at least one important public-health problem, preterm birth, has worsened in the past decade.

The Lancet Editorial 2006;368:339

Institute of Medicine Report

Preterm Birth: Causes, Consequences, and Prevention

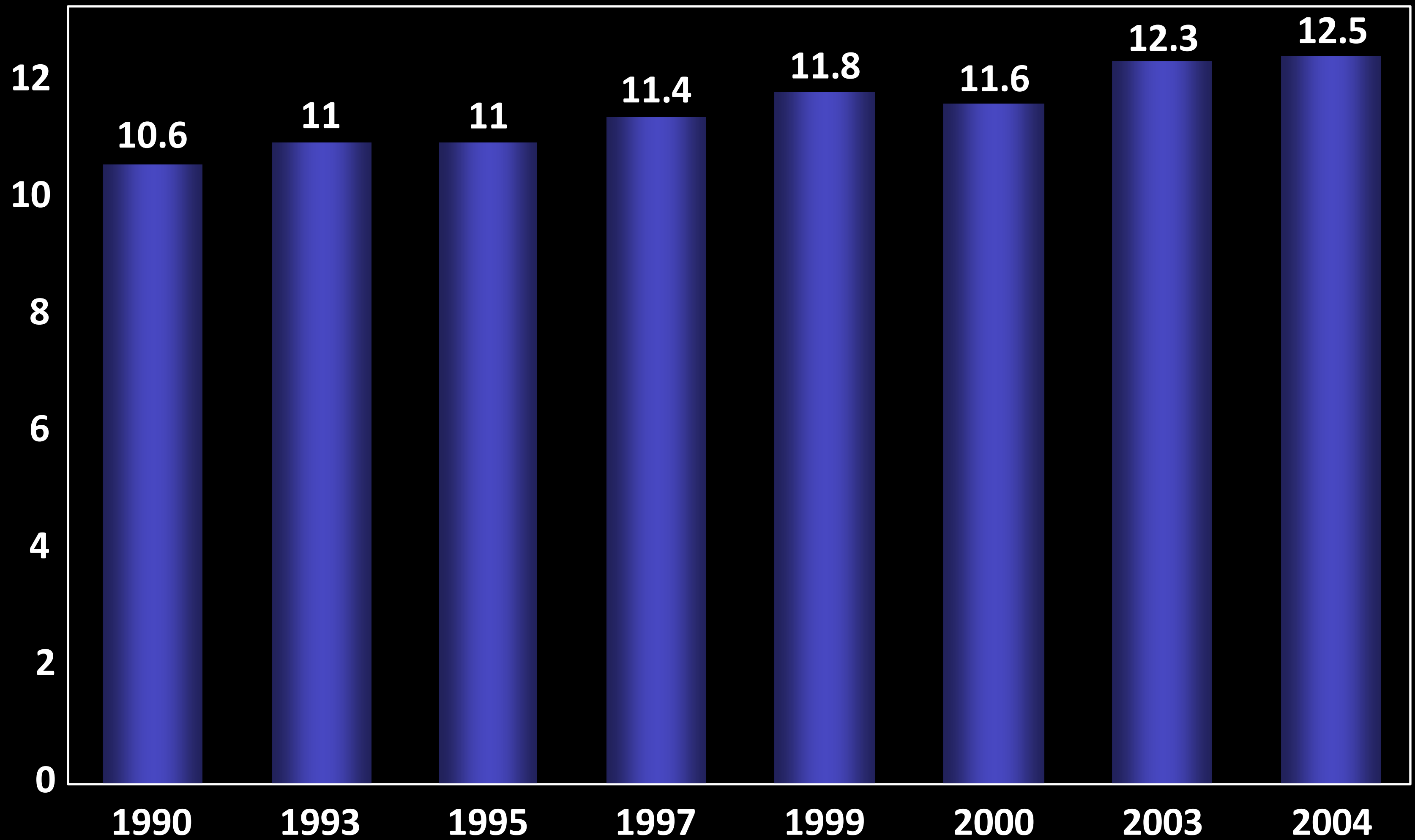
Richard E. Behrman, Adrienne Stith Butler, Editors

Institute of Medicine of the National Academies, 2006

Magnitude of the Problem

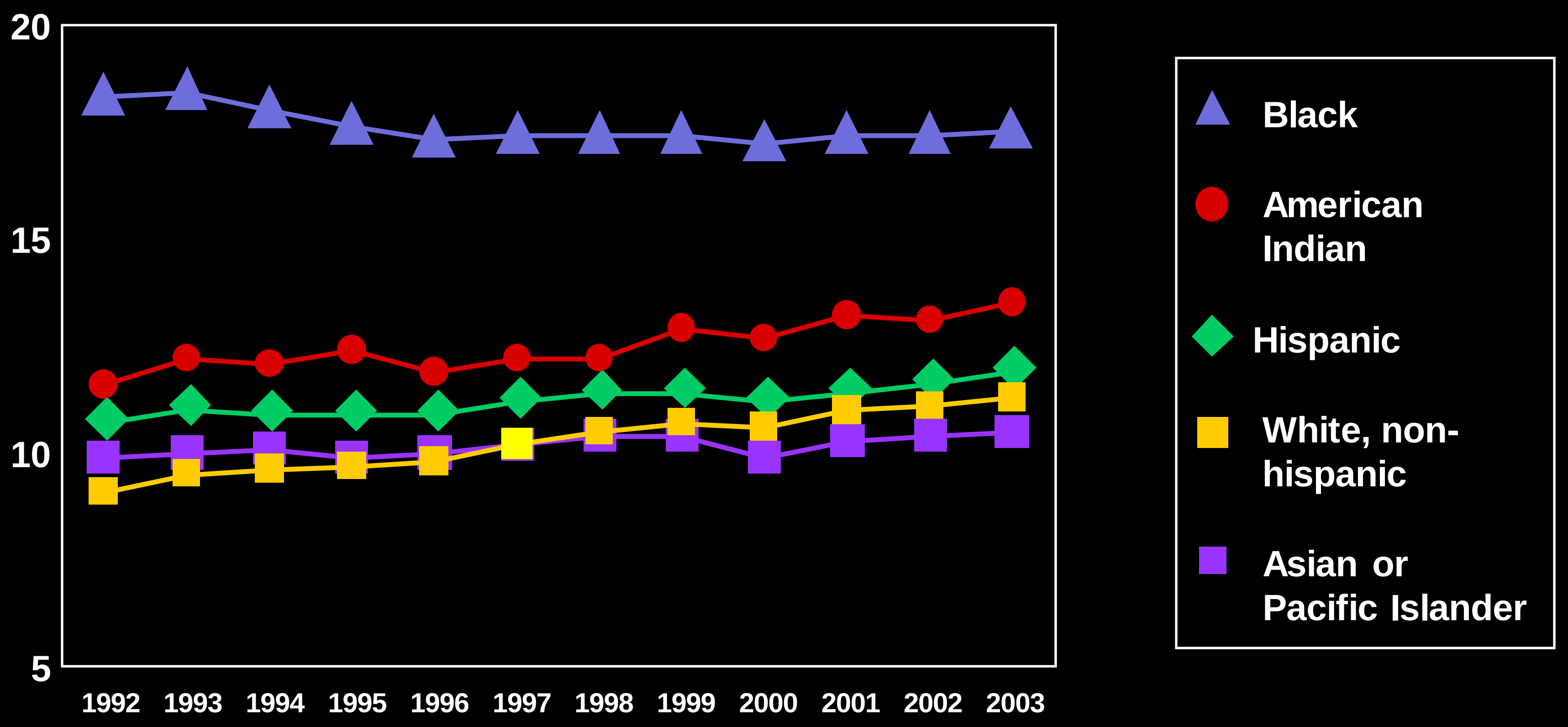
- Definition (< 37 weeks)
- 2004: more than 500,000 neonates were born preterm
- Frequency: 12.5 %

Preterm Births as a Percentage of Live Births in the United States, 1990 to 2004



Institute of Medicine. PRETERM BIRTH: CAUSES, CONSEQUENCES, AND PREVENTION. 2006.

Preterm Births as a Percent of Live Births, by Race and Ethnicity, 1992 to 2003



CDC 2004.

Frequency of Preterm Birth by Ethnic Group

Non-Hispanic African-American	17.8%
American Indians/Native Alaskans	13.5%
Hispanics	11.9%
Whites	11.5%
Asian and Pacific Islanders	10.5%

Source: CDC 2004 Births: Preliminary Data for 2003
http://www.cdc.gov/nchs/data/nvsr/nvsr53/nvsr_09.pdf (accessed August 30, 2005)

Cost of Preterm Birth

- <u>Medical care services</u>:
  - 16.9 billion ($ 33,200 per preterm infant) - 2/3 total cost
- <u>Maternal delivery cost</u>:
  - 1.9 billion ($ 3,800 per preterm infant)
- <u>Special education services</u>:
  - 1.1 billion ($ 2,200 per preterm infant)
- <u>Lost household and labor market productivity</u>:
  - 5.7 billion ($11,200 per preterm infant)

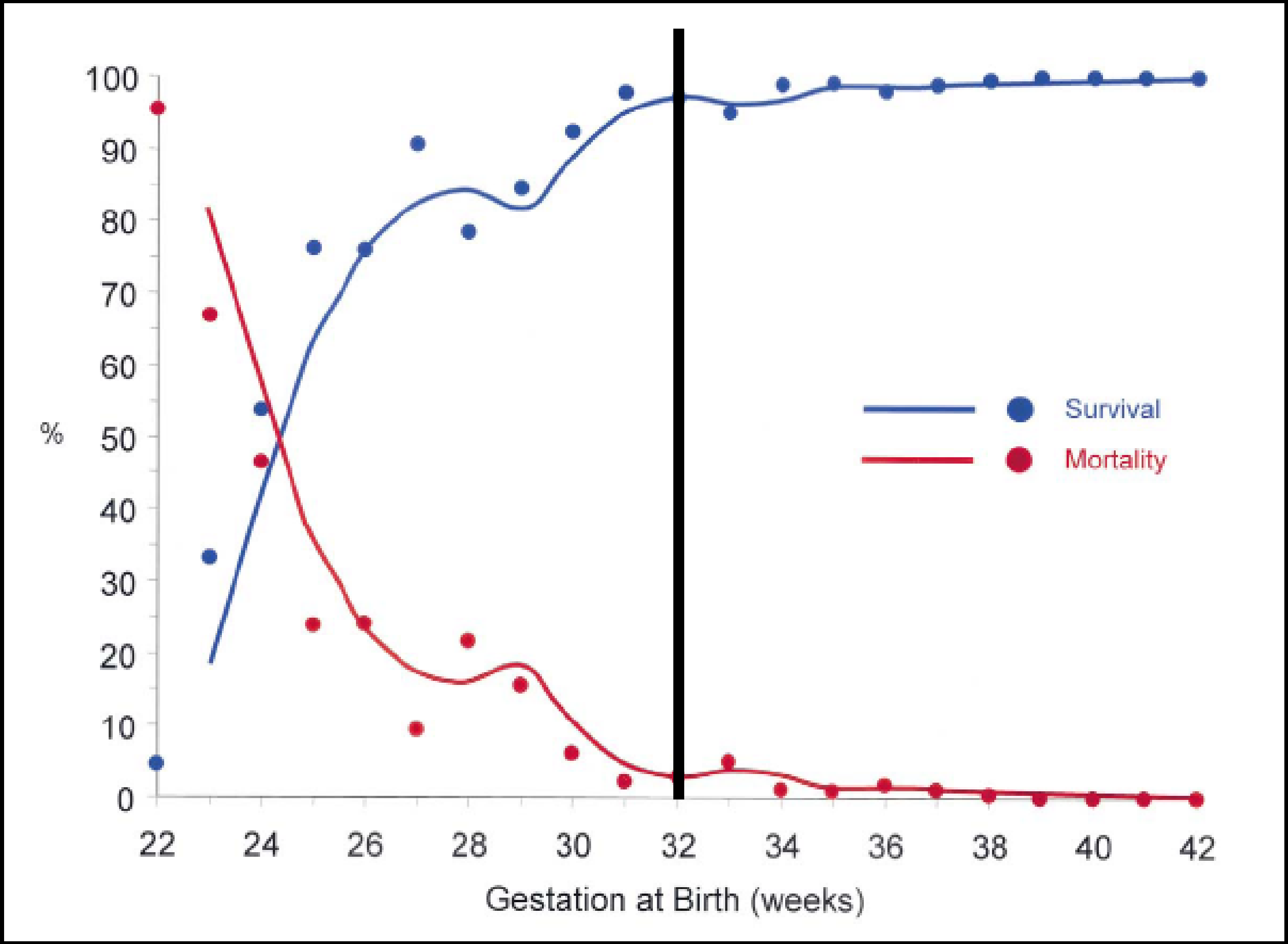
Source: Institute of Medicine of the National Academies 2006, page 47

The Annual Societal Economic Burden associated with Preterm Birth in the United States

In excess of $26.2 billion in 2005

The Prognosis of Preterm Neonates is a Function of Gestational Age at Birth

Survival by gestational age among live-born resuscitated infants



Results of a community-based evaluation of 8523 deliveries, 1997–1998, Shelby County, Tennessee

Mercer BM Obstet Gynecol 2003;101:178–93.

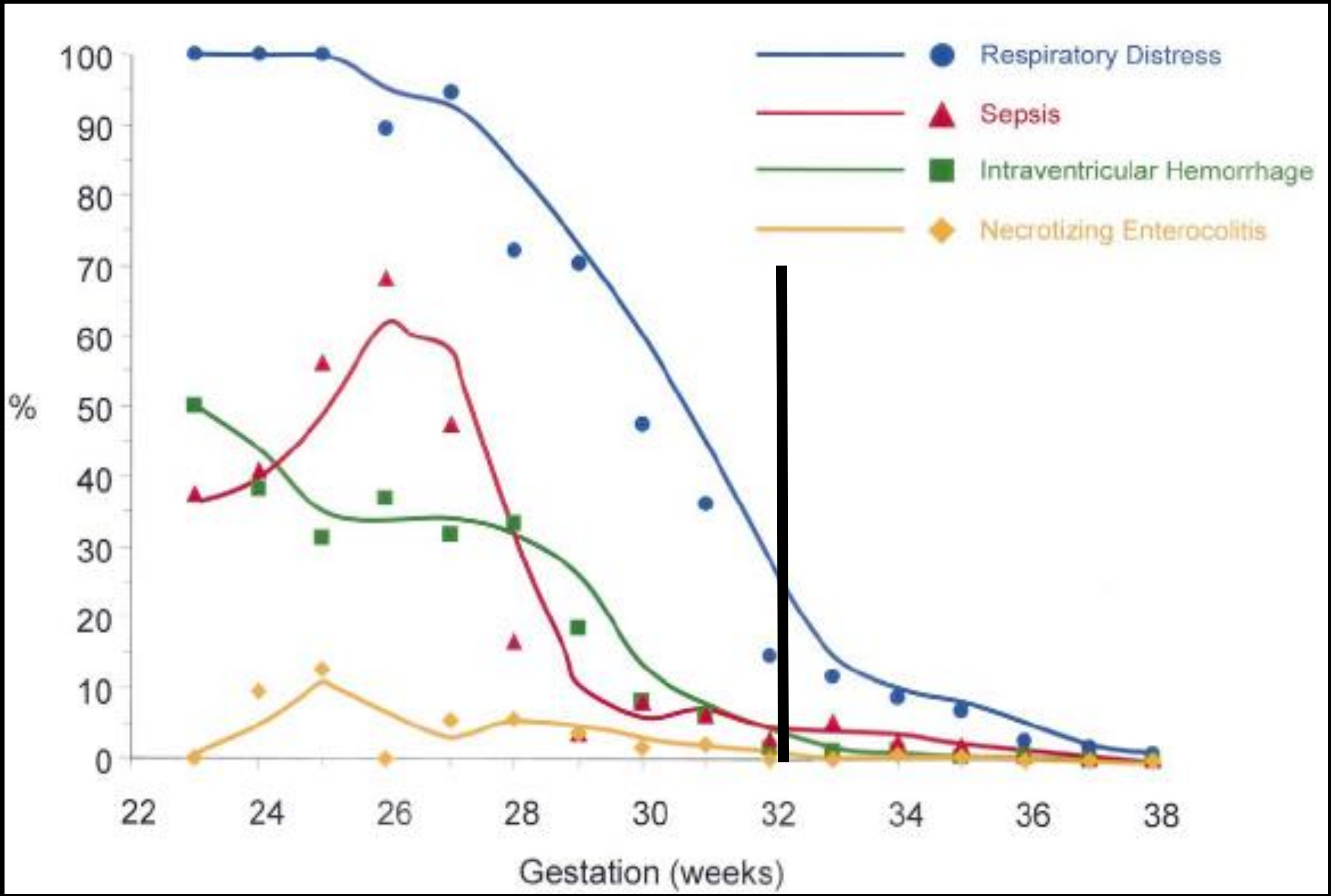
Magnitude of the Problem

- The infant mortality rate for very preterm infants (delivered < 32 weeks of gestation) was 186.4, nearly 75 times the rate for infants born at term (2.5) (37–41 weeks of gestation)

- 20% all infants born <32 weeks do not survive the first year of life

Mathews TJ. et al. National Vital Statistics Reports 2004;53:1-32

Acute morbidity by gestational age among surviving infants



Results of a community-based evaluation of 8523 deliveries, 1997–1998, Shelby County, Tennessee

Mercer BM Obstet Gynecol 2003;101:178–93.

IOM Report – July 2006

- **"Babies born before 32 weeks have the greatest risk for death and poor health outcomes, however, infants born between 32 and 36 weeks, which make up the greatest number of preterm births, <u>are still at higher risk for health and developmental problems compared to those infants born full term</u>**

IOM Report page 72

Frequency of preterm birth by gestational age (1995-2000)

- < 28 weeks : 0.82 %
- < 32 weeks: 2.2 %
- 33-36 weeks: 8.9 %
- < 37 weeks: 11.2

IOM Report-July 2006- page 72/2006
Alexander GR et al 2006 (under review)

Complications of "Late Preterm or Near Term Infants"

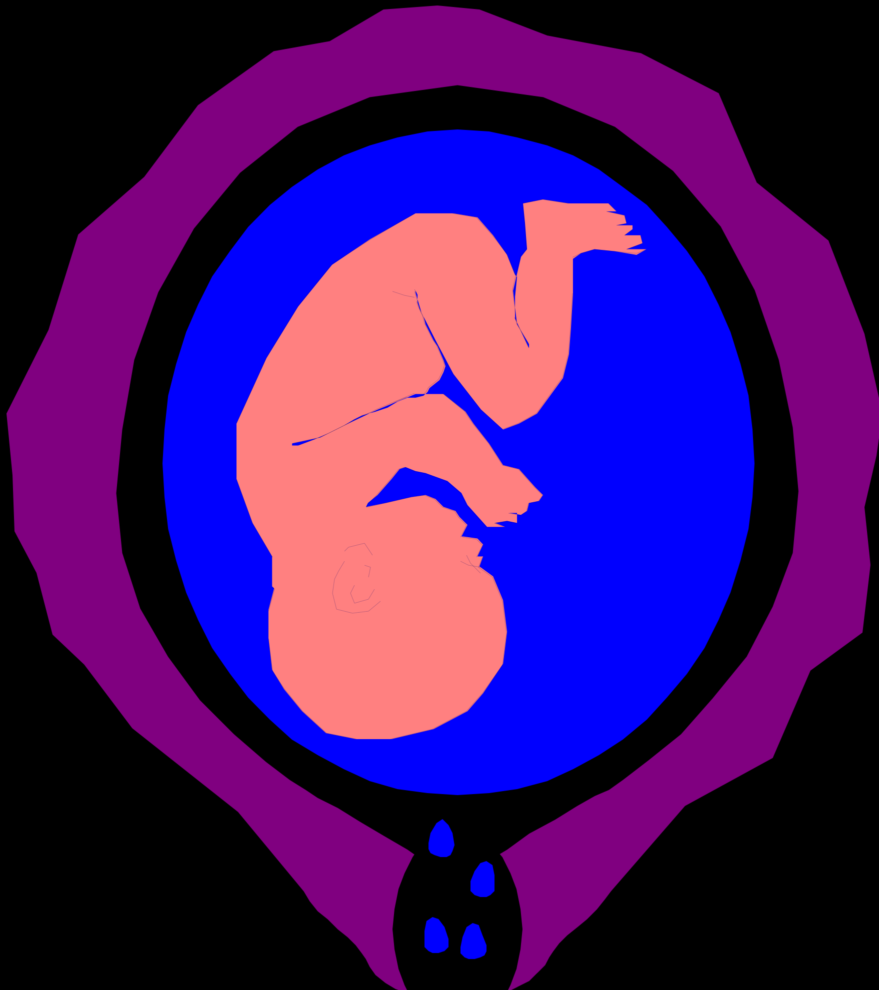
- Cold Stress
- Hypoglycemia
- RDS
- Jaundice
- Sepsis

IOM Report-July 2006- page 72/2006

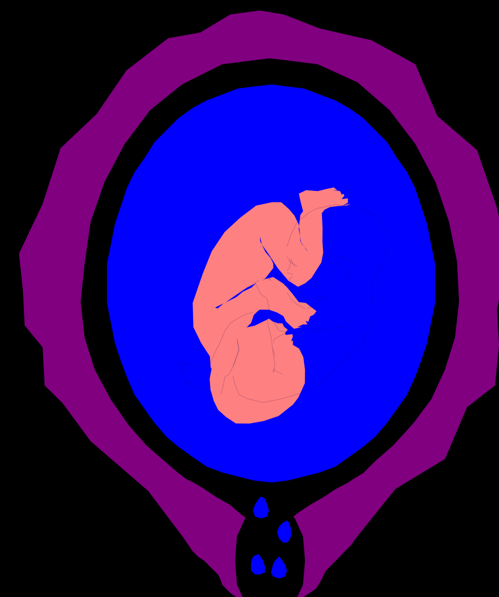
Clinical Circumstances Associated with Preterm Birth

- Spontaneous preterm labor with intact membranes
- Preterm PROM
- Indicated preterm delivery
  - Maternal (e.g. pre-eclampsia)
  - Fetal (e.g. SGA/fetal compromise)

Is preterm labor simply “labor before its time” ?



Term Labor



Preterm Labor

Common Uterine Features of Term and Preterm Labor

- Increased myometrial contractility
- Cervical ripening (dilatation and effacement)
- Decidual/membrane activation

Romero R, Mazor M, Munoz H et al: The Preterm Labor Syndrome. Ann NY Acad Sci 1994;734:414

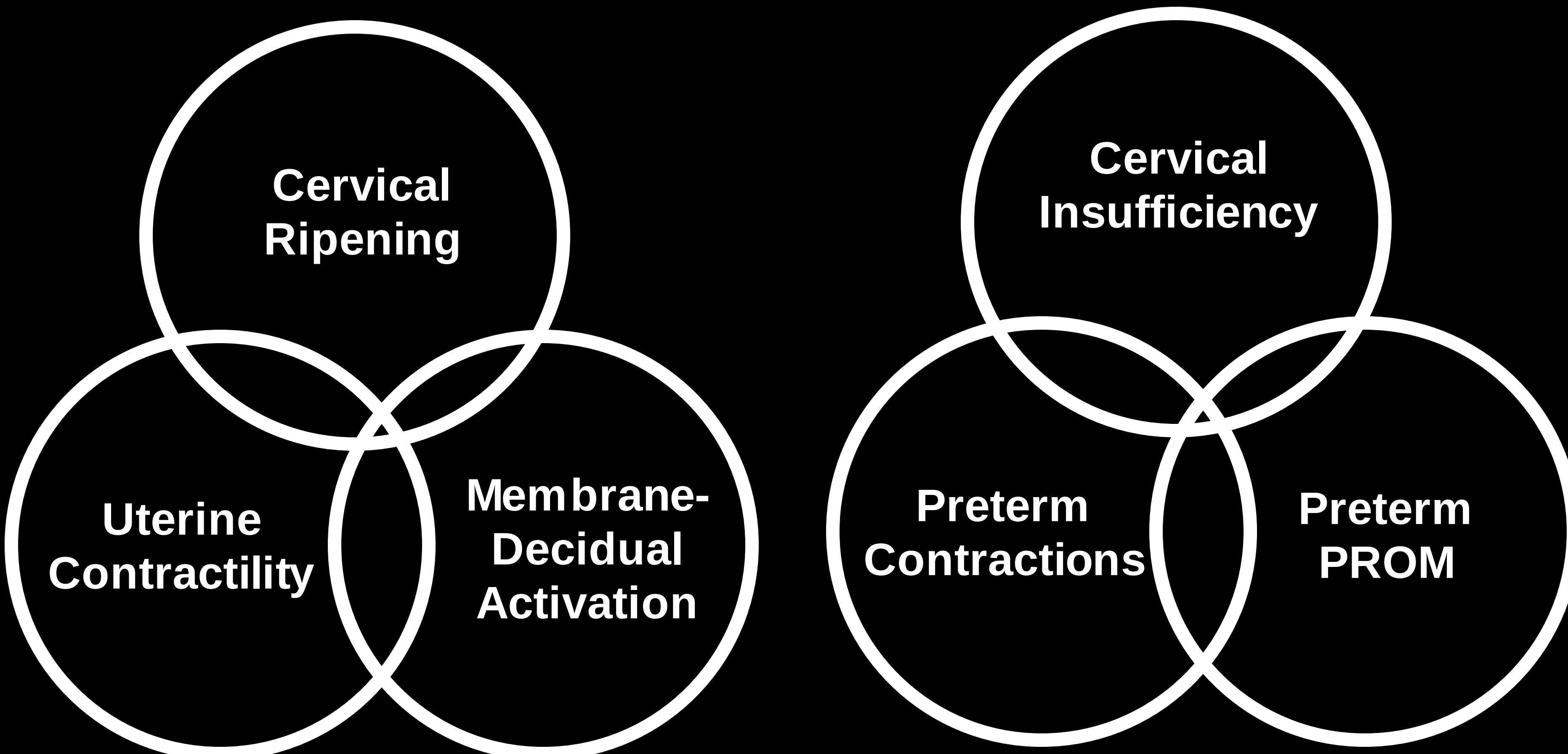
Common Pathway of Parturition

- Anatomic, physiologic, biochemical, endocrinologic, immunologic, and clinical events in the mother and/or fetus in both term and preterm labor

Romero R, Mazor M, Munoz H et al: The Preterm Labor Syndrome. Ann NY Acad Sci 1994;734:414

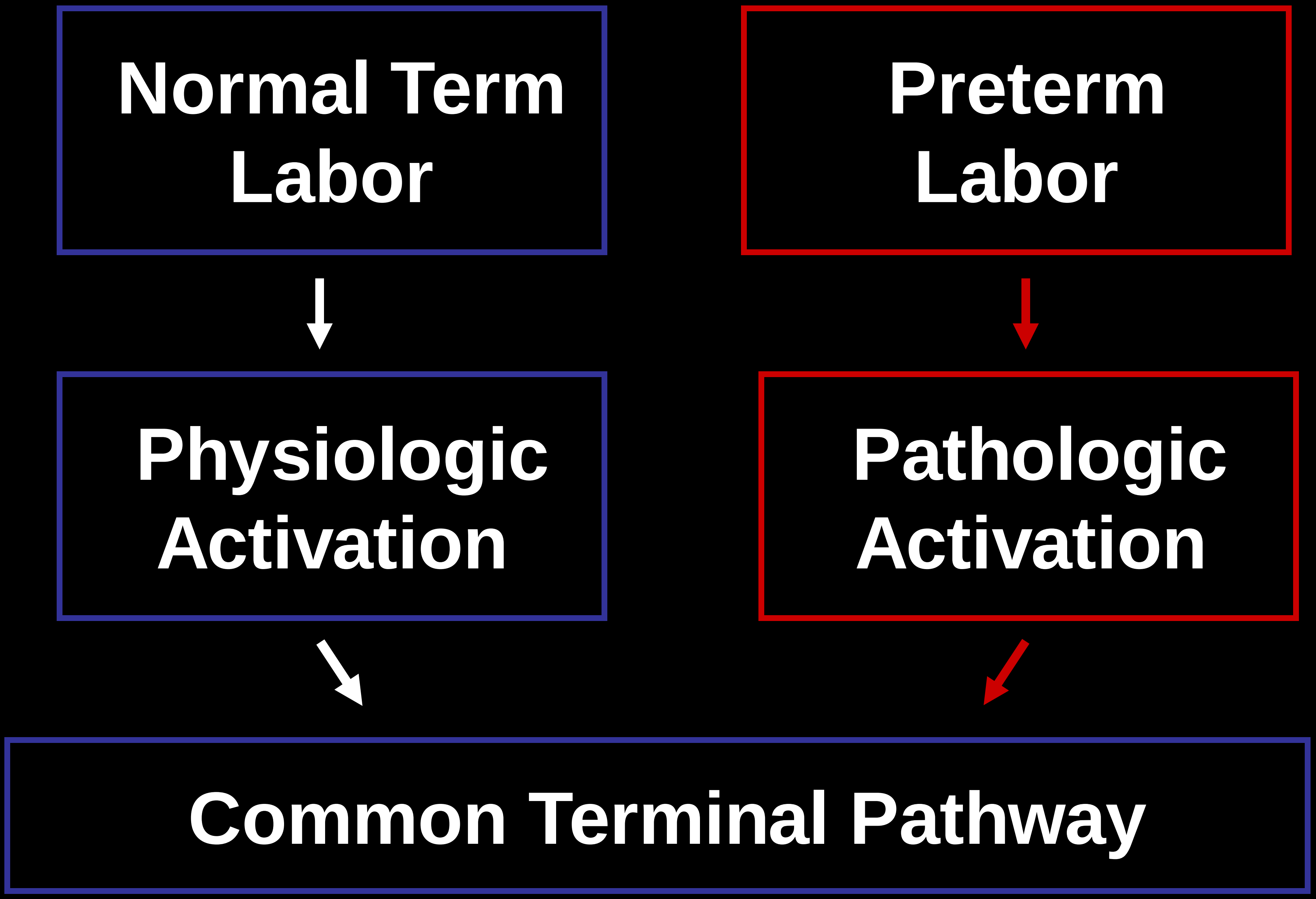
The “phenotypes” of spontaneous preterm parturition

Synchronous and Asynchronous Activation of Labor



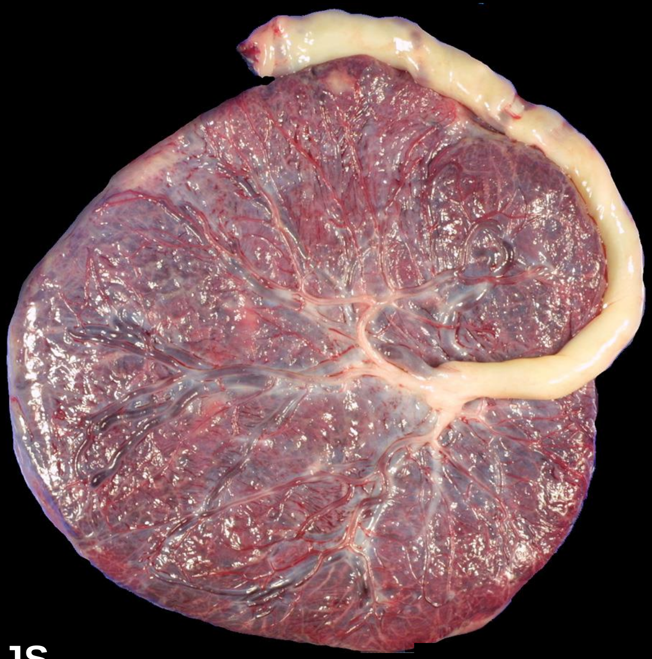
Approaches for the Prevention of Preterm Birth

Component	Test	Treatment
Myometrium	Uterine Monitor	Tocolysis
Cervix	Ultrasound	Cerclage
Membrane/Decidua	Fetal Fibronectin	Antibiotics

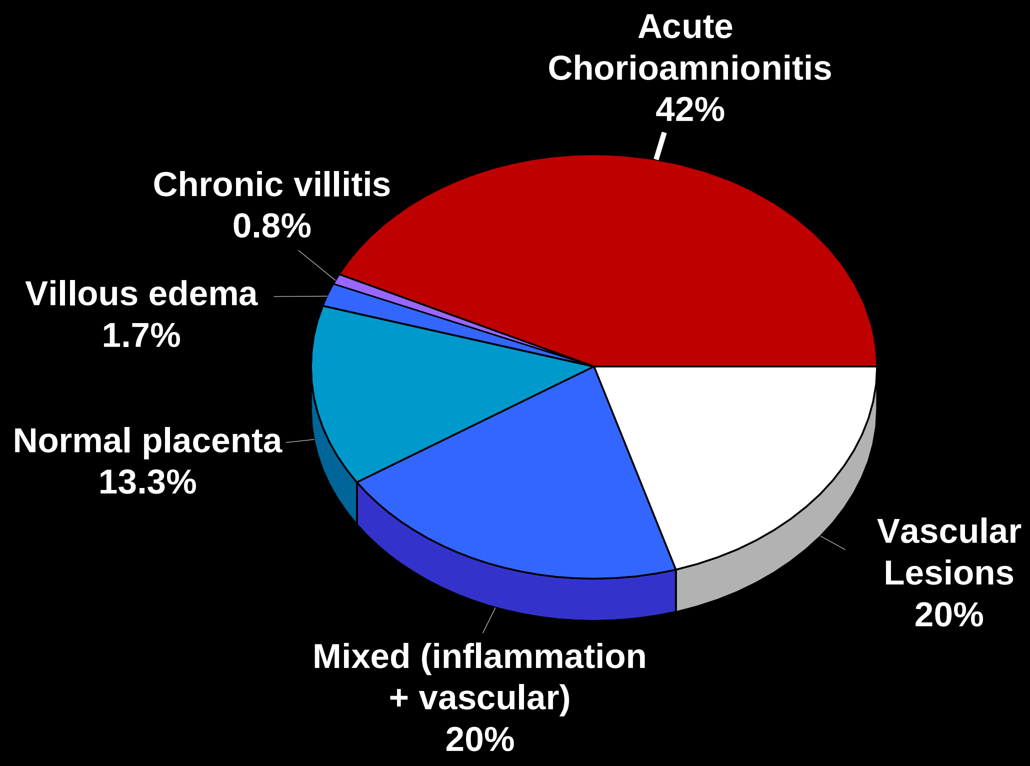

Normal Term Labor
Preterm Labor
Physiologic Activation
Pathologic Activation
Common Terminal Pathway

What causes pathologic activation of the pathway ?

Placental Pathology in Prematurity



© PJS



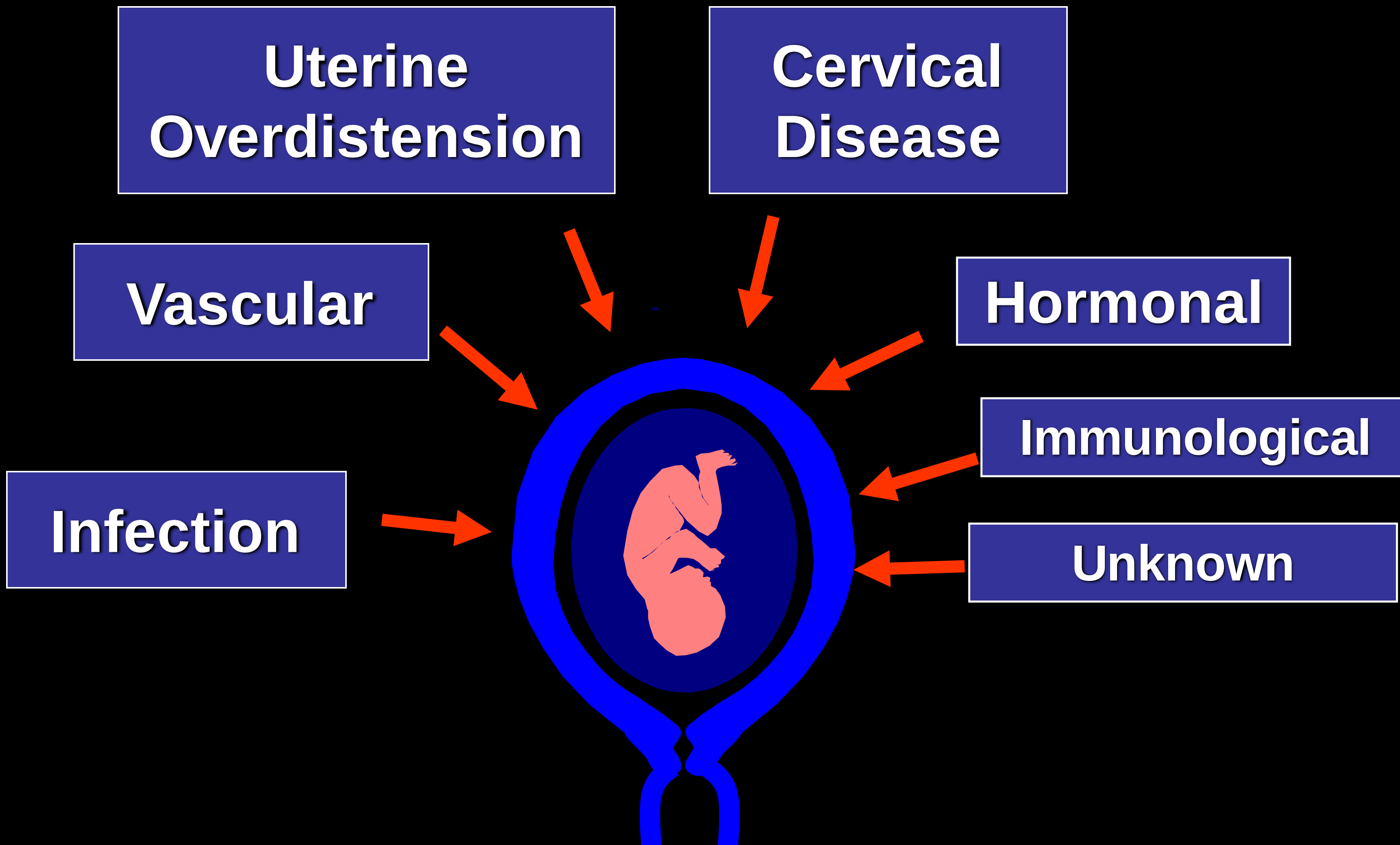
Arias et al. Obstet Gynecol 1997;69:285.

“Great Obstetrical Syndromes”

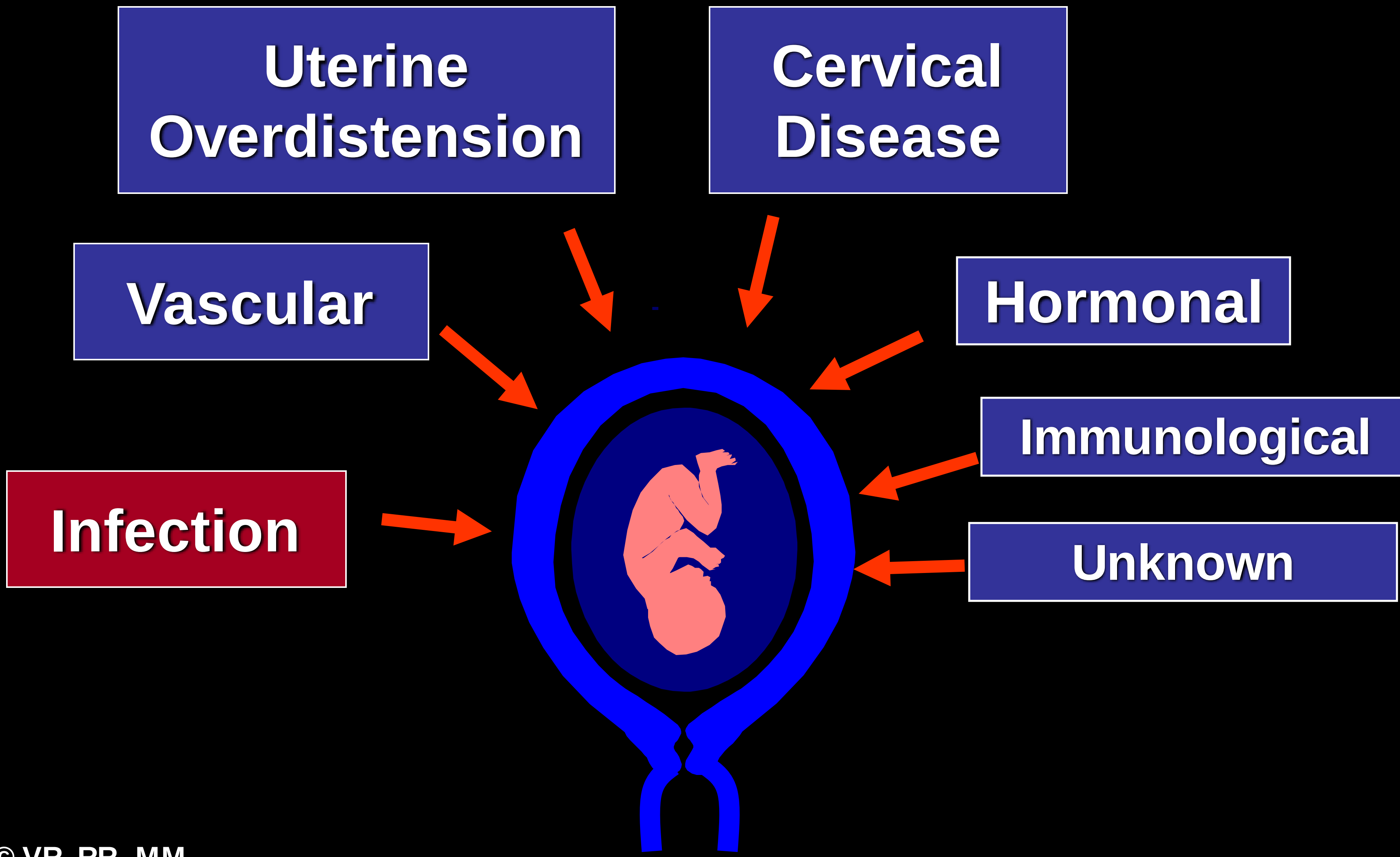
- Multiple etiologies
- Chronicity
- Fetal diseases
- Clinical manifestations are adaptive
- Symptomatic treatment is ineffective
- Genetic/environmental factors

Romero R J Prenat Neonat Med 1996;1:8-11

The Preterm Parturition Syndrome



The Preterm Parturition Syndrome



Intraamniotic Infection

- <u>Frequent: 25 % (at presentation)</u>
- Sub-clinical
- Fetal disease
- FIRS
- Host defense

Sub-clinical

Clinical Chorioamnionitis

- 12% of preterm labor
- 20% of preterm PROM

FIRS

- Impending preterm delivery
- Severe neonatal morbidity
- Fetal multisystem involvement

Fetal Inflammatory Response Syndrome

- Hematologic Abnormalities
- Endocrine System
- Cardiac Dysfunction
- Pulmonary Injury
- Renal Dysfunction
- Brain Injury (PVL)

How common is sub-clinical intra-amniotic infection in asymptomatic midtrimester pregnancy

Infection in mid-trimester

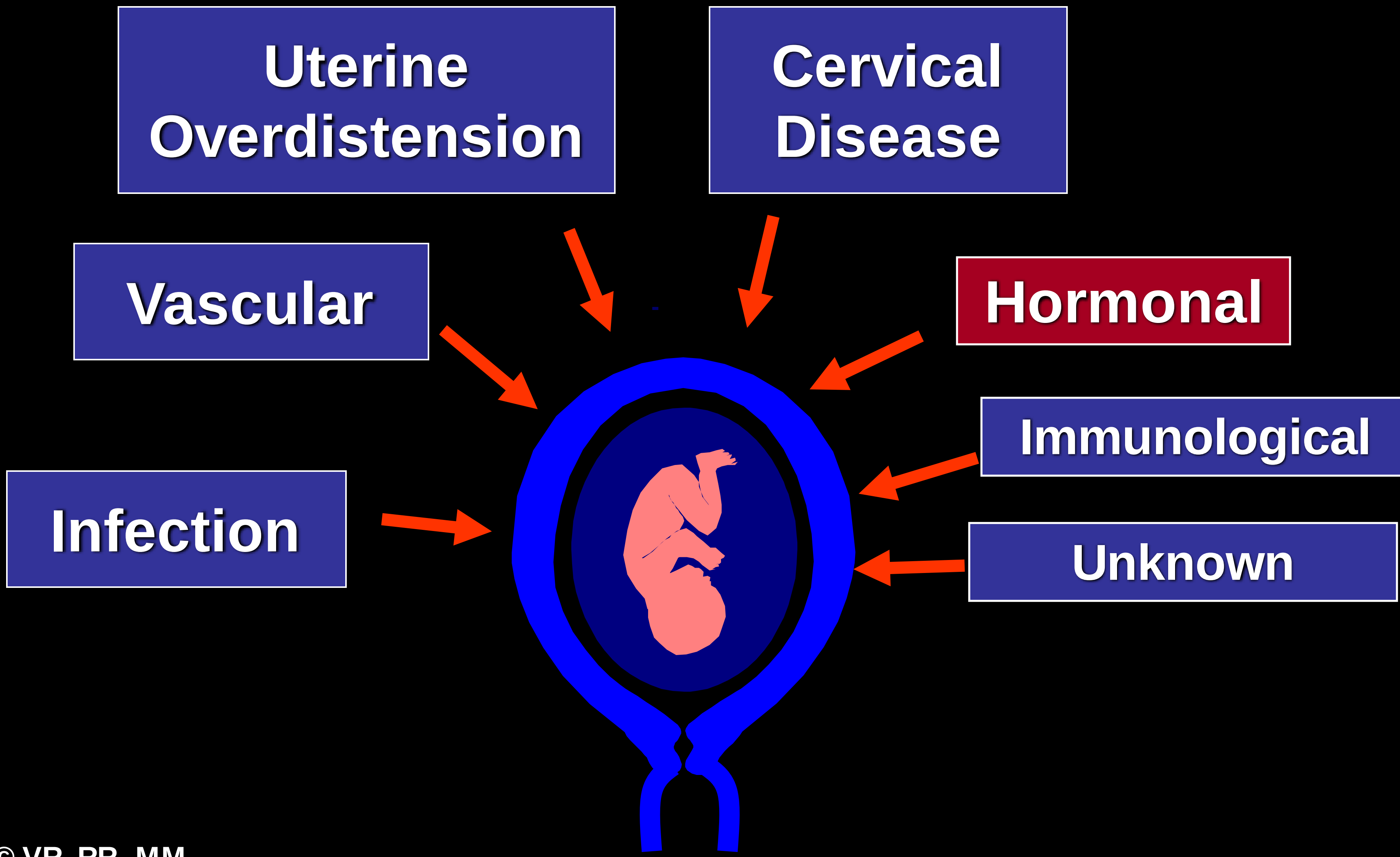
- **2461 midtrimester amniocenteses**
- **9 patients with *U. urealyticum* (0.4%)**
- **8 continuing pregnancies**
  - **6 spont. abortions within 4 weeks**
  - **2 preterm labor**
  - **8 histologic chorioamnionitis**

Gray DJ. Prenat Diagn 1992;12:111

Prevention of Preterm Labor/Delivery

- Important and desirable goal
- Only proven beneficial strategy is eradication of asymptomatic bacteriuria
- Limited attributable risk
- Patients with previous preterm birth are at increased risk for recurrence
- Potential beneficial effect of progesterone administration
  - 17OHP-C and vaginal progesterone

The Preterm Parturition Syndrome



“Progesterone deficient state” has been proposed to be a Mechanism of Disease in Preterm Labor

Corpus Luteum

http://medstat.med.utah.edu/

http://www.siumed.edu/~dking2/erg/enguide

Effects of luteectomy and progesterone replacement therapy in early pregnant patients

A. I. CSAPO
M. O. PULKKINEN
W. G. WIEST
St. Louis, Missouri, and Turku, Finland

AJOG 1973;115:759-65

THE EFFECT OF LUTEECTOMY-INDUCED PROGESTERONE-WITHDRAWAL ON THE OXYTOCIN AND PROSTAGLANDIN RESPONSE OF THE FIRST TRIMESTER PREGNANT HUMAN UTERUS

A.I. Csapo, M.O. Pulkkinen and H.L. Kaihola

Prostaglandins 1973;4:421-9

The significance of the human corpus luteum in pregnancy maintenance

I. Preliminary studies

A. I. CSAPO
M. O. PULKKINEN
B. RUTTNER
J. P. SAUVAGE
W. G. WIEST
St. Louis, Missouri, Turku, Finland, and Nagykoros, Hungary

AJOG 1973;115:759-65

What is the Effect of Luteectomy on Human Pregnancy?

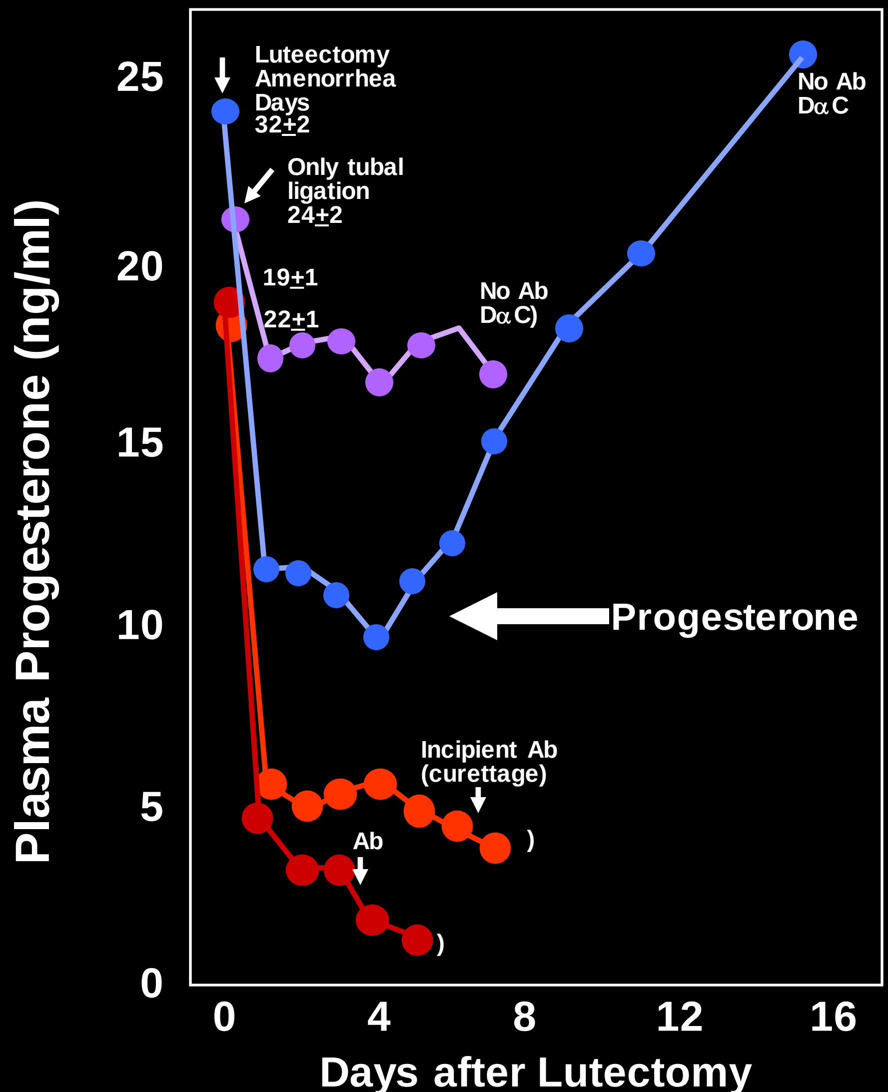
- 64 pregnant women (< 5 weeks)
- Desired tubal ligation
- IRB approval
- Allocated to:
  - Tubal ligation (control group)
  - Tubal ligation + luteectomy
  - Tubal ligation + luteectomy + progesterone

American Journal of Obstetrics and Gynecology: 1972

Prostaglandins: 1973

Ciba Symposium 47: 1977

Pregnancy outcome after lutectomy



Csapo AI The Fetus and Birth. Ciba Foundation Symposium 47; 1977.

Arpard Csapo

- Progesterone is “indispensable” for normal pregnancy
- Progesterone withdrawal is a prerequisite of normal pregnancy termination

Progesterone in Pregnancy Maintenance

- Myometrial quiescence
- Down-regulate gap junction formation
- Inhibit cervical ripening

A progesterone withdrawal "prepares" the uterus for the action of uterotonic agents

Evidence that suspension of progesterone action is important in human parturition

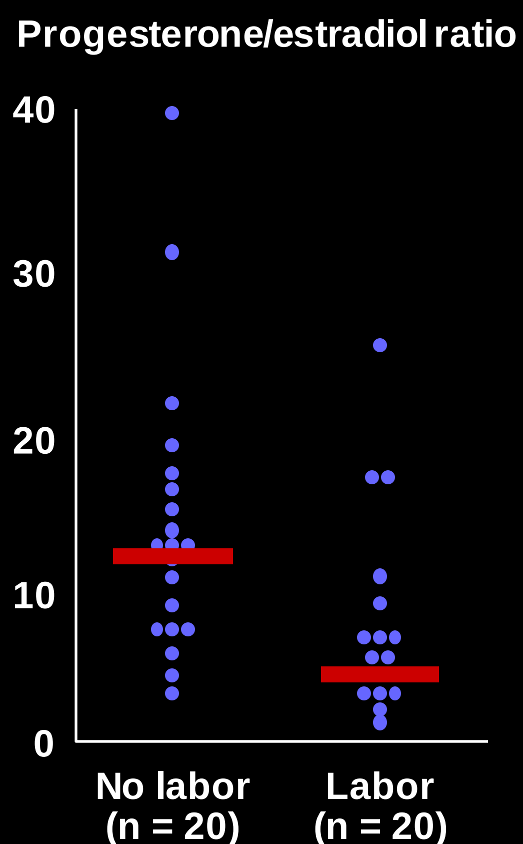
Administration of anti-progestins (RU-486 or onapristone) can induce abortion and cervical ripening

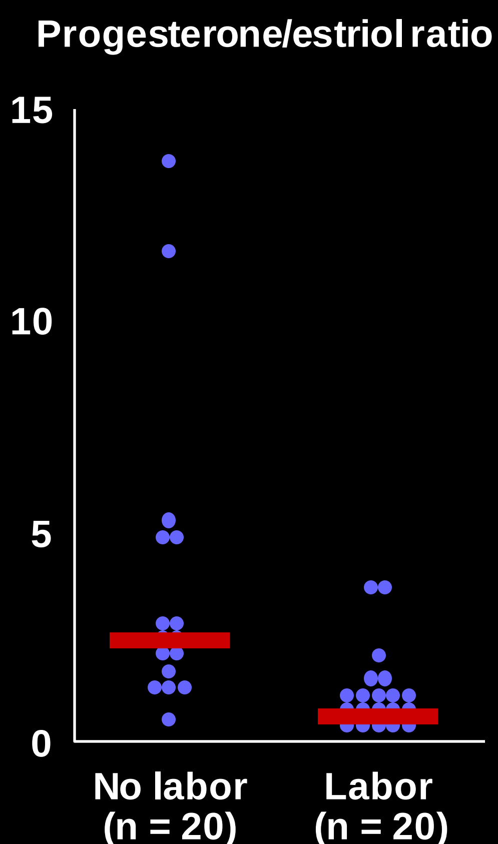
Kovacs L et al. Contraception 1984; 29: 399
Crowley WF. N EJM 1986; 18: 1607
Chwalisz K. 1994 Human Reproduction 1994;9:131
Bygdeman et al. Human Reproduction 1994;9:120

Evidence for a local change in the progesterone/estrogen ratio in human parturition at term

Roberto Romero, MD,[a]* Bert Scoccia, MD,[b] Moshe Mazor, MD,[a] Ying King Wu, MD,[a] and Robert Benveniste, PhD[b]

New Haven, Connecticut, and Chicago, Illinois





Romero R et al AJOG 1988;150:650-60

Progesterone

- Key hormone for pregnancy maintenance
- "Progesterone withdrawal":
  - Concentration
  - Receptor (A and B)

Mesiano S, Chan E, Fitter JT, Kwek K, Yeo G, and Smith R.
J Clin Endocrinol Metab 2002; 87:2924

  - Functional (NF-kB)

Allport VC, Pieber D, Slater
DM, Newton R, White JO and Bennett PR.
Mol Human Reprod 2001; 7:581-6

The clinical trials and meta-analysis of progesterone will be analyzed by FDA staff and the sponsor

Interventions for the prevention of preterm birth

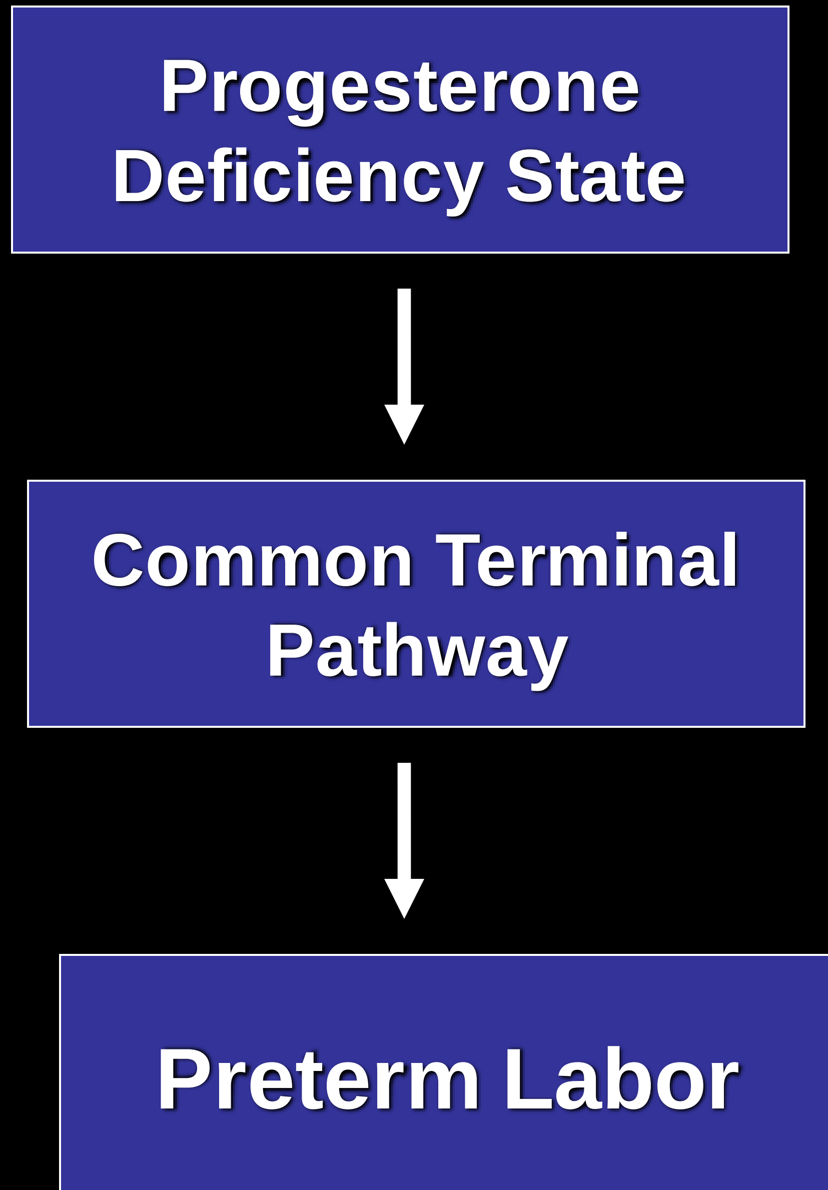
- Efficacy
- Safety

Criteria for Efficacy

- Prevention of preterm birth
  - 37 weeks
  - 35 weeks
  - 32 weeks
- Prolongation of pregnancy
- Neonatal morbidity and mortality

Safety

- Fetal
- Neonatal
- Infant
- Maternal


Progesterone Deficiency State
Common Terminal Pathway
Preterm Labor

ACOG

Committee on
Obstetric Practice

Committee Opinion

Number 291, November 2003

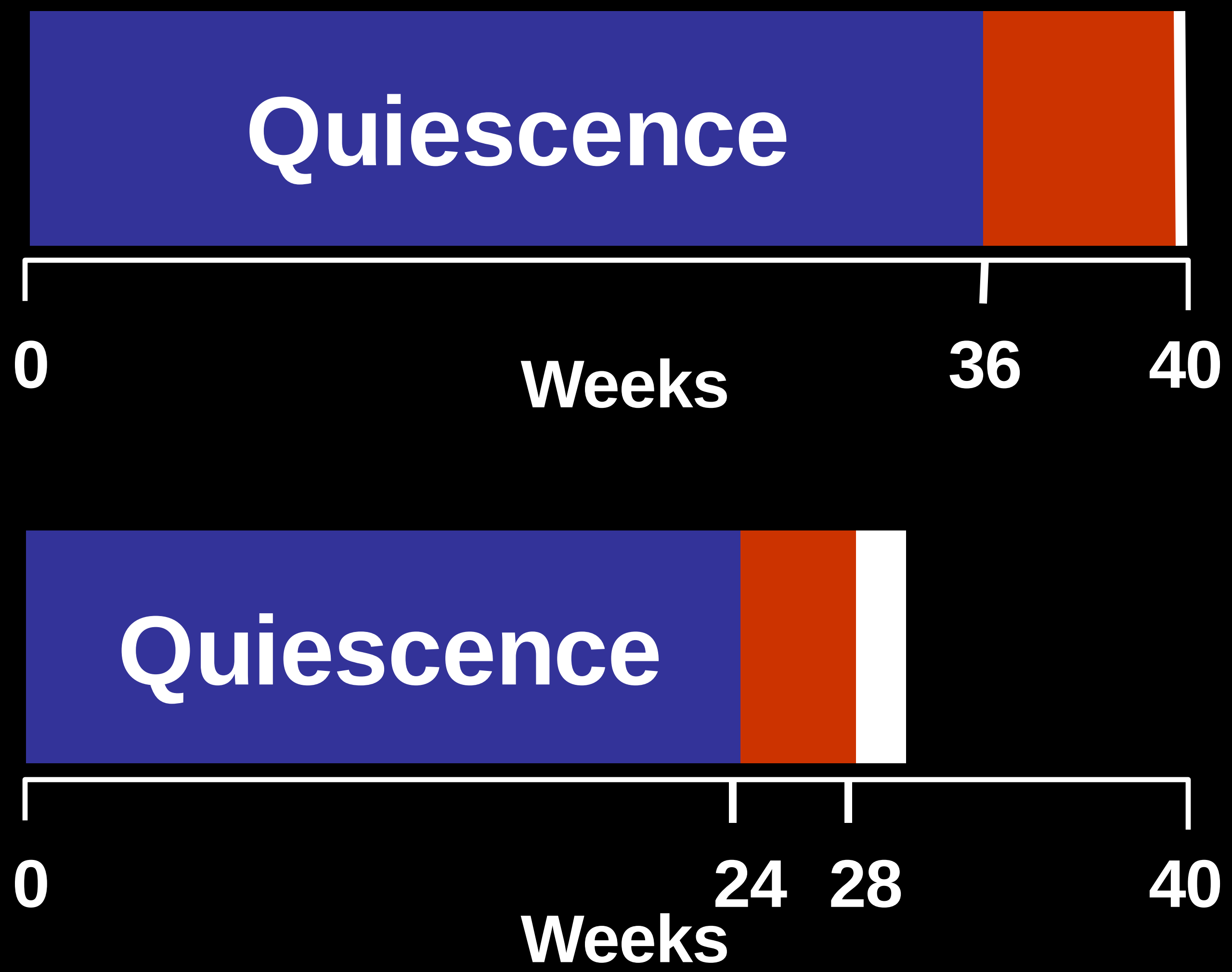
Use of Progesterone to Reduce Preterm Birth

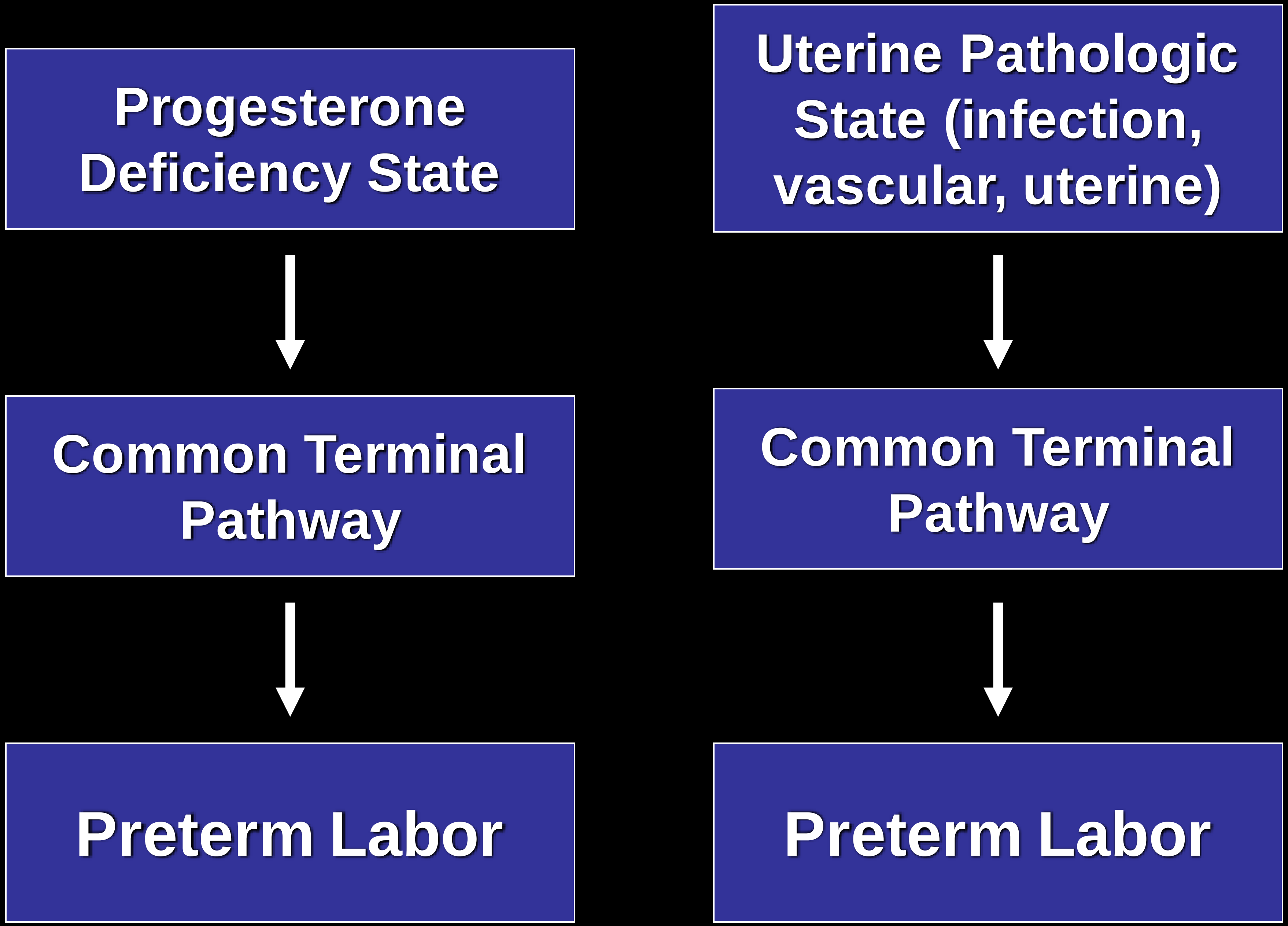
Obstet Gynecol 2003;102:1115-6

When progesterone is used, it is important to restrict its use to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug.

Obstet Gynecol 2003;102:1115-6

The preparatory stage of labor




Progesterone Deficiency State
Common Terminal Pathway
Preterm Labor
Uterine Pathologic State (infection, vascular, uterine)
Common Terminal Pathway
Preterm Labor

Meeting of the Advisory Committee for Reproductive Health Drugs

August 29, 2006

Barbara Wesley, M.D., M.P.H.
Division of Reproductive and Urologic Products

NDA 21-945
17α Hydroxyprogesterone Caproate (Gestiva)

Proposed Indication

- Gestiva is indicated for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth

Dosage & Administration

- Gestiva is to be administered IM at a dose of 250 mg once a week beginning between 16-weeks 0-days (16^0 weeks) and 20-weeks 6-days (20^6 weeks) gestation to week 37 of gestation or birth

Overview of Clinical Studies

Study 17P-IF-001

- Randomized, vehicle-controlled study with target enrollment of 500 subjects
- 150 subjects enrolled and treated
- Study terminated prematurely: recall of study drug

Study 17P-CT-002

- Principal efficacy and safety study
- Terminated prematurely: crossed efficacy threshold
- 463 of 500 planned subjects enrolled and treated
  - 17OHP = 310; vehicle = 153

Study 17P-FU

- Follow-up for long-term health and development
- 278 subjects enrolled: 17OHP = 194; vehicle = 84

Study 17P-CT-002

Design

- Double blind, vehicle-controlled with subjects randomized 2:1 to 17OHP or vehicle

Inclusion Criteria

- History of spontaneous singleton preterm birth
- Gestational age of 16^0 to 20^6 at randomization

Main Exclusion Criteria included

- Known major anomaly
- Prior progesterone or heparin Rx in current pregnancy
- Hx of thromboembolic disease
- Maternal medical/obstetrical complications including
  - Current or planned cerclage
  - Hypertension requiring medication
  - Seizure disorder

Study 17P-CT-002

Study Medications

- 17α-hydroxyprogesterone caproate (250 mg/mL) in castor oil, benzyl benzoate, and benzyl alcohol
- Vehicle

Dosing Regimen

- Weekly IM injection through Week 36^6 or delivery

Primary Efficacy Endpoint

- Birth < 37^0 weeks

Additional Efficacy Endpoints (post hoc)

- Birth < 35^0 weeks and < 32^0 weeks
- Composite index of neonatal morbidity
  - Death, RDS, bronchopulmonary dysplasia, Gr. 3 or 4 IVH, proven sepsis, necrotizing enterocolitis

Overview of Subject Disposition
Study 17P-CT-002

	17OHP N=310 n (%)	Vehicle N=153 n (%)
Completed Treatment	279 (90.0)	139 (91.0)
Withdrawn from Treatment	27 (8.7)	14 (9.2)
Due to Adverse Event	6 (1.9)	3 (2.0)
Lost to Follow-up	4 (1.3)	0

Preterm Births <37^{0} Weeks Gestation in ITT Population (Study 17-P-CT-002)

Primary Efficacy Endpoint

17OHP N = 310	Vehicle N = 153	% Difference [Adjusted 95% Confidence Interval]
Number (%) Preterm Births		
115 (37.1%)	84 (54.9%)	-17.8% [-28%, -7%]

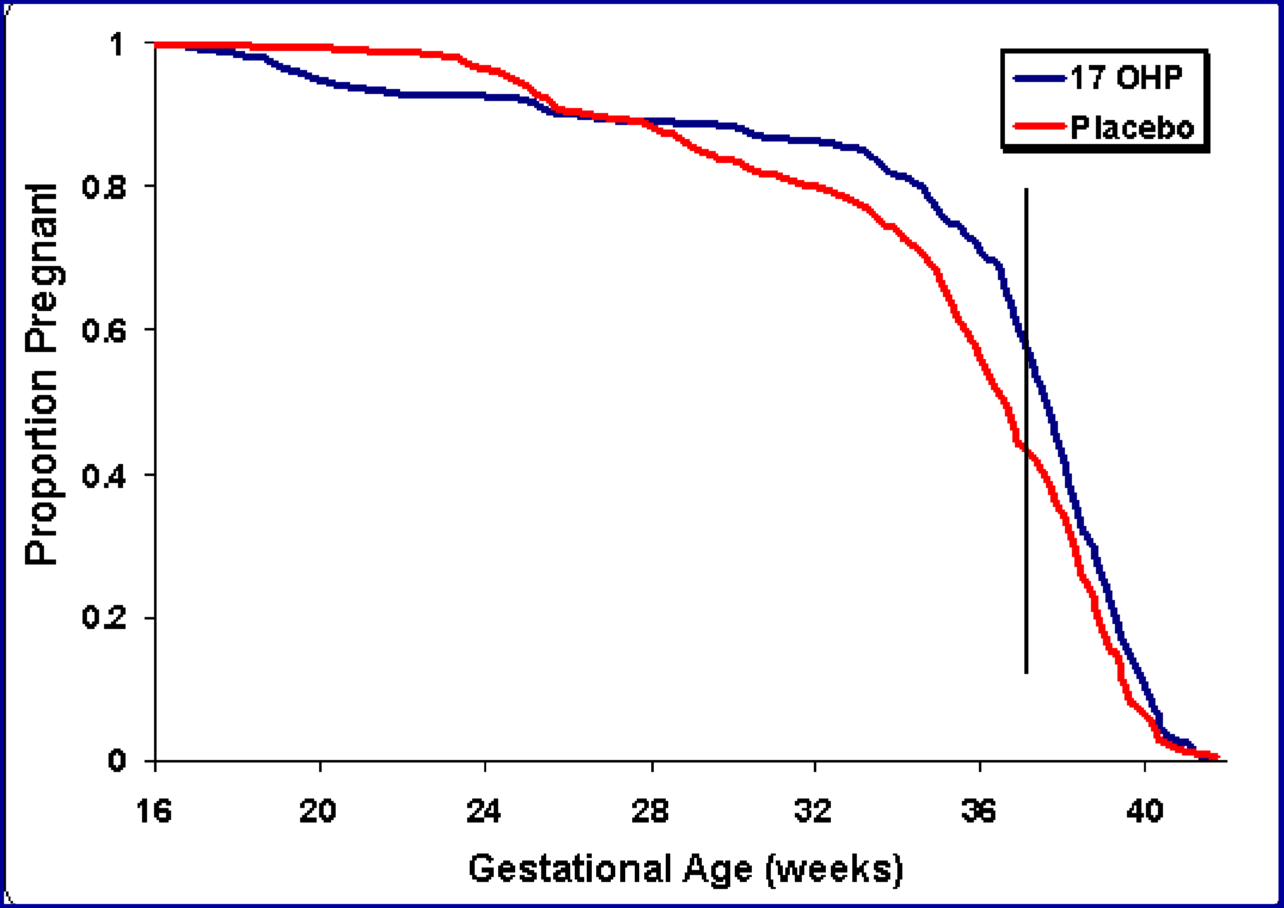
- PTB rate of **54.9%** in vehicle arm considerably greater than rate in other MFMU Network studies
- PTB rate of **37.1%** in 17OHP arm similar to PTB rate in control arms in another MFMU Network studies

Percent of Preterm Births in Revised ITT Population (Study 17-P-CT-002)

Age at Delivery (Weeks)	17OHP N=310	Vehicle N=153	% Difference [Adjusted 95% Confidence Interval]
	Percent Delivered		
< 37^0	37.1	54.9	-17.8% [-28%, -7.0%]
< 35^0	21.3	30.7	-9.4% [-18.7%, -0.2%]
< 32^0	11.9	19.6	-7.7% [-15.5%, 0.1%]
< 28^0	9.4	10.5	-1.1% [-7.4%, 5.2%]

Confidence intervals adjusted for the interim analyses and the final analysis. To preserve overall Type I error rate of .05, p-value boundary of .035 used for the adjustment (equivalent to a 96.5% confidence interval).

Proportion of Enrolled Subjects Continuing to be Pregnant by Gestational Age



Gestational Age (Weeks) at Delivery (Study 17P-CT-002)

	17OHP N=306	Vehicle N=153
Median	37.5	36.5
Mean	36.2	35.2
Min, Max	18.1, 41.5	20.3, 41.6

Difference between groups (mean)

1.0 week [95%CI: 0.3,1.5]

Birthweight (Study 17P-CT-002)

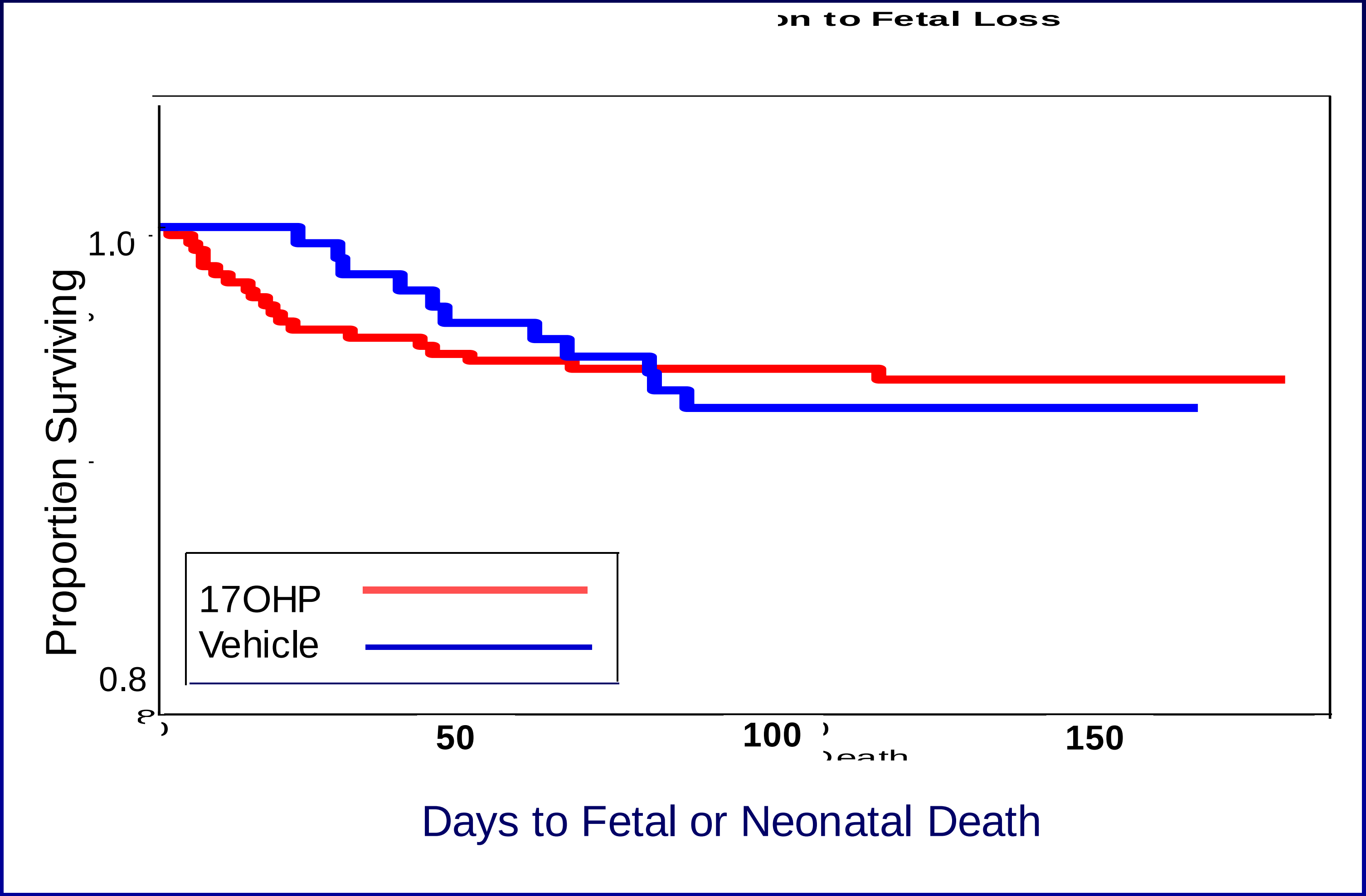
	17OHP N=301	Vehicle N=151
Mean Weight (gm)	2760	2582
Gm Difference [95%CI]	178.2 [-13, 290]	
Birthweight	n (%)	n (%)
<2500 gm	82 (27.2%)	62 (41.1%)
% Difference [95%CI]	-13.8% [-23, -4.5]	
<1500 gm	26 (8.6%)	21 (13.9%)
% Difference [95%CI]	-5.3% [-11.6, 1.1]	

Miscarriages, Stillbirths, and Neonatal Deaths (Study 17P-CT-002)

Pregnancy Outcome	17OHP N=306 n (%)	Vehicle N=153 n (%)
Miscarriages (16 to <20 weeks)	5 (1.6)	0
Stillbirths	6 (2.0)	2 (1.3)
Neonatal Deaths	8 (2.6)	9 (5.9)
Total Deaths	**19 (6.2)**	**11 (7.2)**

- **No net survival benefit**

Days from Onset of Treatment to Fetal or Neonatal Death



Literature Reports of Fetal Loss in Women Treated with 17-hydroxyprogesterone Caproate

Study	17OHP n N	Vehicle n N
LeVine (1964)	3/15	7/15
Shearman (1968)	5/27	5/23
Johnson (1975)	3/23	0/27
Yemini et al. (1985)	8/39	3/40

n = Number of fetal losses
N = Number of subjects in treatment group
From: Keirse MJ, Brit J Obstet Gynecol 1990; 97(2):149-54

Composite Neonatal Morbidity (Study 17P-CT-002)

Morbidity	17OHP N=295 n (%)	Vehicle N=151 n (%)
Death (live births only)	8 (2.6)	9 (5.9)
Respiratory Distress Syndrome	29 (9.9)	23 (15.3)
Bronchopulmonary Dysplasia	4 (1.4)	5 (3.3)
Gr. 3/4 Intraventricular Hemorr.	2 (0.7)	0 (0.0)
Proven Sepsis	9 (3.1)	4 (2.6)
Necrotizing Enterocolitis	0 (0.0)	4 (2.7)
Composite Index of Morbidity*	**35 (11.9%)**	**26 (17.2%)**

* No. subjects with one or more of the listed morbidities.

Maternal Safety Findings (Study 17P-CT-002)

- Adverse event (AE) data not collected in usual manner
  - Subjects asked if had any symptoms related to study medication
- No maternal deaths
- 3 reports of serious AEs – all in 17OHP group
  - Pulmonary embolus 8 days post delivery
  - Cellulitis at study medication injection site
  - Postpartum hemorrhage, respiratory distress, endometritis
- 11 subjects discontinued because of an AE
  - 7 (2.2%) in 17OHP group
    - Urticaria (n=3), injection site pain/swelling (n=2) arthralgia (n=1), weight gain (n=1)
  - 4 (2.6%) in control (vehicle) group
    - Pruritus (n=2), injection site pain (n=1), urticaria (n=1)

Common Adverse Events (Study 17P-CT-002)

Preferred Term	17OHP N=310 n (%)	Vehicle N=153 n (%)
Injection site pain	108 (34.8)	50 (32.7)
Injection site swelling	53 (17.1)	12 (7.8)
Urticaria	38 (12.3)	17 (11.1)
Pruritus	24 (7.7)	9 (5.9)
Injection site pruritus	18 (5.8)	5 (3.3)
Nausea	18 (5.8)	7 (4.6)
Contusion	17 (5.5)	14 (9.2)
Injection site nodule	14 (4.5)	3 (2.0)
Vomiting	10 (3.2)	5 (3.3)

Selected Pregnancy Complications (Studies 17P-CT-002 and 17P-IF-001)

Pregnancy Complication	Study	17OHP		Vehicle	
		n	(%)	n	(%)
Gestational Diabetes	CT-002	17	(5.6)	7	(4.6)
	IF-001	8	(8.6)	0	(0.0)
Oligohydramnios	CT-002	11	(3.6)	2	(1.3)
	IF-001	2	(2.2)	1	(1.9)
Preeclampsia	CT-002	27	(8.8)	7	(4.6)
	IF-001	6	(6.5)	2	(3.8)

Overview of Study 17P-IF-001

- Study Design
  - Double blind, vehicle controlled, randomized 2:1
  - Identical to that of Study 17P-CT-002
- Terminated prematurely: recall of study drug
  - 150 subjects randomized before recall
- 104 subjects completed treatment or withdrew for reasons other than recall of study drug
  - 17OHP group: 65 subjects
  - Vehicle group: 39 subjects

Key Findings from Study 17P-IF-001

Efficacy (Subjects not affected by recall)

- Subjects with delivery < 37 weeks
  - 17OHP – 43.1% (28 of 65)
  - Vehicle – 38.5% (15 of 39)

Miscarriages, Stillbirths, and Neonatal Deaths

Pregnancy Outcome	17OHP N=93 n (%)	Vehicle N=54 n (%)
Miscarriages (16 to <20 weeks)	1 (1.1)	1 (1.9)
Stillbirths	1 (1.1)	2 (3.7)
Neonatal Deaths	2 (2.2)	0
Total Deaths	4 (4.4)	3 (5.9)

Overview of Study 17P-FU

Objective

- Follow–up of children whose mothers were treated with either 17OHP or vehicle in the principal study

Study Population

- 14 of original 19 study sites eligible to participate (children from 374 of original 463 patients - 80%)

- 278 of 374 (80%) of eligible children enrolled
  - 17OHP: 194 children (82%)
  - Vehicle: 84 children (74%)

Demographics of Children in Study 17P-FU

- Mean Gestational Ages

Study	Gestational Age (Weeks)	
	17OHP	Vehicle
17P-CT-002	36.2	35.2
17P-FU	37.3	36.2

- Age at Evaluation in Study 17P FU

	Months	
	17OHP	Vehicle
Mean	47.2	48.0
Range	30.2, 63.9	33.5, 64.3

Endpoints (Study 17P-FU)

- Primary: Ages & Stages Questionnaire (ASQ)
  - Communication
  - Gross motor
  - Fine motor
  - Problem solving
  - Personal/social
- Positive Screen: score 2 S.D. below mean in any of 5 areas
- Secondary: Survey Questionnaire
  - Activity/motor control
  - Vision/hearing
  - Height/weight/head circumference
  - Gender specific play
  - Diagnosis by a physician
- Subjects also underwent physical exam

Number (%) of Children with ASQ Scores Suggestive of Developmental Problem

	17OHP N=193		Vehicle N=82	
Area of Development	n	(%)	n	%
Communication	22	(11.4)	9	(11.0)
Gross Motor	5	(2.6)	3	(3.7)
Fine Motor	40	(20.7)	15	(18.3)
Problem Solving	20	(10.4)	9	(11.0)
Personal-Social	7	(3.6)	1	(1.2)
Developmental problem in one or more areas	53	(27.5)	23	(28.0)

Number (%) of Children with Low ASQ Score & Independent Diagnosis of Developmental Delay

	17OHP (N=193) n (%)	Vehicle (N=82) n (%)
Total Number Affected	13 (6.7)	8 (9.8)
Area of Development		
Communication	9 (4.7)	7 (8.5)
Gross Motor	3 (1.6)	2 (2.4)
Fine Motor	10 (5.2)	3 (3.6)
Problem Solving	5 (2.6)	5 (6.1)
Personal-Social	5 (2.6)	1 (1.2)

Summary of Issues

- Applicant is seeking approval for 17OHP based on
  - Findings from a single clinical trial
  - A surrogate endpoint for infant mortality/morbidity (preterm birth < 37 weeks)
- Concern about applicability to other populations
  - Preterm birth rate in vehicle arm that is higher than that reported in another MFMU Network trial
- Safety concern
  - Potential safety signal of increased fetal wastage in 17OHP group

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

FDA REPRODUCTIVE HEALTH ADVISORY COMMITTEE

MEETING ON GESTIVA

Gaithersburg, Maryland
August 29, 2006

CONSULTANTS AND GUESTS

SGE Consultants (Voting)

Maria Bustillo, M.D.
Sandra Carson, M.D.
Daniel Gillen, M.D.
Julia V. Johnson, M.D.
Ezra Davidson, M.D.
Gary Hankins, M.D.
Karin B. Nelson, M.D.
Hyagriv, Simhan, M.D.
Rose Marie Viscardi, M.D.
Vivian Lewis, M.D.
Joseph Harris, M.D., FACOG
Cassandra Henderson, M.D.
Katharine Wenstrom, M.D.
James Liu, M.D.
Elizabeth Shanklin-Selby

Guest Speaker (Non-Voting)

Roberto Romero, M.D.

F.A.C.P. Acting Industry Representative

Steven Ryder, M.D.

FDA Center for Drug Evaluation and Research Participants at the Table

(Non-Voting)
Daniel Shames, M.D.
Scott Monroe, M.D.
Lisa Soule, M.D.
Lisa Kammerman, Ph.D.
Barbara Wesley, M.D., M.P.H.
Julie Beitz, M.D.

COMMITTEE MEMBERS

Teresa A. Watkins, R.PH., Designated Federal Official

Arthur L. Burnett, II, M.D.

Ronald S. Gibs, M.D. - Absent

Charles J. Lockwood, M.D. - Absent

Diane Merritt, M.D.

James R. Scott, M.D.

William D. Steers, M.D.

Jonathan A. Tobert, M.D., Ph.D. - Absent

Lorraine J. Tulman, R.N., D.N.Se.

O. Lenaine Westney, M.D.

P R O C E E D I N G S

DR. DAVIDSON: Good morning. It is time for us to begin business today so I would declare the committee meeting open for business. First, there is a rather large assemblege around the table here so why don't we begin by brief introductions. Give your name and position and I will await my turn when it gets around to me. Why don't we start with Doctor Beitz.

DR. BEITZ: Yes my name is Julie Beitz and I'm the acting director of the Office of Drug Evaluation three and CDER.

DR. KAMMERMAN: I'm Lisa Kammerman, FDA Statistician.

DR. MONROE: I'm Scott Monroe the Acting Director of Reproductive and Urologic drug products.

DR. WESLEY: I'm Barbara Wesley, I'm a medical officer in the division of Reproductive and Urologic products and the primary reviewer of this application.

DR. HANKINS: I'm Gary Hankins, I'm maternal fetal medicine clinician, practicing in Galveston, Texas at the University of Texas.

DR. NELSON: Karin Nelson, I'm a child neurologist at NINDS/NIH.

DR. BURNETT: Good Morning, I'm Arthur Burnett, a urologist at Johns Hopkins and a committee member.

DR. BUSTILLO: I'm Maria Bustillo, I'm a reproductive endocrinologist at the South Florida Institute for Reproductive Medicine in Miami.

DR. MERRITT: Diane Merritt, Professor of OBGYN, Washington University, Saint Louis.

DR. JOHNSON: Thanks. Julia Johnson, I'm the Director of Reproductive endocrinology and infertility at the University of Vermont and a new member to the committee.

DR. STEERS: William Steers, Professor and Chair at the Department of Urology at the University of Virginia.

DR. LIU: Jim Liu, I'm a Reproductive endocrinologist, I'm chair at Chase Western Reserve.

DR. SINHAM: Hy Simhan. I'm a maternal fetal medicine doctor at the University of Pittsburgh, Magee Women's Hospital.

DR. LEWIS: I'm Vivian Lewis, I'm a Reproductive endocrinologist and professor of obstetrics and gynecology at the University of Rochester Medical Center.

DR. DAVIDSON: I'm Ezra Davidson, professor of obstetrics and gynecology at the Charles R. Drew University and the David Geffen School of Medicine at UCLA in Los Angeles. Also maternal fetal medicine.

MS. WATKINS: I'm Teresa Watkins, the designated federal official for this committee.

MD. WENSTROM: I'm Cathy Wenstrom, I'm a professor of OBGYN and human genetics at Vanderbilt.

DR. HARRIS: I'm Joseph Harris, I'm in maternal fetal medicine specialist in Reno Nevada.

DR. GILLEN: Daniel Gillen, I'm assistant professor in the department of statistics at the University of California, Irvine.

DR. SCOTT: Jim Scott, professor and former chair of the OBGYN department at the University of Utah, also the editor of the Green Journal, obstetrics and gynecology.

DR. CARSON: Sandra Carson, professor of obstetrics and gynecology at Baylor College of Medicine, I'm a reproductive endocrinologist.

DR. WESTNEY: Lenaine Westney, I'm associate professor, residency program director, and interim division director of University of Texas Health Science Center, division of urology.

MS. SELBY: I'm Elizabeth Shanklin-Selby and I am the patient representative.

NURSE TULMAN: Lorraine Tulman, associate professor at the school of nursing at the University of Pennsylvania. And I'm the consumer rep to the committee.

DR. RYDER: Steve Ryder and I'm a non-voting industry representative. I'm an endocrinologist in Pfzier research in Eastern Connecticut and I'm sitting in for Jonathan Tobert who could not make this meeting.

DR. DAVIDSON: Thank you. Doctor Watkins.

DR. WATKINS: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms all regulated by the Center for Drug Evaluation and Research present no potential for appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), Doctor Cassandra Henderson has been granted a full waiver for her unrelated speakers bureau activities for the sponsor for which she receives less than $10,001.00 per year.

Waiver documents are available at FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be attained by submitting a written request to Agency's Freedom of Information Office, room 12-A30 of the Parklawn Building.

We would also like to note that Doctor Steven

Ryder has been invited to participate as a non-voting industry representative acting on behalf of regulated industry. Doctor Ryder is employed by Pfizer. In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm their product which they wish to comment upon. Thank you.

DAVIDSON: Doctor Monroe.

MONROE: Good morning and I'll just reintroduce myself briefly. I'm Scott Monroe and I'm the Acting Director of the Division of Reproductive and Urologic Drug products. On behalf of the division, I'd like to welcome all of you to this meeting of the advisory committee for reproductive health drugs. I also want to convey the division's appreciation to the members of the advisory committee who have found time in their busy schedules to participate in this meeting.

Today, the committee will be reviewing a new drug application submitted by Adeza Biomedical for 17-hydroxy progesterone caproate with the proposed trade name Gestiva. The proposed indication is prevention of pre-term birth in pregnant women with a history of at least one spontaneous pre-term birth. The adverse consequence of pre-term birth is a major public health problem. Approximately twelve percent of all live births in the United States are pre-term, defined as birth before thirty-seven weeks gestational age. Pre-term birth is the leading cause of neonatal death and a major cause of early childhood morbidity and mortality including pediatric neuro-developmental problems.

Currently there is no approved drug product in the United States for the prevention of pre-term birth. The medical need for an effective approved drug for prevention of pre-term birth is particularly acute because there are also no approved drug products for pre-term labor currently marketed in the U.S. Although several drugs with tocolytic properties are used off label for pre-term labor. Randomized controlled trials have failed to demonstrate that these drugs improve perinatal outcomes.

17-hydroxyprogesterone caproate is not a new drug and was initially approved for marketing by the FDA in 1956 largely on safety considerations. In 1956, approval for marketing for a new drug did not require substantial evidence of effectiveness. Suggested uses of 17-hydroxyprogesterone caproate also known by the trade name Delalutin included treatment of habitual, recurrent, or threatened abortion. Delalutin was withdrawn from marketing in 2000 at the request of the NDA holder. The withdrawal was not related to safety concerns. Presently 17-hydroxy progesterone caproate is available only from compounding pharmacies.

In 2003, the findings from a randomized, double blind control trail of 17-hydroxyprogesterone caproate for the prevention of pre-term birth sponsored by the National Institutes of Child Health and Human Development, were published in the New England Journal of Medicine.

The study reported a significant reduction in the rate of pre-term births prior to 37 weeks gestational age and possibly at earlier gestational ages as well.

The new drug application that will be discussed today is based largely on this trial and a follow-up safety study of children whose mothers had participated in the earlier trial.

The application that the Committee will be reviewing and discussing today, poses several challenging issues for the division.

It is primarily because of these issues that the division is seeking guidance from the Committee.

The clinical issues that are of concern to the division include the following three items:

First: Are the clinical data adequate to support the claim of effectiveness for 17-hydroxyprogesterone caproate for prevention of pre-term birth.

Second: The pre-term birth rate in the vehicle, or control arm, of the principal study was 55 percent.

This rate was considerably higher than the expected rate of approximately 36 percent and is considerably higher than that generally reported in the literature.

Finally, there is a possible safety concern based on the increase in the percentage of second trimester miscarriages and stillbirths observed in the 17-hydroxy caproate arm compared to the control arm.

In regard to the adequacy of clinical data needed to support effectiveness of a new drug product, the FDA generally requires two adequate and well-controlled studies for substantial evidence of effectiveness.

A circumstance in which a single trial may be adequate would include a trial that has shown a meaningful effect on mortality, irreversible morbidity, or prevented a disease with a potentially serious outcome, and a situation in which confirmation of the result in a second trial would be either logistically impossible or ethically unacceptable.

In the present application, the applicant is seeking approval of 17-hydroxyprogesterone caproate based on findings from a single clinical trial and on a surrogate endpoint for infant and neonatal morbidity and mortality; namely, reduction in the rate of pre-term births prior to 37 weeks of gestational age.

I would now like to briefly present the questions that the members of the Committee will be asked to consider.

First: Is the primary endpoint, prevention of pre-term birth prior to 37 weeks gestation, an adequate surrogate for reduction in fetal and neonatal morbidity or mortality?

If not, would prevention of pre-term birth prior to 35 weeks or prior to 32 weeks gestational age be adequate?

Second: Does the high rate of pre-term birth, approximately 55 percent in the vehicle arm of the principal trial, indicate the need to replicate the findings in a confirmatory trial?

Third: Do the data provide substantial evidence that 17-hydroxyprogesterone caproate:

(1) Prevents pre-term birth prior to 35 or prior to 32 weeks gestational age; or,

(2) Reduces fetal and neonatal morbidity or mortality?

Is further study needed to evaluate the potential association of 17-hydroxyprogesterone caproate with increased risk of second trimester miscarriage and stillbirth?

If so, should this information be obtained prior to approval for marketing or post-approval?

And, lastly, are the overall safety data provided in the application adequate and sufficiently reassuring to support marketing approval of 17-hydroxyprogesterone caproate without the need for additional pre-approval safety data?

The agenda for the remainder of the day is listed on this slide.

In a moment, Dr. Roberto Romero, who is Chief of Perinatology at the NICHD, will make a presentation entitled, "Causes of Premature Birth: The Premature Parturition Syndrome."

This will be followed by the applicant's presentation.

After a brief break, the FDA will make its presentation.

Following lunch, there will be an Open Public Forum, and this will be followed by discussion and questions by the Committee, concluding with Committee voting.

I think, now, Dr. Romero, I would like to turn the podium over to you.

I think there's going to be a moment here while we do an equipment swap-out.

(Long Pause.)

DR. ROMERO: Good morning, Dr. Davidson, Dr. Scott Monroe, Dr. Wesley, Distinguished Members of the Advisory Committee and the Sponsor, ladies and gentlemen.

I hope that this slide is going to work, but I would like to begin by indicating that I am here in my official capacity as a member of NICHD, the Perinatology Research Branch, which I direct as part of the Division of Intramural Research of the Institute.

And the trial that will be subject of in- depth discussion today was conducted by the Extramural Program of our Institute, NICHD.

I did not participate in the design, execution, analysis or reporting of such trial.

Therefore, this trial has been conducted independently of the Perinatology Research Branch, and I have no conflict of interest to report with the sponsor of this application.

The editorial of the last issue of the Lancet remarked that in the United States at least one public health problem, pre-term birth, has worsened in the past decade.

However, it entitled the piece: "Pre-term Birth: Crisis and Opportunity," to stress the importance of this condition and the urgency with which the questions posed by premature labor and delivery must be addressed.

On July 28th of this year, the Institute of Medicine released a report entitled "Pre-term Birth: Causes/Consequence of Prevention." And the report is particularly timely because this Advisory Committee has been convened to consider the issue of prevention.

Pre-mature birth is defined, conventionally, as one that occurs before 37 completed weeks of gestation.

In 2004, more than 500,000 neonates were born pre-term in the United States, with a frequency of 12.5 percent.

This bar graph illustrates a cycle of trends in the frequency of pre-term birth, as a percentage of live birth in the United States between 1990 and 2004. An increase from 10.6 in 1990 to 12.5 in 2004 can be noted.

There is a large disparity in the proportion of pre-term birth among racial and ethnic groups in the United States which has persisted and remains concerning.

The frequency of pre-term birth among non-

Hispanic Americans was 17.8 percent, among American Indians and Native Alaskans 13.5 percent, Hispanics 11.9 percent, Whites 11.5, and among the Pacific Islanders, 10.5 percent.

Now the cost of pre-term birth, in medical care services, has been estimated to be $16.9 million, approximately 33.200 dollars per pre-term infant.

In maternal delivery cost, $1.9 million dollars.

The cost for special education $1.1 million dollars, and the lost household and labor market productivity is estimated at $5.7 million dollars.

So the annual society economic burden associated with pre-term birth in the United States is in excess of $26.2 million dollars, according to the estimates of the Institute of Medicine.

Now, the prognosis of pre-term birth, neonates, is a function of gestational age at birth.

And I regret that a part of these slides are not showing, so I'll do my best with the material that we have here.

This is work reported by Dr. Brian Mercer, in the Journal of Obstetrics and Gynecology.

And in the vertical axix is percentage, and the horizontal axix is gestation.

And, as you can see, in red is mortality, in blue is survival.

And this slide is at 32 weeks of gestation, and the point of the slide is mortality changes dramatically at 32 weeks of gestation.

The magnitude of the problem, the infant mortality rate for very pre-term infants are those delivered at less 32-weeks of gestation, was 186.4 per 1,000, which is 70 times -- 75 times the rate for infants born at term, which is 2.5 per thousand weeks of gestation.

So 20 percent of all infants born at less than 32 weeks of gestation do not survive beyond the first year of life, and that is the importance of 32 weeks of gestation.

In of acute morbidity by gestational age among surviving infants, this is also data from Brian Mercer, published in 2003, in Obstetrics and Gynecology, and is a result of a community-based evaluation of 8,523 deliveries between 1997 and 1998 in Shelby County, Tennessee.

In the horizontal axis, cut on the slide, approximately over here, 32 weeks of gestation will be approximately over here, and you can see that the rate of complications -- respiratory distress syndrome, sepsis and intra-ventricular hemorrhage -- increased dramatically before 32 weeks of gestation.

The Ailien (ph) report, in July of 2006, concluded that babies born before 32 weeks of gestation have the greatest risk for death and poor health outcomes. However, infants born between 32 and 36 weeks of gestation, which make up the greatest number of pre-term birth, are still at higher risk for health and developmental problems compared to those infants born full term.

So infants born after 32 weeks of gestation are common and also remain at high risk for health and developmental problems.

Now the frequency of pre-term birth, by gestational age, based on data from 1995 to 2000, was infants born at less than 28 weeks of gestation,

.82 percent; less than 32 weeks, 2.2 percent, between 33 and 36 weeks, 8.9 percent. And less than 37 weeks of gestation, 11.2 percent.

Now, the complications of the late-term, or near term infant, include cold stress, hypoglycemia, respiratory distress syndrome, jaundice, and sepsis.

And the clinical circumstances that result in the birth of a spontaneous pre-term birth are, fundamentally, three:

One: Is spontaneous pre-term labor with intact membranes;

The second is pre-term birth. So these two are the result of spontaneous pre-term birth; and,

The third is indicative pre-term delivery that results from maternal indications, such as pre-eclampsia or fetal indications, such as an infant that is small for gestational age or has fetal compromise.

Now, one of the key questions is whether pre-term labor is simply labor before its time. So "term" is between 38 and 42 weeks of gestation.

And the question is, whether premature labor, is simply the untimely onset of the physiologic or the phenomenon of labor.

And if you looked and you compare a patient who has term labor over here and a patient who has a pre-term gestation, there are clearly events in common.

Myometrial contractions are common in both pre-term labor and term labor, cervical dilatation and effacement occurs in both, and premature rupture of membranes, or membrane decidua activation, is also a common feature of the two conditions.

So we have defined the common uterine features of term and pre-term labor as including increased myometrial contractility, cervical ripening, which includes dilatation and effacement.

And, finally, decidua and membrane activation.

Now this common terminal pathway can be defined as the anatomic physiologic, biochemical, endocrinologic, immunologic, and clinical events in the mother and/or fetus that are shared by both term and pre-term parturition.

Now, what are the phenotypes of spontaneous pre-term parturition?

The phenotypes can be derived from understanding the activation of the common terminal pathway.

So, here, we have cervical ripening. Here, uterine contractility; and, here, membrane and decidua activation.

Now, in this part of the screen, I'm going to show you the activation, let's say, of cervical ripening over here, untimely activation of cervical ripening when you rise to cervical insufficiency. That used to be known as cervical incompetence.

Untimely activation of uterine contractility would lead to pre-term uterine contractions.

And untimely activation of the membrane and decidua would lead to premature rupture of membranes. And, of course, there is a combination of the two.

So could be synchronous activation of these components, or synchronous activation, and the phenotypes or presentation will be different -- cervical insufficiency, pre-term uterine contractions, premature ruptured membranes, and the combination of the three.

The approaches that have been used so far for the prevention of pre-term birth have taken a uterocentric approach to the common pathway.

So investigators interested in activation of the myometrium have used the uterine monitor to test activation of this component and tocolysis to arrest uterine contractions.

Those interested in the cervix have used ultrasound to detect cervical shortening and use a cerclage to prevent dilatation of the cervix.

Those interested in membrane decidua activation have looked at fetal-fibrinectin, a marker of extracelluar metric segregation.

And these patients have a very high risk for pre-term delivery, and antibiotics have been used in an attempt to prevent pre-term delivery in patients at risk.

A positive fetal fibrinectin confers a relative risk of approximately 60 antibiotic administrations in a randomized clinical trial conducted by the extramural program of our Institute, indicated that there was no benefit.

A similar story can be said of the uterine monitor and tocolysis. Tocolysis is able to prolong pregnancy for a short period of time but has not been demonstrated to decrease the rate of pre-term delivery.

The result of a cerclage is somewhat controversial, but most of the literature indicates that placement of a cervical cerclage is ineffective in preventing pre-term delivery, perhaps with the exception of one trial in Europe.

So the view that we propose is that normal labor at term is the result of physiologic activation of the common terminal pathway of parturition.

That will be crossed over here.

And in contrast, premature labor results from pathologic activation of this common terminal pathway.

Now, what is the evidence that the pathologic activation of the pathway is the cause of premature labor and delivery?

Well, examination of the placenta, by a number of investigators in patients who deliver pre-term, have indicated that acute chorioamnionitis, that are inflammatory lesions of the placenta, are present in 42 percent of the cases;

That vascular lesions are present in 20 percent;

Mixed inflammation of vascular lesions in 20 percent;

Chronic vellitis in .8 percent;

Velliserema, 1.7; and,

A normal placenta, in which the pathologist is not able to identify a lesion 13 percent.

Now we have coined the term, "The great obstetrical syndromes," to collectively refer to a number of conditions that are -- you know, are daily problems in obstetrics and have the following features.

First: They have multiple etiologies;

Second: They are chronic in nature, although they are generally diagnosed in the third trimester.

Often, there is fetal involvement.

Fourth: The chemical manifestations of the syndromes are adapted.

Symptomatic treatment is largely ineffective, and they result from gene and environmental interactions.

And all these postulates are met by the pre-term parturition syndrome.

So we have proposed that the pre-term parturition syndrome is defined by the presence of uterine contractility, activation of membrane and decidua, cervical dilatation, and it has multiple etiologies -- infection, vascular, uterine distention, cervical disease, hormonal disorders, immunological problems.

And we have left room for unknown mechanisms yet to be discovered.

Now, of all these potential causes for the pre-term parturition syndrome, the only one that has been causally linked to spontaneous labor is infection.

In intra-amniotic infection that means that the presence of microorganisms in the amniotic cavity is a frequent complication of pre-term labor; is present in 25 percent at the time of presentation. That is, not endometrial by the time of presentation in the onset of labor.

These infections are subclinical in nature, may affect the fetus, may elicit a fetal inflammatory response syndrome, and this is considered a host defense mechanism.

Now, the evidence that these infections are subclinical in nature is that clinical chorioamnionitis, defined by the presence of fever and other findings, are present in 12 percent of patients with premature labor and 20 percent of patients with pre-term PROM.

Now, the fetal inflammatory response syndrome occurs because, in some instances, microbial invasion of the amniotic cavity gain access to the fetus.

The fetus mounts a systemic inflammatory response that is very much like the adult, and this leads to three distinct outcomes:

The impending onset of premature labor and delivery;

The second: Severe neonatal mobidity and mortality that can be the most treated in the neonatal period; and,

Third: The presence of fetal multi-systemic involvement, that can be the most treated in utero.

So the fetal inflammatory response syndrome includes hematologic abnormalities, red blood cells, white blood cells, abnormalities in the endocrine system, the concentrations of cortisol are elevated.

Another form of cardiac dysfunction, in which the fetal heartbeat becomes floppy;

Pulmonary injury because the fetus aspirates bacteria and inflamed amniotic fluid.

Add to this, one can have renal dysfunction and also potentially brain injury.

Now, how common is subclinical intra-amniotic infection in a symptomatic mid-trimester pregnancies?

Because the figures that I have just given you, the 25 percent, reflects the patients who presents with a sort of premature labor and intact membranes or pre-term problem.

Well, the data that we have available here come from a study performed by a private practitioner in Ohio, published in "Prenatal Diagnostics," in 1992.

And what this private practitioner, Dr. Gray, did is to perform 2,461 myometrial amniocentesis and culture all the amniotic fluids for genital micro-plasmas.

Nine (9) patients have positive cultures with chorioplasma, relating to giving a frequency of .4 percent, in the prevalence of microbial invasion for genital micro-plasma.

One (1) patient elected to terminate the pregnancy, and eight (8) continued the pregnancy without treatment.

Six (6) patients had spontaneous abortions within four weeks of the amniocentesis, two (2) had premature labor.

All cases had histologic evidence of

inflammation, suggesting that these infections could be present in the mid-trimester.

They are relatively rare because they account for .4 percent, but once the infection is present, the prognosis of pregnancy is poor.

Now, in terms of prevention of pre-term labor and delivery, we believe, as obstetricians, that this is an important and desirable goal, that the only proven beneficial strategy so far is irradication of a symptomatic bacterurea, but this condition has a limited attributable risk.

Patients with a previous pre-term birth have an increased risk for recurrence, and this has been well established.

And the potential beneficial effect that we are considering today is progesterone administration, and this is derived from trials with 17-hydroxyprogesterone and natural volume of progesterone administration.

Now, the possibility that there is a hormonal etiology for the pre-term parturition syndrome, is something that has been seriously considered and has been resolved for several decades.

A progesterone deficiency state has been proposed to be a mechanism of disease in premature labor for several decades.

The corpus luteum is the source of progesterone in early pregnancy.

Now, this source of progesterone is quickly shifted towards the placenta in the human.

And the studies of Arthur Shappel (ph) were key in elucidating the role of progesterone in pregnancy maintenance.

And these are the three papers published by Arthur Shappel illustrating that point.

So what is the effect of luteectomy in human pregnancy?

And this is the result of our study, or a series of studies,

In 64 pregnant women that were in very early pregnancy, less than five weeks, who desired a tubal ligation, and, after IRB approval, were allocated to three groups.

A group that underwent tubal ligation, that is, a control group;

A group that underwent tubal ligation and luteectomy; and,

The third group that is cut in this slide: Tubal ligation, luteectomy, and progesterone supplementation.

And the results, I illustrated over here.

This is a group of patients in the vertical axis, is plasma progesterone; in the horizontal axis, at days after luteectomy, and I regret that the horizontal axis is not visible.

But here are patients who only underwent a tubal ligation with a mild drop in progesterone but no spontaneous abortion.

The second group and the third group, labeled in orange and red, includes patients who have a luteectomy and went on to have a spontaneous abortion, one within four days, the ones in red, and the other ones within seven days.

The other group is this one, who underwent a luteectomy, but then after a drop in progesterone had progesterone replacement, and these patients continued the pregnancy, had no spontaneous abortion.

So Arthur Shapell proposed that progesterone is an indispensable hormone for normal pregnancy and that progesterone withdrawal is a prerequisite for normal pregnancy termination, be that in the mid-trimester in early pregnancy or at the time of parturition at term.

Now, the role of progesterone in pregnancy maintenance has been proposed to be to maintain myometrial quiescence, to down regulate the production of gap-junctions, and gap-junctions are important to accelerate the transmission of the electrical stimuli among myometrial cells.

And the third is to inhibit cervical ripening.

A progesterone withdrawal is thought to prepare the uterus for the action of utero-tonic agents such as oxytocin and other agents capable of stimulating myometrial contractility.

Now, the evidence that supports a suspension of progesterone action is important in human parturition, is derived from a number of studies in which the administration of anti-progesterones, such as RU-486 or onnapreston (ph) can induce abortion and cervical ripening in patients in the mid-trimester and also at term.

Now, evidence that there could be a change in the ratio of progesterone to estrogen in human parturition, has been gathered both at term and in pre-term gestation.

And over here, in the left, is the ratio between progesterone/estradiol.

The first column represents women who are not in labor at term; the second column, women in labor at term.

Women in labor at term had a significant decrease in the progesterone to estradiol ratio.

And the same is the case for the progesterone/estriol ratio.

So progesterone is considered a key hormone for pregnancy maintenance, and, hence, its name progesterone.

A progesterone withdrawal has been proposed, and it occurs in other animal species or the mammalian species when there is a decrease in the concentration of progesterone; however, this has not been demonstrated in humans.

So the postulated mechanism for progesterone withdrawal in humans are a change in the isoforms of the receptors from "A" to "B," and perhaps an involvement of the "C" isoform of the receptor, or a function of progesterone block.

That is, maybe a description factor, NF-kappa B.

I will now be discussing the clinical trials of meta-analysis of progesterone that will be analyzed by the FDA staff and the sponsor. And the reason for that is because our institute is one of the -- participated in the design/execution of this trial.

The interventions for the prevention of pre-term birth need to meet the standards of efficacy and safety.

The criteria for efficacy are generally prevention of pre-term birth, defined as 37 weeks, 35 weeks, and 32 weeks, prolongation of pregnancy; and, perhaps more important, neonatal morbidity and mortality.

In terms of safety; fetal, neonatal, infant, and maternal safety.

Now, the fundamental construct is a progesterone deficiency state which may not be reflected in concentrations but simply a change in the isoforms or a suspension of progesterone action will activate the common terminal pathway of parturition, and this will result in premature labor.

To close, let me just say that the American College of Obstetrics and Gynecology, through its Committee in Obstetrical Practice, issued in November 2003, a Committee Opinion on the use of progesterone to reduce pre-term birth.

An excerpt of that Committee Opinion is that, when progesterone is used, it is important to restrict its use to only women with a documented history of previous cutaneous pre-term birth, at less than 37 weeks of gestation, because unresolved issues remain, such as the optimal drug of delivery and long-term safety of the drug.

The Committee Opinion also recognized that there were other indications for premature -- for progesterone that needed to be considered and subject of further investigation, and that included patients who have multiple gestations, and patients with a short cervix.

A trial in multiple gestations, in twins and triplets, has been conducted and sponsored by NICHD.

At trial in women who have a short cervix that have been randomized to placebo or natural volume of progesterone, will be presented next week in London, and be conducted by the Fetal Medicine Foundation (ph), but the results are not available at this time.

Thank you very much for your attention.

(Applause.)

DR. DAVIDSON: Thank you, Dr. Romero.

I think we can now proceed to the sponsor's presentation.

(Pause.)

DR. HICKOK: Give us just a moment, if you will, to see if we can get these slides lined up correctly.

DR. DAVIDSON: While they are setting up, I've been instructed to provide the following statement, which I was going to give after this presentation and before the break, but I will take advantage of this interlude.

In the spirit of the Federal Advisory Committee Act and its Sunshine Amendment, we ask that the Committee limit their discussion of the topic to the Open Forum of the meeting.

To assist them, we also ask that the audience and press not ask them questions about the meeting during the breaks.

I also have in this instruction some suggested alternative topics, but I'll leave that to your vivid and wide imagination.

(Laughter.)

(Long Pause.)

DR. DAVIDSON: Fortunately, Dr. Romero left you some technical adjustment time here.

(Long Pause.)

DR. HICKOK: Good morning. It looks like our audio-visual equipment is back to functioning here.

My name is Durlin Hickok, and I will be the principal speaker this morning for Adeza; and, in addition, the moderator for the question and answer session for Adeza's responses.

As way of introduction, in terms of the presentation -- in terms of the presentation today -- I'll be speaking briefly about Adeza Biomedical, and then Dr. Nageotte will be speaking on the medical need to prevent pre-term birth.

From there, we will move to a clinical review of the efficacy and safety findings from the study and then a discussion of the risks and benefits.

So, again, my name is Durlin Hickok. I'm the Vice President of Medical Affairs for Adeza.

And the person presenting the medical need will be Dr. Michael Nageotte, who is a Professor of Obstetrics and Gynecology, at the University of California at Irvine.

Other experts that we have available to the Committee today are Dr. Paul Meis, who is a Professor of Obstetrics and Gynecology at Wake

Forest University; and, indeed, was the PI of the NICHD 17-hydroxyprogesterone caproate for prevention of pre-term/premature labor trial.

Ms. Gwendolyn Norman is a Perinatal Research Nurse from Wayne State University, and she was also the active point person as the nurse coordinator for the study site at Wayne State.

Dr. Michael O'Shea is a professor of Pediatrics and a Neonatologist from Wake Forest University.

Dr. Melissa Parisi is an Assistant Professor of Pediatrics and Medical Genetics at the University of Washington.

Dr. David Savitz is a Professor of Community and Preventive Medicine at Mount Sinai School of Medicine, and his expertise is Reproductive Epidemiology.

Finally, Dr. Frank Stanczyk is a Professor of Obstetrics and Gynecology at the University of Southern California, and his expertise is progesterone chemistry.

In terms of Adeza Biomedical, Adeza is a medical technology company that is focused on pregnancy-related and female reproductive disorders, with a special interest in pre-term birth and infertility.

We're here today because we have submitted a new drug application for FDA approval to market 17-p in the U.S. for prevention of recurrent pre-term birth.

I'd first like to describe the names that we are going to use today for the chemical entities and drug products.

17-hpc is 17-hydroxyprogesterone caproate. It is the active ingredient of 17-p, which was used in the clinical study and was the study formulation of 17-hpc for injection.

Gestiva, as mentioned before, as Adeza's proposed trade name for 17-p, and Delalutin was the trade name for the previously-marketed 17-hpc.

17-alpha hydroxyprogesterone caproate is the active pharmaceutical ingredient of 17-p.

It's created by the addition of a six (6) carbon chain at the 17 position, as you can see here.

Studies have shown that 17-hpc exhibits substantial progestational activity and a prolonged duration of action, with a half-life of approximately seven to eight days.

17-p ias provided as a sterile solution for injection containing 17-hpc, 250mgs per milliliter, in Castor Oil, along with Benzyl benzoate and Benzyl alcohol.

17-p was used in the NICHD clinical studies and is identical in composition to the previously marketed Delalutin.

As mentioned before, Delalutin was first approved by the FDA in 1956, so we actually have a long history of use in pregnancy, dating back to this time.

Its approval was for the indications of treatment of habitual and recurrent miscarriage, threatened miscarriage, postpartum after pains, and advanced uterine cancer.

Delalutin was voluntarily withdrawn from the U.S. market in 1999, for reasons not related to safety or efficacy.

There has been multiple other studies that have evaluated the safety and efficacy of 17-hpc for the prevention of pre-term birth, and I am going to describe several of these to you here now.

One of the first studies that we could find on 17-p in pre-term birth was that of Levine, that was published in the United States in 1964.

The inclusion criteria for this study was three or more miscarriages, and 17-p was initiated at less than 16 weeks and continued until 36 weeks.

A beneficial effect of 17-p was demonstrated by the odds ratio that you see here, of 0.63. However, the results were not statistically significant.

This was followed by Papiernik's (ph) study, in France, in 1970.

Papiernik and his colleagues randomized women on the basis of a high pre-term, risk labor, score.

17-hpc was initiated between 28 and 32 weeks of gestation and given for 8 doses or less.

This study also demonstrated a beneficial effect of 17-hpc, with an odds ratio of 0.24, and this result was statistically significant

A third study was published by Johnson and was a U.S. study, again.

And the inclusion criteria in this study included two or more miscarriages, and two or more prior pre-term births.

17-hpc was initiated at the first prenatal visit and continued until 37 weeks of gestation.

This widely-quoted study exhibited an odds ratio of 0.12. Again, demonstrating substantial effectiveness and was statistically significant

A study by Dr. Hauth in 1983 took a different approach, and included women who were active in active-duty military as a high-risk group.

These were women who were randomized to 1,000 mgs per week of 17-hpc versus placebo.

The drug was instituted at 16 to 20 weeks and continued until 36 weeks of gestation or delivery.

The odds ratio for this trial was 1.11, clearly showing a non-benefit to these women that were active-duty military.

A study by Yemeni, out of Israel, published in

1985, had inclusion criteria of two prior pre-term births or two miscarriages.

17-hpc was initiated early in pregnancy in both, and in the active drug group. The mean gestational age was 12.2 weeks.

Again, this study was continued until 37 weeks, or delivery.

The odds ratio for the Yemeni study was 0.30, and the confidence intervals did not bound one, indicating a significant effect.

Finally, the last study that I would like to report is that by Sauvonna Kode (ph), out of Thailand, published in 1986.

Again, the inclusion criteria for this study were a combination of one pre-term birth or two or more prior, mid-trimester miscarriages.

The drug was initiated at 16 to 20 weeks at gestation and terminated at 37 weeks, or delivery, whichever occurred first.

This study also showed a significant benefit for 17-hpc treatment, with an odds ratio of 0.29.

In this study, we have summarized these

findings from the studies that I have just showed you, in the form of a Forrest plot.

Please note here that we did not include the NICHD 17-p study.

The overall summary suggests a 70 percent reduction in the risk of pre-term birth, as you can see here. And, again, the confidence interval suggests that this is a substantially-significant result.

Because of the promising findings of the previous studies, the NICHD decided to investigate further the 17-hpc potential in a large multi-center trial.

With the unmet need for an FDA-approved product that has standardized manufacturing and labeling, Adeza approached NICHD and was granted access to the clinical data set from the 17-p study.

The results of the NICHD study provide the primary basis for the efficacy claim of Adeza's NDA submission for 17-p.

I would like to draw attention to the fact that this was a large multi-center trial. Nineteen (19) study sites were involved in this study.

The results were highly statistically significant for the efficacy findings.

And, also, of importance, this study was stopped early by the Data Safety and Monitoring Committee because of efficacy. In other words, it crossed efficacy bounds before the trial was completed.

And, finally, we'll show you, shortly, the results were consistent across subsets of patients, thus, leading to a conclusion that it is highly generalizable.

Lastly, we would like to note that we have proposed labeling for our formulation of 17-p, and it will be named Gestiva. And, as Dr. Monroe said, Gestiva is indicated for the prevention of pre-term birth in pregnant women with a history of at least one spontaneous pre-term birth.

At this point, I would like to turn the podium over to Dr. Michael Nageotte, who will describe the medical need.

Again, Dr. Naggeotte is a Professor of

Obstetrics and Gynecology at the University of California-Irvine,and is the immediate past president of the Society for Maternal Fetal Medicine.

DR. NAGEOTTE: Good morning.

As has been elegantly introduced to you by Dr. Romero, pre-term birth continues to be a critical problem in this country.

Defined as any birth occurring prior to the completion of 37 weeks gestation, pre-term birth represents an ever-constant and, indeed, increasing societal challenge, which has, thus far, been resistant to multiple efforts to decrease its incidence.

Despite our having a better understanding of some of the etiologies of pre-term birth, the incidents of this serious pregnancy complication continues to increase, with the CDC reporting an increase of some 33 percent since 1981.

Pre-term birth now represents some 12.5 percent of all births in the United States, resulting in a significant cost and contributing to the overwhelming majority of all neonatal morbidity and mortality

To place this complication into some perspective, a pre-term birth occurs in this country approximately every moment, of every hour, of every day.

Recently, the March of Dimes has launched its largest initiative in an effort to address this daunting public health problem.

However, beyond dramatic increases in mortality risk, when compared to term infants, pre-term neonates are at significantly increased risk for several important morbidities.

These include respiratory distress syndrome, a disease resulting from immature lung development, and surfactant inefficiency, intra-ventricular hemorrhage; peri-ventricular leukomalacia, which is strongly associated with adverse neurological sequelae, including cerebral palsy, necrotizing enterocolitis, a disease of the premature gut; apnea, jaundice, anemia, and infections due to presumed immaturity of the immune system, in addition to these immediate morbidities of the neonatal period.

Long-term morbidities are also increased, including cerebral palsy, mental retardation, learning disability. and attention deficit disorders. And with the rising rate of pre-term birth, all of these morbidities are rising as well.

Now several risk factors for pre-term birth have been identified from various epidemiological studies. These include bacterial vaginosis, vaginal bleeding, and race.

Most importantly, a history of a previous pre-term birth, nearly triples the risk of pre-term birth in any subsequent pregnancy.

This slide presents the data regarding the relative risk of experiencing a pre-term birth for these various risk factors.

The population with a prior spontaneous pre-term birth represents a logical group for the testing of various intervention strategies.

This slide demonstrates the improved survival by gestational age of neonates born pre-term.

When discussing this problem with prematurity, we tend to only focus on the very small and very premature babies; those with very low birth weight or the micro-preemies. However, late pre-term birth, defined as birth between 34 and 0/7th weeks and 36-and-6/7th weeks, represents a very large and also growing cohort whose morbidity and mortality risks are unappreciated.

While all pre-term births have increased, late pre-term birth has increased as well, some 14 percent between 1992 and 2002, with the rate going from 6.9 to 7.7 percent of all births, with late pre-term birth now making up over 70 percent of all pre-term births.

These late pre-term birth newborns are often mistakenly believed to be as physiologically and metabolically mature as term infants.

As we will see, this is untrue, yet has led to an almost cavalier approach to the management of pregnancies at risk for birth between 34 and 37 weeks.

As this slide demonstrates, the length of stay is significantly reduced with each advancing week of gestation through 37 weeks, suggesting benefit with prolongation at each week up to the 37th completed week of pregnancy.

Here is the distribution of pre-term birth at different premature gestations.

These data, from the March of Dimes, demonstrate the frequency of some 70 to 75 percent for late pre-term birth between 34 and 37 weeks. This represents over 300,000 newborns every year in this country.

Beyond 34 weeks, it is not the standard of care to administer cortical steroids to the mother nor to consider tocolysis.

So the obstetrical options are minimal to non-existent. Yet, infants born between 34 and 37th weeks have a 4.6-fold increase risk for neonatal mortality. When compared with term infants, that is, 4.1 versus 0.9 per 1,000 live births.

Further, their infant mortality is threefold greater than that of infants who are born at term.

In addition, greater risks of morbidity include respiratory distress, apnea, temperature instability, hypoglycemia, clinical jaundice, and feeding difficulties, as well as a significant increased risk for hospital readmission.

The lack of appreciation for this issue of late pre-term infants is considered a problem by the American College of Obstetrics & Gynecology, such that they are addressing this currently through their Committee structure.

Available treatment of pre-term labor are limited and not without controversy.

The use of tocolytic therapy may, at best, prolong a gestation for 24 to 48 hours, enough time to perhaps administer corticosteroids to the mother, but without significantly lengthening the overall length of gestation.

However, no current approaches to the prevention of pre-term births have been shown to be efficacious prior to these recent reports of 17-p.

As we have heard, ACOG has recommended progesterone to be used to prevent pre-term birth in specific patient population, following the publication of Dr. Meis' study in 2003.

Although widely appreciated by the OB-GYN community, there remains specific problems in the appropriate usage of this therapy for women, who would potentially benefit most from such treatment.

Unfortunately, due to the limited availability of this product, it is severely underutilized.

Lacking FDA approval, access to this drug has been dependent upon individual physician practices developing personal relationships with various compounding pharmacies.

Reimbursement issues are daunting, with most states not covering this cost for appropriate high-risk pregnant women, with Medicaid and various insurance plans choosing to cover or, more commonly, not cover this cost.

There is limited FDA oversight, no regulation of product consistency, and no requirement for reporting of adverse events, or even significant adverse events.

In conclusion, there is a compelling societal need to address this rising incidence of pre-term birth and the associated costs and morbidities.

There are clear benefits with prolonging pregnancy at any pre-term gestational age, whether early or late, and, in the appropriate patient with the appropriate history, there is a need for approval of this product.

Thank you very much

DR. HICKOK: Thank you Dr. Nageotte.

We'll now move on to the clinical review.

And, as I say, we have had a history of being able to review the studies that led to the NICHD clinical study, and now we will move on specifically to the study that the NICHD conducted.

The National Institutes of Child Health and Human Development, as mentioned before, are part of the National Institutes of Health.

As such, the objectives are to identify the causes of prematurity and to evaluate safety and effectiveness of new treatments.

The Maternal Fetal Medicine Unit's Network consists of major training institutions that engage in multi-center collaborative investigations.

In the next slide you will see the Institutions that participated in the NICHD/MFMU Network sites for the 17-p study.

To be included into the Network, the clinical studies undergo a competitive selection every five years. They are chosen to participate based on leadership, number of deliveries, state of the art facilities, and the sub-specialty support that is available to them.

Study 002 was initiated in 1999 and completed in 2002. It was a randomized placebo-controlled, double-blind, multi-center clinical trial.

Weekly injections were begun between 16 weeks/zero days and 20 weeks/6 days of gestation and continued until 36 weeks/6 days of gestation or birth.

The study enrolled 463 patients in a 2-to-1 ratio of active to placebo that was pre-specified.

As I mentioned before, the Data Safety and Monitoring Committee recommended that the study be halted early.

This occurred after an interim analysis was conducted on 351 completed patients, revealing that the boundary for test significance had been crossed and that there was a benefit for 17-p in reducing pre-term birth. And, again, these results form the primary basis for efficacy.

Study 001 is a study that was initiated in 1998, prior to the completed 002 trial. It was terminated due to a manufacture and FDA recall of the study drug.

At the time that it was terminated the study enrolled only 150 of the 500 planned patients.

Following termination of the 001 trial, NICHD made the decision to initiate a new 17-p study, and that study that we we'll describe again is Study 002.

An additional study that we'll be describing today is the follow-up study. This study was conceived by NICHD, and it was initiated following completion of the 002 Study. In this study, the design was discussed with NICHD prior to the enrollment of subjects.

And, again, the follow-up study was an

observational safety study designed to assess the long-term safety outcomes of infants exposed to 17-p in utero.

It looked at the health and development of infants born during the study. It was conducted at 15 Maternal Fetal Medicine Unit Network study centers, and it enrolled 278 children.

In terms of the efficacy and safety databases, the completed 002 Study, with its 463 enrolled patients, forms the bases of the efficacy assessment.

An overall safety assessment was generated by integrating the 002 Study with the 001 Study.

The Observational Infant Follow-Up Study is an additional component to the Safety Assessment.

We will now turn to the efficacy results.

Pregnant woman with a documented history of a previous spontaneous, previous singleton spontaneous pre-term birth, and gestational ages between 16 and 21 weeks, were randomized.

The exclusion criteria included the items that you see here in front of you:

Multi-fetal gestation, no major anomaly or fetal demise, prior progesterone treatment during the current pregnancy, prior Heparin therapy during the current pregnancy, a history of thrombo-embolic disease, or a history of several other medical or obstetrical complications that you see here listed.

A total of 463 patients were enrolled with a 2-to-1 randomization of Active 2 placebo.

This resulted in 310 patients in the 17-p group and 153 in the placebo group.

90.3 percent of patients completed injections through 36 weeks, 6 days, or birth, resulting in a 90.0 completion rate in the 17-p group and a 90.8 percent completion in the placebo group.

In examining the baseline demographic characteristics and risk factors, no differences were observed in the following characteristics:

Mean age, self-reported race or ethnic group, marital status, and years of education.

I might add that this population is relatively representative of the population of women who have experienced one or more prior pre-term births.

Nor were there differences observed between the 17-p and placebo groups for body mass index, presence of diabetes, those who smoke cigarettes during pregnancy, had alcoholic drinks, or used street drugs during pregnancy.

In addition, the duration of gestation at the time of randomization was very similar -- 18.9 weeks in the 17-p group and 18.8 weeks in the placebo group.

However, there was a statistically significant difference in the number of previous spontaneous deliveries between the 17-p and placebo groups, as you see here.

1.3 in the 17-p group and 1.5 in the placebo group.

We'll demonstrate later to you how we adjusted for this imbalance and determined that the imbalance did not impact the interpretation of the efficacy results.

There was not a difference between the 17-p and placebo group for gestational age at the qualifying delivery and the frequency of previous miscarriage.

The primary efficacy endpoint that was predefined was pre-term birth less than 37 weeks of gestation.

I'd like to note that miscarriages that occurred before 20 weeks of gestation were also included in the primary efficacy outcome.

The primary efficacy results that you see here are represented in two ways.

First: There's a traditional intent to treat analysis of all women who are randomized, which counted all patients lost to follow-up as treatment failures.

I'd like to note that this is a fairly conservative approach.

In the second analysis, an all-available data analysis is presented, which was published by Dr. Meis and colleagues in the New England Journal of Medicine.

This analysis excludes women who are lost to follow-up during the study.

In the second row for each analysis. we have present a "p" value from a logistic regression, adjusting for the number of previous pre-term deliveries.

And, as you can see in these adjusted values, they do not differ in a meaningful way from the unadjusted values.

Despite whatever data analysis population we evaluated, the results were consistent with the fact that 17-p treatment significantly reduced the incidence of pre-term birth.

A sub-group analysis was also performed to further evaluate the impact of the pre-term birth imbalance.

We stratified patients, as you see in this slide, by the number of prior pre-term births, and found that 17-p treatment reduced the risk of pre-term birth.

And, again, the 17-p groups are represented in yellow, and the placebo in gray.

The data were consistent across the strata, demonstrated by a non-significant value for the Breslau Day test.

Similarly, we stratified by race, specifically, African-American versus non-African-American. In both groups, as you can see, 17-p was, again, found to reduce the risk of pre-term birth.

Again, the data were very consistent across the strata, demonstrated by a non-significant value for the Breslau Day test.

In the third stratified analysis, we examined subsets of patients with or without bacterial vaginosis, which, as Dr. Nageotte pointed out to you, is a significant risk factor for pre-term birth.

In women, both with and without bacterial vaginosis, 17-p was found to reduce the risk of pre-term birth.

Finally, we stratified by the gestational age of the qualifying pre-term birth. In this analysis, once again, you see a significant benefit that is very consistent across strata for the 17-p group versus the placebo group.

I would like to note that the implications for these four stratified analyses are very important.

They suggest that the results are highly generalizable, despite whatever patient population 17-p is administered.

We will now address the secondary endpoints.

In addition to pre-term birth, defined as less than 37 weeks, we also looked at pre-term birth less than 35 weeks, less than 32 weeks, and less than 30 weeks.

There was a similar decrease in the placenta pre-term births at less than 35, less than 32, and less than 30 weeks of gestation.

However, the reduction did not reach statistical significance for the less than 30 gestational age group.

These endpoints are important, as they demonstrate, again, the beneficial effect of 17-p applies throughout pregnancy.

This graph summarizes the key measures of efficacy and reinforces that 17-p reduces pre-term birth, however it is defined. I would like to note, again, the consistent decreases in the 17-p rate for each of the endpoints that you see.

And, again, for less than 37, the values are at 32.4 percent; for less than 35, 30.6 percent; 39.3 percent for less than 32 weeks, and 38.2 for less than 30 weeks.

We can also look at these data in terms of the gestational age intervals at which the pre-term birth occurred in each group.

For example, beginning at the 24- to 27- week interval, there was a lower percentage of patients delivering in each interval, up until term.

So, in other words, in each of these intervals here, beginning at 24 weeks, we see the percent delivering within this interval in the 17-p versus the placebo groups, all the way up until term, at this point.

An alternative measure of this effect is the hazard ratio. And the hazard ratio shows the likelihood that a woman who enters into any of the following gestational age windows will actually deliver within the window.

This can be interpreted much like a relative risk.

Again, beginning at 24 to 28 weeks, we see a consistent decrease in the hazard ratio, as shown here.

And, again, these hazard ratios can be interpreted as relative risks, and all of these, again, show protective effects.

Two important measures in looking at neonatal outcomes are the birth weight and NICU admissions.

As we can see on this slide, the incidence of birth weight less than 2,500 grams was significantly reduced in the 17-p. group.

A similar decrease was observed in the less than 1,500 grams, although, this did not reach statistical significance.

Mothers receiving 17-p were less likely to have their child admitted to a neonatal intensive care unit. And if their child was admitted, the median days in the NICU were shortened.

Although this study was not powered statistically to detect differences in these outcomes, the outcomes that you see in yellow on this slide are morbidities that occurred in a less -

- less frequently in a statistically-significant fashion.

These include necrotising enterocolitis, intra-ventricular hemorrhage -- this is any graded -- supplemental oxygen, and days of respiratory therapy.

In addition, there were decreases in the percent requiring ventilatory support, those who experienced transient kypnea, respiratory distress syndrome, and the outcomes of bronco-pulmonary dysplasia, and patent ductus arteriosis.

In general, these data suggest that infants whose mothers were treated with 17-p were generally healthy, healthier during their initial hospital experience.

A composite neonatal morbidity index was conducted as a post-hoc analysis.

Although there is not a universally- accepted standard for the components of this index, we define the index similar to other studies that were the percent of infants experiencing one or more of the following morbidities; that is, death, respiratory distress syndrome, broncho-pulmonary dysplasia, a Grade 3 or 4 intra-ventricular hemorrhage, proven sepsis, or necrotizing enterocolitis.

The index of 11.9 for the 17-p group, compared to 17.2 in the placebo group, represents a 31 percent decrease in the morbidity index. However, this difference did not reach statistical significance.

Please recognize, however, that this study was not designed, nor was it powered, to detect a difference in these measures.

In summary of the efficacy findings, weekly administration of 17-p reduces the rate of recurrent pre-term birth at less than 37, less than 35, and less than 32 weeks of gestation.

17-p resulted in prolonged gestation, and this is very consistent with the other studies that we have previously showed you.

The neonatal outcomes were improved, resulting in a reduced percentage of infants born less than 2,500 grams, and a reduced rate of admission to the Neonatal Intensive Care Unit.

17-p was also found to reduce specific neonatal morbidities, including necrotizing enterocolitis, intra-ventricular hemorrhage, use of supplemental oxygen, and mean days of respiratory therapy.

Of the neonatal endpoints that did not reach statistical significance, the direction to the change in each case was in the favor of 17-p.

We will now move to the safety findings from the study.

As I mentioned previously to you, the completed 002 Study, with its 463 enrolled patients, formed the basis of the efficacy assessments.

The overall safety assessment was generated by integrating data from the 001 and 002 Studies, along with the observational infant follow-up study, which was an additional component. And we will describe that separately.

In the combined 001 and 002 Studies, a total of 613 patients received at least one study injection, and, again, accounting for the 2-to-1 randomization ratio, this resulted in 404 patients in the 17-p group, and 209 in the placebo group.

In evaluating the Maternal Safety Data captured in the 001 and 002 Studies, we found no differences in the occurrences of pregnancy complications.

This slide shows pregnancy-related procedures, such as admission for pre-term labor and cerclage placement.

The occurrence of these pregnancy complications was not different between the 17-p and placebo groups.

I might add that the difference you see in the denominators here, from the previous slide, represent a decrease due to patient's loss to follow-up or early withdrawals.

Similarly, when other pregnancy complications were considered, there were still no differences observed between the 17-p and placebo groups.

The most commonly reported pregnancy-related complications were pre-eclampsia, or gestational hypertension, and diabetes, as you see here.

While the rates were higher in the 17-p group, this was not a statistically significant difference between the two groups.

Other pregnancy complications occurred in similar rates between the 17-p and placebo patients, including abruption, significant antepartum bleeding, clinical chorioamnionitis, and other complications.

As shown in this slide, the percentage of subjects reporting adverse events were comparable in the 17-p and the placebo groups, 59.2 versus 56.5.

The most frequently reported AEs in the 001 and 002 Studies were injection site reactions.

Other commonly reported AEs included urticaria, puritis, contusion, and nausea. These, again, occurred at similar rates.

The percentage of patients discontinuing early and the percent in each group was very similar in the two treatment groups. 2.2 percent in the 17-p group, 3.3 percent in the placebo group.

Specifically, the types of AEs that most commonly led to early discontinuation, were injection site reactions.

However, there was no particular pattern observed to those that discontinued for other reasons.

This is the low rate of discontinuation due to injection site reactions: 1.0 percent in the 17-p group, 1.4 percent in the placebo group.

It indicates that 17-p treatment was generally well tolerated by women in this study.

Serious adverse events were collected according to NICHD standardized procedures and included all deaths; that is, maternal, neonatal, and fetal.

And I might note, also, that this analysis included congenital anomalies.

This chart summarizes the non-fatal serious adverse events. The rates of these events was very similar between the 17-p and placebo groups, as you see here, 9.4 versus 10.5.

The greatest contribution to non-fatal SAE rate was congenital anomalies, and there did not appear to be any particular pattern that was evident for the other reported serious adverse events, as you see in this list.

SAEs due to congenital anomalies at birth were also comparable between the two groups. As you can see, 2.2 percent in the 17-p group, 1.9 percent in the placebo group.

Overall, congenital, and not just congenital anomaly rate, is very comparable to reports in other population surveys.

There did not appear to be any particular pattern in terms of type or organ system.

The data for miscarriages, stillbirths, and neonatal deaths are shown here.

The percent of patients experiencing each of these events was generally comparable. The neonatal death rate was lower in the 17-p group compared to the placebo group. However, the miscarriage rate was higher, 1.5 percent versus 0.5 percent.

I might add that none of these differences, however, reached statistical significance.

It is also important to note that investigators were asked to evaluate each of these cases, and, in all cases, the opinion of the investigator was that no neonatal death, stillbirth, or miscarriage was considered related to the study drug.

In addition to the investigators' assessments, we examined these cases and found that these mothers had many other risk factors, placing them at high risk for miscarriages.

In order to place the miscarriage rate in perspective, we examined miscarriage rates between 16 and 20 weeks, in similar subsets of women from other network studies, and I'd like to describe these, briefly.

Again, in the 17-p study, we found a 1.5 percent rate of miscarriage in the 17-p treated mothers versus 0.5 percent in the placebo mothers. These bars represent the 95 percent confidence intervals.

The two other studies that we examined were both NICHD, MFM Unit, network trials, that, again, had similar populations to the 17-p study.

In the pre-term birth prediction, which studied over 3,000 women, there were 485 who were multiparous and had a prior pre-term birth.

And, as we can see here, the miscarriage rate, this is between 16 and 20 weeks of gestation, was 3.1 percent.

In additional Maternal Fetal Medicine Unit's Network Study, was a Factor 5 Lydein Mutation Study (ph).

This was an observational study with no intervention being offered. And, again, of the 581 mothers that you see here, this represents a subset of mothers who are multiparous and had had a prior pre-term birth.

And what I would like to point out from this analysis that you see, first, that the numbers are fairly low, but there is great consistency between the current 17-p study, the pre-term birth prediction study, and the Factor 5 Lydein Mutation with great overlap between the 95 percent confidence intervals.

Finally, in our examination of potential causative relationships between 17-p and miscarriage, we reviewed all literature on the subject that we could find.

Oates-Whitehead published a Cochrane data base review in 2003 on the subject of progestins and prevention of miscarriage.

In the studies that examined 17-hpc for miscarriage prevention, 17-hpc compared comparably to placebo with an odds ratio of 0.77, suggesting a slight benefit that was not statistically significant.

Of importance, however, is that the results of this study do not demonstrate an increased risk for miscarriage.

In terms of the safety conclusions from the 001 and the 002 Studies, the study results demonstrate that 17-p was safe and well-tolerated by pregnant women.

It was also safe for the developing fetus and neonate with comparable rates of stillbirth, miscarriage, and neonatal death.

The rates of congenital anomalies, of 2 to 3 -- of 2 percent, were also very similar to the population rates that are often quoted in the 2 to 3 percent range.

As described previously, a follow-up study was designed and performed to examine the long-term effects of 17-p. And, as I stated previously, this study was initiated subsequent to the completion of the 002 trial.

This study enrolled 278 children born of women enrolled in Study 002.

In the 17-p group, there were 194 patients, representing 68 percent of the eligible births, and, in the placebo group, there were 84 infants representing 59 percent of the births.

The age range at the time of the examination was 30 to 64 months.

And I might remark that this is an incredibly high percent of enrolled patients considering the time interval that followed after birth.

The demographic characteristics of the patients, including age, self-reported race, or ethnicity, and sex or gender, of the infants enrolled in the follow-up study, were comparable between the treatment groups.

The mean age of enrollment was approximately four years of age, and there were a higher percent of males in the 17-p group, as you can see here.

Note that the gestational age at birth for the

17-p infants was approximately one week higher than the placebo infants, likely due to the fact that only live-born infants, clearly, were included in the study.

None of the differences in these demographic characteristics reached statistical significance.

I'd like to go into a little bit of detail now, at this time, on the components of the 17-p follow-up study.

There were three components, and these were based on surveys and physical examinations.

The first component was the Ages and Stages Questionnaire, so-called ASQ.

The second was a set of survey questions; and,

The third, a physical examination.

I'll describe each of these separately.

` The ASQ is a widely-used and validated tool to identify children who are at risk for a developmental delay.

The ASQ is comprised of multiple age- specific batteries of questions that are designed to identify children that are at risk for developmental delay in five general areas.

And, again, as I mentioned, this questionnaire is widely used and has been validated in a number populations.

In this slide, we've presented you with random questions from different developmental areas.

For example, in the area of communication, a question would be: Does your child make sentences that are three or four words long? In the gross mortar category, does your child jump with both feet, leaving the floor at the same time, and so forth for other general areas?

The response to the ASQ question is either "Yes," "Sometimes," or "Not Yet."

The primary endpoint for the Ages and Stages Questionnaires was the percent of the infants scoring below a pre-specified cut-off in at least one developmental area.

As we can see from this table, there were no statistically significant differences between the two groups in terms of the percentages with and the occurrence of a score below the cut-off. Nor were there differences detected for one area of development versus another.

The conclusion from this study was that there were no differences observed between the 17-p and placebo groups for the ASQ questionnaire.

A second assessment was a Survey Questionnaire that was developed specifically by NICHD for this follow-up study.

This questionnaire was comprised of questions that were selected from several validated sources, as you can see here.

These questions are used in a number of governmental and non-governmental agencies to screen for developmental abnormalities in children and have been used in some cases for several decades.

Here, we present a random sample of the questions from the Survey Questionnaire, again, with the area of interest.

Communication problem solving: Does your child pronounce words, communicate with, and understand others, in terms of motor skills and activity?

Do you have any concern about your child's overall activity level, and so forth, for the other developmental areas?

The Survey Questionnaires results revealed no significant differences in the following areas:

Physical growth, motor skills, and activity levels, communication and problem solving, overall health, reported diagnosis by health professionals, hearing, vision, and use of special equipment, and gender-specific play, which was one of the specific questionnaires.

A third component of the follow-up study was a general physical examination. This was conducted by a pediatrician or a nurse practitioner in each one of the study sites.

A physical examination included standard measurements of the child's weight, height, head circumference, and blood pressure, as well as documentation of any abnormality in the child's history.

In addition, a part of the examination was specifically directed towards identification of genital abnormalities.

Physical examination findings were generally comparable between the 17-p and placebo groups, as you see here.

The most common abnormalities were of the skin, followed by palpable inguinal nodes.

5.3 percent of infants were described as having abnormalities on examination of the heart.

These abnormalities included murmurs and irregular rhythms.

I might note that when we examined the follow-up study reports and looked at other areas for documentation of problems, we found no evidence of any functional impairment in any of these infants in the category of heart.

Although we did not find an excess in problems, as we described to you before, we did look to the Safety literature in terms of epidemiologic studies that looked at birth defects and exposure to progestins during pregnancy.

Three (3) fairly large studies are examined and presented to you here.

First: The Michaelis Study in Germany involved several thousand infants, of which 462 were specifically exposed to either 17-hpc or 17-hpc and other agents.

Riceggi (ph), in the Mayo Clinic, reported in 1985 a very large study that included follow-up from several thousand women in Olmsted County, Minnesota.

Of those, 649 were specifically exposed to 17-hpc.

This study is quite remarkable in that it included a follow-up, a mean follow-up, of up to 11.5 years for these infants.

So there was a lot of opportunity to capture birth defects in the Riceggi Study.

Finally, in another large study of Katz, out of Israel, 1,608 women were observed for birth defects following exposure to 17-hpc or other progestins.

The conclusion from all of these studies was that there was no association between 17-hpc exposure and congenital anomalies.

Finally, FDA itself, reviewed these studies and other information and stated in the background of the 1999 ruling on the Assessment of Progestin

Class, and I quote, "The reliable evidence, particularly from controlled studies, shows no increases in congenital anomalies, including genital anomalies, in male or female infants, from exposure during pregnancy to progesterone or hydroxyprogesterone."

The following safety conclusions were made from the results of the NICHD studies.

First: 17-p is considered safe and well tolerated in pregnant women.

17-p administration is also safe for the developing fetus and neonate based on comparable percentage of surviving offspring and rates of congenital anomalies that were very similar to general population estimates of 2 to 3 percent.

17-p administration was also safe for the child, as evidenced by lack of any untoward effects, on the developmental milestones or physical health, determined at the follow-up safety examination.

17-p is also safe, based on literature review, as we have previously shown you. And, in fact, the

FDA assessment on the progestigen class.

In turning to the overall benefits and risks of 17-p administration for recurrent pre-term birth prevention, I believe that we would all agree on the compelling need to reduce the rising rate of pre-term birth in the U.S.

Pre-term birth is well-recognized as the leading cause of neonatal mortality and morbidity, and the incidence is increasing. In fact, there is a pre-term birth that occurs every minute in this country.

The financial costs are staggering, as well as the emotional costs, from both early and late pre-term birth.

17-p has been shown to be remarkably effective against this unmet medical need. It reduces pre-term birth, regardless of how it is defined and, on average, increases gestation by about a week.

This is translated to fewer low birth-weight infants.

As we've shown you also in stratified analysis, these results are applicable, irrespective of the race of the mother, the number of previous pre-term births, the gestational age at the previous pre-term birth, or the presence of bacterial vaginosis.

In addition, 17-p led to reduced admissions to the NICU and fewer morbidities.

17-p also leads to healthier neonates.

Again, treatment lengthens the mean gestational age at birth and results in fewer infants under 2,500 grams. Specifically, we showed a 34 percent reduction. It also reduces admissions to the NICU by approximately 24 percent.

Specific neonatal morbidities were reduced, including the need for respiratory therapy and the incidence of necrotizing enterocolitis or any grade of intra-ventricular hemorrhage.

17-p treatment has been shown to be safe for the mother, the developing fetus, and the child.

No identifiable risks were found to the fetus and neonate, with comparable rates of neonatal deaths, miscarriages, and stillbirths.

In addition, there was no evidence that 17-p is a teratogen.

Congenital anomalies occurred at similar rates and 17-p exposed in placebo mothers, and this was also confirmed by the 1999 FDA assessment.

I might add, also, that if one is concerned about 17-p administration during pregnancy, recall that all of the patients in the study began their administration in the second trimester of pregnancy.

In addition, there were no unidentified risks for the child.

There was no association with developmental delays or other issues in children between 30 and 64 months of age.

In closing, 17-p is both safe and effective, and the benefits clearly outweigh the risk.

As a result, we believe that 17-p merits approval for this indication as proposed, and we would like to thank you for your attention this morning.

DR. DAVIDSON: Thank you.

Since we have a break scheduled at 10:30, you have given us some additional time, perhaps for -- Dr. Hickok? Not quite, not quite.

(Laughter.)

DR. DAVIDSON: Perhaps we can use a part of this time, if there are questions or comments, from the Committee to the Sponsor, or maybe even to Dr. Romero, in terms of constructively using this time.

DR. DAVIDSON: Yes?

DR. JOHNSON: When you talked about the physical exam for the follow-up on the children, you said you specifically identified whether or not there were genital abnormalities.

Can you tell me what the percentage of genital abnormalities were for the 17-p group and the placebo?

DR. HICKOK: Yes. Let me actually show you those specific cases, as I can. There is very few of them, and we'll run through them. We'll run through them quickly.

(Pause.)

DR. HICKOK: We're pulling up specific case history slides for you, and we'll go through these in detail, and I apologize for -- just for the delay here.

DR, DAVIDSON: While you're on that question, on the physical examinations, I see there were five or so heart abnormalities in the 17-p group and none in the placebo group.

Could you characterize those? Were they similar or dissimilar abnormalities?

DR. HICKOK: Yes, Dr. Davidson.

Let me turn to the genital abnormalities, first, and then I'll get back to discussing the heart abnormalities, as you requested.

In terms of the physical examination and the genital abnormalities, in the 17-p group, there was 1.5 percent; in the placebo group, 1.2 percent.

And let me go over just with you, you know, what those abnormalities were.

DR. JOHNSON: I'm sorry. Were these at birth, or were these at the follow-up visit?

This is Dr. Johnson asking.

DR. HICKOK: Okay. These, were the abnormalities that were at the follow-up study.

Would you like me to start with birth first?

DR. JOHNSON: Oh, no. No. I just wanted to make sure because this doesn't quite match with the information I have. But go ahead.

DR. HICKOK: Yes.

And let me explain, first, if you're looking at the Adeza briefing package -- and there were two additional cases that we listed in there -- one of those cases was a child who was initially classified as having labial-scrotal fusion, and a second one was a child that was originally described as having clitoral hypertrophy.

NICHD went back on these individual cases and actually examined a lot of pieces of evidence because of, of, again, a concern and a real focus on their part to, you know, try to get an idea, you know, was this a teratogen in terms of genital abnormalities.

They went back, and, for example, looked at a lot of data from examination at the time of birth.

In many cases, there was evidence from multiple well- child visits.

In one case, a child had --and let me give you an example of one such infant.

And this is the child that was originally classified as having labial-scrotal fusion. This child, again, was age five at the time of the follow-up study.

The labia was described as being fused together at the follow-up study examination.

But, again, when NICHD went back, and they looked at kind of all-available evidence, they found that, for example, the genital exam at the time of birth was normal and that this young child had multiple-infant exams between one week and three years of age, where, repeatedly, the genital examination was reported as normal.

And, again, they felt that this mitigated, you know, against this being a true case of labial scrotum fusion, and it probably represented benign labial adhesions rather true labial scrotal fusion.

And, again, other evidence that NICHD took from the literature was, for example, good data showing that the urogenital sinus fuses at 12 weeks of gestation, so that if you have a drug exposure, or other exposure after that, you really can't develop labial scrotal fusion after the 12th week of pregnancy.

If I can move on to the case of clitoral hypertrophy next, which I think is the next slide.

(Pause.)

This was a child, again, that was age four at the time of the follow-up study examination, and the genital examination was reported at the time of birth of being completely normal.

This infant, because of the concern, the original examiner that said, gee, I think that, you know, this child may have clitoral hypertrophy, was brought back in by the same follow-up study investigator and reexamined four months later and, at that exam, the investigator said, hey, you know, this child is completely normal, and actually described a measurement of the transverse diameter of the clitoral shaft being less than 5mms at that time.

Does that cover your question, then, on the genital abnormalities or?

DR. JOHNSON: Let's go ahead and look at the four cases that you then considered true abnormalities.

DR. HICKOK: Okay. Great.

We'll go back to that prior slide on abnormalities identified.

And, again, your question was that -- to clarify and give you what you need, at the time of the follow-up examination?

DR. JOHNSON: Correct.

DR. HICKOK: Okay. Great.

Here are the other -- let me just precede that by saying, so, you know, in the spirit of full disclosure on the part of Adeza, we wanted to put that in our briefing package to make sure that everybody on the Committee was aware that these were identified and then considered to be reclassified by NICHD.

So the other cases in terms of genital and reproductive track abnormalities notes there were noted was one child, where there was a question of early puberty in the 17-p group.

And this child, again, was age 3.6 years at the time of the follow-up examination, and there was a question as to whether or not there were breast buds observed without other signs of precocious puberty.

One of the things that was felt to be a confounding factor by NICHD in their review of this child is that was -- this young girl, unfortunately, weighed 66 pounds at the time of her follow-up at 3.6 years of age. So she was quite obese and was actually in the 100th percentile of BMI at that time.

The second case that was a question of precocious puberty, was a young child that was examined at 3.5 years of age, who had been born at 25 weeks of gestation, and had a fairly stormy neonatal course.

On her examination, she had quote, "Four or five long pubic hairs at the time of the follow-up study," but, again, no other indications that this was precocious puberty.

DR. JOHNSON: And then there were two boys with

--

DR. HICKOK: There were two boys, and we'll show those to you here shortly.

(Pause.)

DR. HICKOK: I apologize. We're having a little technical difficulties here.

Let me describe them to you even without the slide.

There were two cases of micro-penis that were identified, you know, at the time -- here we go -- two cases of micro-penis that were identified, and I'll go through those two cases with you shortly here.

That was the slide I wanted. Here we go. Okay.

The first was a case of a child born at 38 weeks of gestation and was age 4.5 at the time of follow-up study.

This child was described as having micro-penis, which, as you know, can be a very difficult diagnosis to make. And, in fact, there's often times not good diagnostic criteria for this.

NICHD went back and identified, again, all the records they could find and felt that it was especially significant that the genital examination at the time of birth was completely normal. And that's a time where it would be very sensitive.

In addition, there was a second case of micro-penis identified in a child who was three-and-a-half years at the time of follow-up study.

This infant had Down's Syndrome, and micro-penis is also a commonly associated finding in children with Down's Syndrome.

I'd also like to just invite Dr. Melissa Parisi to the podium very briefly.

She is a pediatric geneticist who is head of the Gender Assignment team at University of Washington.

So this is something she does, you know, everyday, every week, and she'll remark a little bit about genital exams on children, and variability, and all.

DR. PARISI: Melissa Parisi, University of Washington, in Seattle.

First of all, I'd like to comment that in my role as a geneticist and with a particular interest in urogenital anomalies, that these can be challenging examinations.

And I also think it is important to note that, in the context of the follow-up study, the physicians and the nurse practitioners were directed to look specifically at the genitalia, whereas most pediatricians do not routinely measure clitoral diameters nor phallic lengths in children, particularly at this age range.

So I think there may have been a little bit of an ascertainment by us on that account.

I also had the opportunity to review these five to six cases in great detail, and I feel that the evidence is fairly compelling that these are not likely to be related to exposure to the medication in utero, particularly during the time period of the drug exposure, which is well beyond the first trimester.

And, finally, I'd like to point out that when you look at the development of the external genitalia, that prior to seven weeks gestation the appearance of the genitalia is identical in males and females.

However, starting at about eight weeks gestation under the influence of the testosterone produced in the fetal male testes, you start to see differentiation at about nine weeks gestation.

And then subsequent fusion of the urogenital folds in male to form the penis and in the female forms the labia menorrha, with final closure of the labial scrotal swellings in the male by 12 weeks gestation, to form the scrotum, and that is retained in the female labia majora.

So, in conclusion, I think the combination of the nature of the follow-up study and the attention to the genitalia provided in the directions to the providers, as well as the careful review of these case reports and the period of drug exposure, means that these genital anomalies are unlikely to be related to the actual exposure to the drug during a later time of gestation.

DR. JOHNSON: Thank you very much.

Just one very brief question, and then I'll let you move on.

Was there an internal examination on the females or just external?

DR. PARISI: My understanding is that, for the females, particularly those who had the concerns about the clitoromegaly and the labial scrotal fusion or the other?

DR. JOHNSON: All infants.

DR. PARISI: I do not believe there was an internal examination. That was not the standard of the physical exam.

DR. JOHNSON: Thank you.

DR. VISCARDI: Thank you. I am an neonatologist, so some of my questions are going to focus on the neonatal outcomes.

I guess my first comment is, as I looked at the table that was provided to us on outcomes, all of the morbidities were fairly low.

And then I realized that, yes, these are -- many of these are babies who are born greater than 32 weeks, but I also wondered if the incidences that are given -- for instance, like for intra-ventricular hemorrhage, to diagnose that, you have to have done a cranial ultrasound.

And was this just recorded if they had an ultrasound done, or was that part of the protocol?

And how many ultrasounds did each of the babies have?

Because, again, you're only going to ascertain whether they had that outcome if you did more than one ultrasound.

The other cranial ultrasound outcome that would have been of considerable interest is peri-ventricular luekomalacia and that was not reported.

So I was just curious as to whether that just was not found in any of the infants or whether that wasn't looked for or recorded?

And the other incidence that was reported to be different was the patent ductus arteriosus.

And, again, depending on the unit, they may diagnose that either as a clinically significant PDA on clinical findings, whereas other units might make that diagnosis by screening all infants of a particular size by doing a cardiac echocardiogram.

So, again, I wasn't sure if there was specific criteria for which some of these diagnoses were made?

DR. HICKOK: Yes. Let me review with you just briefly the findings on this.

And, again, in the study, because these were not primary endpoints of the study that were looked at, there was not a pre-specified, for example, you know, an intra-cranial ultrasound shall be done on all infants and shall be done every two to three days, or things like that.

So we do know that the physicians managing these patients actually manage them clinically as they would, and there was not, you know, pre-specified tests that would be ordered at a regular interval like this, and that the intra-ventricular hemorrhage was a diagnosis by ultrasound.

Your second question, I think, unless you have another comment about that, relates to PDAs?

DR. VISCARDI: Well, I guess this would actually go towards both of those, in that the incidences are then given for the total sample when and what should have happened is the incident should have been given for those who actually had a scan done.

And I don't know if that was different between the two samples.

So could the difference that you're seeing just be because you did more scans in one sample than the other?

Because the other thing I can tell you is in most units they're not going to do ultrasounds routinely in babies over 32 weeks unless there is some clinical reason to suspect an intra-cranial problem, like seizures or an enlarged head, or, you know, some clinical indication. But they're not going to screen all those children.

And some units have a very specific criteria for which they -- you know, they do one in the first week, and a month of age, and prior to discharge, and may do several in between.

And the number of scans matter as to whether you'll make that diagnosis or not.

DR. HICKOK: Again, I believe that the study was done, and these findings recorded, based on clinical examination, with the assumption that the most severe intra cranial hemorrhages, at Grade 3s and Grade 4s, that the majority of those would probably be detected because of suspicion from, you know, the clinical findings of the baby.

But we do not have, you know, pure incidence rates, as you have pointed out.

DR. VISCARDI: I guess the other thing to point out, was you reported the total incidence of IVH, but, in fact, since severity is Graded from 1 to 4 with 1 and 2 being considered more mild and maybe having less impact on the child's later development; but, as you point out, Grade 3 and 4 being more severe, there was no Grade 3 and 4 in the placebo group. The only Grade 3 and 4s were reported in the treatment group.

DR. HICKOK: Yes. And --

DR. VISCARDI: And the only reduction in IVH was in Grade 1 and 2.

DR. HICKOK: Yes. And the data that you're referring to, again, when we broke these -- I'm sorry, when we broke these out by Grade 3 versus Grade 4, there were, you know, two cases in the 17-p group, Grade 3 or 4 versus none in the placebo group.

And other rates of intra-cranial hemorrhage; again, 0.3 percent versus, I'm sorry, I can't see, thank you, versus 1.3 percent.

But, again, there's a lot of variability in these numbers because, as you pointed out, they're low-level incidence rates.

And the study, itself, was looking primarily at pre-term birth prevention and prolongation of pregnancy.

These neonatal outcomes are certainly of importance, but it would have been a much more complicated study had there been a lot of pre-specified examinations done on children during that time period.

You also asked me a question about patent ductus arteriosus, and I would be pleased to --

DR. VISCARDI: I guess my question was, was that diagnosis made if it was a clinically diagnosed PDA, or was it on the basis of a cardiac echocardiogram, which gets back to the same point that -- with the IVH; that if it's based on a screening test, then the denominator should be the number of children who were screened?

DR. HICKOK: Yes. I'd like to actually ask Dr. Michael O'Shea, a neonatologist, at Wake Forest University, and ask him, at Wake Forest, at the time that this was done what general diagnostic criteria were used, Dr. O'Shea, at that point?

Again, recall that Wake Forest was one of the 17-p study centers.

DR. O'SHEA: Mike O' Shea from Wake Forest.

I think Dr. Viscardi's point is well taken. There probably is an ascertainment bias, in that, at Wake Forest, and I suspect many center, cardiac echos are done not on a screening basis but rather if symptoms develop, then later dependency.

I think the same is also true for the ascertainment of intra-ventricular hemorrhage.

However, necrotizing enterocolitis, I would suspect to be less subject to ascertainment bias, and certainly days on the ventilator would be, I think, very unlikely to be very affected by ascertainment bias.

DR. HICKOK: All right. Thank you.

And I certainly don't want to ignore Dr. Davidson and his question about the heart abnormalities.

I would be pleased to turn back to that, if you would like me to, Dr. Davidson?

(Pause.)

DR. HICKOK: In terms of the cardiac findings, as we stated before, there is a low rate of cardiac abnormalities that were observed at birth, in both in the 17-p and the placebo groups.

And these rates were 0.5 percent in the 17-p versus 0.5 percent in the placebo.

And going back to the previous question, just about the incidence of about patent ductus arteriosus, again, it was slightly higher in the placebo group.

At the time of the follow-up study examination, as I mentioned before, there were a number of infants in the 17-p group that had the check box, you know, indicating that there were areas in the heart examination.

And, specifically, 4.6 percent of the infants in the 17-p group had a heart murmur and 0.5 percent were recorded as having an irregular rhythm.

What NICHD did at that time is to go and look at other parts of the follow-up examination in terms of functional capabilities, and things like that.

And then, also, to go back to the initial birth hospitalization and look for, you know, problems that occurred during that period of time.

And it was determined, again by NICHD, that all of these children that had murmurs noted in the infant follow-up study did not have any indication of ongoing functional disorders, and in one case had a cardiac -- one of the cases there was a cardiac anomaly noted at birth with no further follow-up.

One of the cases there was a patent ductus arteriosus.

And, again, I would just like to remind people, as Dr. Parisi pointed out, that the heart is essentially formed by the time 17-p is administered at this point in pregnancy. Nonetheless, these are good questions.

DR. GILLEN: Yes. You noted earlier that, based upon the results of a formal in-term analysis, that DSMC had recommended termination on this study early.

I was wondering if you could specify the stopping rule that was used in the protocol, and also how many previous interim analyses had taken place, if any? And what points, in terms of numbers of patients enrolled, those had taken place?

DR. HICKOK: Yes, thank you.

And I'd like to invite our bio-statistician, Dr. Anita Das, up here to respond to that.

DR. DAS: Anita Das, representing Adeza.

The Data Safety and Monitoring Committee interim analysis, use a land of mats procedure with an O'Brien Fleming (ph) boundary.

And there were two previous analyses conducted.

The first time when 15.2 percent of the patients had been enrolled, and then the second time when approximately 70.2 percent of the patients had actually not been enrolled but completed follow up.

And at the second meeting, the efficacy had crossed the bounds, and the boundary was 0.015, and that's when the DSMC stopped the study.

And, at that time, 463 patients had been enrolled.

DR. GILLEN: And the results that we are seeing, are they adjusted at all in terms of the point estimates or, inference that we're seeing, adjusted for the interim analyses that took place?

DR. DAS: Yes. The primary outcome of pre-term delivery less than 37 weeks is adjusted for the two interim analyses.

The final alpha level is 0.035.

DR. GILLEN: Okay. Thank you.

DR. DAVIDSON: Dr. Steers.

DR. STEERS: Yes.

While it is recognized that 17-p was administered probably after genital development was complete, my theoretical concern is, given this drug has been around since the 1950s, is there any available data at the time of puberty or after puberty, sexual function, fertility and reproductive function in children, who had been exposed in utero to this drug, especially germane with the congenital hyperplasia concerns that have been raised in adulthood and the long-term effects?

Is there -- they had any either animal data with reproductive function or human data that anyone's aware of?

DR. HICKOK: We're not aware of animal data on 17-hpc and reproductive function.

There is some information that I will present to you here that may be pertinent.

Dr. Charney, would you like to describe -- or Dr. Singh?

Dr. Pamela Singh, whose interest is in preclinical studies and toxicology, and she will describe the findings from this one study that is pertinent, I believe, to your question.

DR. SINGH: Pamela Singh, representing Adeza.

Excuse me, first, I'd like to request a different slide.

DR. HENDERSON: I'm sorry?

DR. SINGH: That's all right. I'll ask A/V to help me out with a different slide.

(Pause.)

DR. SINGH: And, specifically, I'm only going to speak to the point of the animal studies, and then, perhaps, I can pass this question on to Dr. Melissa Parisi.

Okay. So the question really was, are there any animal studies that indicate any issues with congenital anomalies.

And, yes, in fact, there were animal studies; however, these were negative.

And I'd like to point you to the slide that will be up shortly.

Okay. So in the rodent model for reproductive toxicity, teratogenicity was evaluated in mice. And, as you can see, in the C-57 block, six mice, there was no teratogenicity or maternal toxicity up to 10 times the clinical dose.

And then, also, in Swiss Webster mice, a different strain, teratogenicity was tested up to approximately 200 times the clinical dose. This, in fact, by a subcutaneous route.

However, at that extreme amount of exposure you would imagine that the systemic exposure was certainly well beyond the clinical.

So, again, you see two negative studies in terms of teratogenicity in mice, with 17-hpc the active.

Now, I'd like for you to look at the non-human primate data.

You'll notice this slide has shifted upwards. I actually -- the title of the slide is "17-hpc Teratogenicity Data in Rhesus and Cynomolgus Monkeys."

So there are actually two different species of monkeys here. You just can't see it because it's above the line on the screen there.

But the important part of this slide is just that studies were conducted in both Rhesus and Cynomolgus monkeys to evaluate teratogenicity in

17-hpc, and no teratogenicity was found.

And I'll point out that, in this study, treatment -- exposure actually occurred earlier than clinically indicated.

It was during the first third of gestation when treatment was initiated; whereas, in the clinic, exposure is not initiated during the first trimester. That is one point to consider.

And then I also want to just point out that this is an intramuscular injection just like the clinical round of exposure.

DR. STEERS: My question isn't directed at teratogenicity; more as, did they let the primates grow through adolescence and adulthood and look at reproductive potential or sexual functioning in these animals? That's the point I'd like to make.

DR. SINGH: Okay. So those two sets of studies in rodents and non-rodents, did not look at an evaluation of sexual functioning, as you say.

They were just under fairly standard teratogenic evaluation, which, as animals go through the Caesarian -- there is the Caesarian section and then there is an evaluation, of the fetuses at that point.

However, there are other studies that I don't actually have a slide prepared for but that did evaluate an F-1 generation in mice.

And there are some data that suggests that there may be interference with male spermatogenesis. But, to my knowledge, that is the only interference that I've seen on a non-clinical.

DR. HICKOK: Dr. Steers, would it help you if we looked more on molecular level to, you know, how 17-p is metabolized, and androgenic or estrogenic properties? Would that be of assistance to you?

DR. STEERS: Well, it is not so much the acute effects, but, obviously, if this is a chronic exposure in uteral to receptor development, et cetera, that you might not see expression until during puberty or later of things like genital growth, things like sexual orientation, things like sexual functioning.

So it would almost be in case reports of anything long-term, or even like fertility, on what would happen with spermatogenesis in particular, if these levels are raised, and what would happen long term.

DR. HICKOK: Yes. I would like to remark that there is, you know, the ADR and AERS database that are available; again -- you know, going back some 30 years, that can be voluntarily brought up, you know, in response to questions about Delalutin because it was approved in 1955.

We have reviewed those data and found really no consistent patterns of things like that that were noted.

Of course, there is not good denominator data for that, but the AERS/ADR database does provide a way at identifying safety concerns.

DR. STEERS: Do we have access to that database from the Delalutin data as long-term?

DR. HICKOK: I'm sorry, I didn't --

DR. STEERS: Do we have access to that database for safe, long-term follow-up from the Delalutin?

DR. HICKOK: There is -- there are database -- the AERS and ADR databases, specifically, for

Delalutin, yes. And we have reviewed those.

DR. DAVIDSON: Dr. Carson.

DR. CARSON: I have several related questions, so let me just ask them and then you can discuss this.

They all are based on the fact that I noticed the impressive wide-range of body mass index in your patients in the study, from a BMI of 15 to 72.

And it made me wonder how you came up with the dose to treat all these patients at the same dose, and whether you compared efficacy in groups of obese, overweight, et cetera, in groups of body mass index?

And, then, finally, what kind of serum concentrations you had in all of these patients?

DR. HICKOK: Let me answer your questions separately here if I can.

The NICHD 17-p study, again, was not a variable dose study. It was to replicate that some of these very promising findings that had been identified before, so there was not consideration given to, you know, looking at variable different doses.

The 250 mgs per week that was administered, you know, again from 16 through 37 weeks of gestation or delivery, was noted to be effective in a number of these other studies, so there wasn't any notion at the time of varying that dose.

And, in fact, the degree of efficacy was so great one might even argue that, you know, why try it when you've got 34 percent reduction in pre-term birth, over all, you know, should you look beyond that.

The second part of your question, I believe, related to serum studies.

Serum studies were not part of the evaluation of the NICHD study. We do have some PK studies that we would -- and serum studies that we would be pleased to present to you, if that would be of help?

DR. CARSON: I would like to see that. Do you have it with you?

DR. HICKOK: Yes. Yes.

DR. CARSON: Oh, great.

DR. HICKOK: I'm going to invite Dr. Martha Charney up, who is going to describe about what is known about pharmacokinetics.

DR. CARSON: And this is in pregnant women?

DR. HICKOK: This is not in pregnant women. This is in a sample of women, as she'll describe to you, that were not pregnant at the time.

DR. CHARNEY: Martha Charney, representing Adeza.

There was one published study, which was all we could find in the literature, on the pharmacokinetics of 17-hpc.

This shows the single -- the plasma concentrations after a single dose of 1,000 mgs of 17-hpc to subjects who had endometrial carcinoma.

Next slide, please, 437.

From that data -- these are the pharmacokinetic parameters, and you can see that the T-Max occurred quite late. That's 4.6 days after injection.

The C-Max was about 30 nanograms per milliliter at this high dose. The half life was 7.8 days.

And it is my opinion, based on the long T-half and the long T-Max, that the driving force in the pharmacokinetics of 17-hpc is actually the release of the drug from the intramuscular depot.

And, given that, I think that would be independent of whether or not it was a pregnant woman or a non-pregnant woman.

There is additional data that came from the same source.

These were, again, patients with endometrial carcinoma who received an initial 5 doses, 1 per day, followed by either once weekly or twice weekly, and continued administration of the 1000 mgs.

And you can see that it does tend to level out and provide a long-term plateau of concentration on that.

DR. CARSON: So, do you -- I'm sorry, I just don't know the nanomole conversion to --

DR. CHARNEY: Oh, yeah. That's a little confusing because they reported it in nanomoles -- or in micro moles -- nanomoles, and the FDA, for its submission, we converted it all to nanograms per milliliter.

But on the single dose study, it was -- C-Max was approximately 60 nanomoles, which converted over to about 30 nanograms per milliliter.

So the other with the multiple dose, which was around 200 nanomoles per liter, would -- I think we -- that would be about four times.

We're talking probably 100 nanograms per milliliter or less.

DR. CARSON: But you're using a quarter of the dose.

DR. CHARNEY: And we're using quarter of a dose. So, yes.

DR. CARSON: So you're probably raising the pregnancy concentration by about 3 percent?

DR. CHARNEY: Oh, if you're talking about --

DR. CARSON: With, with 200, you have your baseline 17-hydroxyprogesterone in pregnancy, and, by giving 250 mgs, you're raising the concentration by maybe 3 percent? Is that right?

DR. CHARNEY: Actually, this is the hydroxyprogesterone caproate. It does not metabolize to either hydroxyprogesterone or progesterone. It has a totally different metabolic pathway, and I think our chemistry expert, if you want, can speak to that.

DR. CARSON: Yes. So you're measuring the hpc rather than just the --

DR. CHARNEY: Yes.

DR. CARSON: Gotcha.

DR. DAVIDSON: Okay. I know we have a number of other Committee members who have questions. I have a list of half dozen. We will probably give you priority later.

I want to thank Dr. Hickok for giving us this bonus question and answer period.

(Applause.)

I think we needed it.

And let's take a 15-minute break and reassemble at 10:45.

(Recess.)

DR. DAVIDSON: We have a large agenda, and it is really important that we stay on schedule.

We next have the presentation for the Agency, and this will be led with Dr. Wesley.

DR. WESLEY: I'll give you a few minutes to get to your seats.

(Pause.)

Advisory Committee members, representatives from Adeza Biomedical, representatives from the FDA, and guests, I am Barbara Wesley, and I am the primary medical reviewer for this new drug application, or NDA.

In my presentation, I plan to review, again, the clinical program of NDA 21-945, provide you with the FDA analyses of the data submitted, and summarize the issues for you to consider.

The proposed indication for 17 alpha hydroxyprogesterone caproate, which I will also call 17 hydroxyprogesterone, proposed name Gestiva, is a prevention of pre-term birth in pregnant women with a history of at least one spontaneous pre-term birth.

Gestiva is to be administered in the intramuscular route at a dose of 250 mgs once a week, beginning between 16 weeks, zero days and 20 weeks, 6-days gestation, until week 37, or birth, whichever occurs first.

An overview of the clinical studies will be presented in the next slide.

This application included data from three studies conducted by the National Institute of Child Health and Development, Maternal Fetal Medicine Network Units.

The initial formulation study, 17-pIF, was a randomized vehicle-controlled study with a target enrollment of 500 subjects, but only 150 subjects were enrolled and treated.

It was terminated prematurely due to a recall of the study drug.

The principal efficacy and safety study, 17pCT-002, had the same design as the initial formulation study.

It also was to enroll 500 subjects; however, because the boundary for the test of significance for the efficacy threshold was crossed before enrollment was completed, enrollment in the trial was stopped prematurely.

A total of 463 subjects were enrolled in this study; 310 in the 17-hydroxyprogesterone arm, and 150 in the vehicle arm.

At the request of the FDA, another study, 17-p follow-up, was conducted.

Children whose mothers participated in the principal safety and efficacy were evaluated for long-term health and developmental milestones.

278 children, from 30 to 64 months of age, were enrolled; 194 from the 17-hydroxyprogesterone arm, and 84 from the vehicle arm.

An overview of the principal study is shown in the next slide.

The principal study was a double-blind, vehicle controlled trial that randomized subjects 2-to-1 to 17 alpha hydroxyprogesterone caproate or vehicle.

Inclusion criteria were pregnant women with a history of a previous spontaneous, singleton, pre-term birth, who were at a gestational age between 16 weeks, zero days, and 20 weeks, 6 days at randomization.

The main inclusion criteria included a known major anomaly.

I want to make sure I said "exclusion criteria."

Included a main -- a known major anomaly, prior progesterone or heparin treatment in a current pregnancy, a history of thrombo embolic disease and maternal medical obstetrical complications, including a current or planned cerclage, hypertension requiring medication, or a seizure disorder.

Studied medications were 17 alpha hydroxyprogesterone caproate, 250 mgs per milliliter, in castor oil, benzyl benzoate, and benzyl alcohol, or vehicle, which also consisted of castor oil, benzyl benzoate, and benzyl alcohol, but without the progesterone.

The dosing regimen was 250 mgs, weekly injection of 17-hydroxyprogesterone or vehicle through week 36, 6 days, or delivery, whichever occurred first.

The primary efficacy endpoint was percent births less than 37 weeks gestation.

Additional endpoints requested by the FDA included percent births less than 35 weeks and less than 32 weeks gestation, and a composite index of neonatal morbidity.

The composite was based on the number of infants who experienced any one of the following: death, respiratory distress syndrome, bronchial pulmonary dysplasia, Grade 3 or 4 intra-ventricular hemorrhage, proven sepsis, or necrotizing enterocolitis.

This study was designed to enroll 500 subjects.

However, as mentioned previously, because the boundary for the test of significance for the efficacy threshold was crossed before enrollment was completed, only 463 subjects were randomized and treated with studied medication; 310 in the 17-hydroxyprogesterone arm and 153 in the vehicle arm.

The disposition of these subjects was as follows:

279 subjects completed the study in the 17-hydroxyprogesterone arm versus 139 in the vehicle arm;

27 subjects withdrew from treatment in the 17-hydroxyprogesterone arm versus 14 in the vehicle arm, but remained in the study.

In the 17-hydroxyprogesterone arm, 6 withdrew due to an adverse event compared to 3 in the vehicle arm; 4 subjects were lost to follow-up, all in the 17-hydroxyprogesterone arm.

The primary efficacy endpoint was percent of pre-term births less than 37 weeks gestation.

The primary efficacy analysis was based on the intent to treat ITT population all subjects who received studied medication.

Of the 310 subjects treated with 17-hydroxyprogesterone, 115 or 37.1 percent, delivered prematurely.

Of the 153 subjects treated with vehicle, 84 or 54.9 percent delivered prematurely.

There was a 17.8 percent reduction in pre-term birth below 37 weeks.

The 95 percent confidence interval for the reduction in pre-term births ranged from minus 28 percent to minus 7 percent.

It is noteworthy that the pre-term birth rate of 54.9 percent in the vehicle arm was considerably greater than the background rate of 36 percent that was used to power this study.

The rate of 54.9 percent pre-term births is also considerably higher than that of the control arm; 36 percent in another Maternal Fetal Medicine Network study, the Home Activity Uterine Monitoring study.

Finally, I bring to your attention that the pre-term birth rate of 37.1 percent in the 17-hydroxyprogesterone arm is no lower than the pre-term birthrate of 36 percent in the control arm of the Home Activity Uterine Monitoring study.

We were particularly interested in the pre-term birth rate at gestational ages less than 37 weeks since births at these lower gestational ages are a more accurate predictor of infant mortality or morbidity.

This slide lists the percentages of pre-term birth at selected gestational ages less than 37 weeks.

The analysis present on this slide is slightly different from that provided in our background package.

In the previous analysis, no data from the four subjects who were lost to follow-up were included, and these subjects were considered as treatment failures at all time points.

In the analysis presented in this slide, all available data from these subjects were included.

In this analysis requested by the FDA statistician, confidence intervals were adjusted for the two interim analyses and the final analysis, using a "P" value boundary of .035 to preserve the overall Type 1 error rate of .05.

The percentages of pre-term births in the 17-hydroxyprogesterone arm, at less than 35 and less than 32 weeks were numerically lower than those in the vehicle arm.

The point estimates of the differences were negative 9.4 percent and negative 7.7 percent, lower than in the vehicle arm at less than 35 and less than 32 weeks, respectively.

However, based on the adjusted 95 percent confidence intervals, the upper limits suggest that 17-hydroxyprogesterone may be no better than vehicle.

In the previous slide, the percent differences in pre-term birth at specific gestational ages, were shown.

In this slide, the proportion of subjects continuing to be pregnant at each week after enrollment is shown.

The vertical line marks 37 weeks gestation, the primary endpoint.

Not shown on the previous slides is that a lesser proportion of subjects in the 17-hydroxyprogesterone arm continued to be pregnant compared to the vehicle arm, up to 24 to 25 weeks gestation.

Beginning at about 27 weeks gestation, a greater proportion of subjects remain pregnant in the 17-hydroxy-progesterone arm, at each week of gestational age.

The early increase in fetal loss in the 17-hydroxyprogesterone arm is of concern. I will further discuss this finding later in my presentation.

Another way to look at the potential efficacy of 17-hydroxyprogesterone treatment is to compare the mean gestational ages between both arms.

The mean gestational age in a 17-hydroxyprogesterone arm was one week greater than the vehicle arm; 36.2 weeks in the 17-hydroxy-progesterone arm versus 35.2 weeks in the vehicle arm.

Consistent with the finding of a higher gestational age in the 17-hydroxyprogesterone arm, the mean birth weight was also 178 grams higher in this arm. However, this difference was not statistically significant.

Another way to assess the effectiveness of treatment is to determine the percentage of birth below 2,500 grams and below 1,500 grams, which is also consistent with 32 weeks gestation.

The percentage of infants less than 2,500 grams was 13.8 percent lower in the 17-hydroxyprogesterone arm.

For infants less than 1,500 grams, the percentage was 5.3 percent lower in the 17-

hydroxyprogesterone arm.

However, based on the 95 percent confidence interval, the percentage of infants less than 1,500 grams in the 17-hydroxyprogesterone arm was not statistically significant.

Reduction of neonatal deaths, without an increase in fetal wastage, is the ultimate goal in preventing pre-term birth.

This slide describes all deaths in the principal study.

There was an observed increase in second trimester miscarriages; 5 in the 17-hydroxyprogesterone arm versus none in the vehicle arm.

In contrast, there was an observed reduction in neonatal deaths in the 17-hydroxyprogesterone arm -- 2.6 percent versus 5.9 percent in the vehicle arm.

However, the observed reduction in neonatal deaths was offset by an increase in second trimester miscarriages and stillbirths; thus, when considering the overall mortality, there was no net survival benefit.

This graph illustrates the proportion of fetal or neonatal deaths from the onset of treatment.

On the "X" axis, you see days from the onset of treatments to fetal or neonatal death.

On the "Y" axis, you see the proportion of fetuses or neonates who are surviving.

The red line represents the 17-hydroxyprogesterone arm, the blue line represents the vehicle arm.

I want to bring to your attention once again, that there is a lower proportion survivors in the 17-hydroxyprogesterone arm until about 75 days after the onset of treatment.

Thereafter, the proportion of survivors in the 17-hydroxyprogesterone arm remain slightly above that in the vehicle arm.

To gain additional insight into the significance of the findings of early fetal losses, we reviewed the literature.

Data in a 1990 review by Keirce described four studies where treatment with 17-alpha-hydroxyprogesterone caproate was begun early in pregnancy, and data on miscarriages were provided.

Two of the trials, the Johnson and Yemeni trials, showed a numerically greater proportion of miscarriages in the 17-hydroxyprogesterone arm.

The other two trials, those by LaVine and Sherman, did not. The LaVine trial reported more miscarriages in the vehicle arm.

In addition to reduction of mortality, reduction of neonatal morbidity is a goal of therapy to prevent pre-term birth.

Major neonatal morbidities are listed on this slide.

We have chosen not to provide "P" values for the differences for several reasons.

These comparisons were post-hoc analyses. Event rates were low, and no adjustments were made for the multiple endpoints.

However, there are some noteworthy observations.

There was a decrease in the percent of respiratory distress syndrome, broncho-pulmonary dysplasia, and necrotizing enterocolitis in the 17-

hydroxyprogesterone arm.

However, there was also a small increase in the percent of Grade 3 and 4 intra-ventricular hemorrhage and proven sepsis in the 17-hydroxyprogesterone arm.

The individual morbidities listed in this slide were grouped to form a composite index of morbidity.

All infants with one or more of the listed morbidities were counted in the index.

A lower percent age of infants in the 17-hydroxyprogesterone arm, 11.9 percent, compared to the 17.2 percent in the vehicle arm, had one or more of the morbidities that comprise the composite index.

However, the difference between the treatment arms was not statistically significant.

I will now turn your attention to maternal safety findings.

Adverse event data were not collected in the usual manner for data submitted to the FDA.

Rather than collecting all adverse events, subjects were asked if they had any symptoms or complaints that they thought were related to the study medication.

There were no maternal deaths.

There were three reports of a serious adverse event, all in the 17-hydroxyprogesterone arm. None were thought to be, by the investigators, to be related to the study drug.

The serious adverse events were a pulmonary-embolus eight days after delivery, a case of cellulitis at the study medication site, and a patient with postpartum hemorrhage, respiratory distress, and endometritis.

Eleven (11) subjects discontinued because of an adverse event;

Seven (7) subjects were in the 17-hydroxyprogesterone arm; 3 with urticaria, 2 with injection site pain or swelling, 1 with arthralgia, and 1 with weight gain.

Four (4) subjects were in the vehicle arm, two with pruritus, one with urticaria, and with injection site pain.

Common adverse events will be described in the next slide.

The majority of all adverse events were related to injection site reactions.

Injection site pain was the most commonly reported adverse event affecting a third of subjects in each arm.

Injection site swelling was the next most common adverse event, followed by urticaria, pruritus, and injection site pruritus.

We identified three out of nine complications of pregnancy reported by the applicant where the percentage of effected subjects was proportionately greater in the 17-hydroxyprogesterone arm.

The pregnancy complications were: Gestational diabetes, oligohydramnios, and preeclampsia.

The numbers of subjects with these complications in both the principle study, CT-002, and the initial formulation study, IF-001, that was terminated prematurely due to a recall of the study drug, are listed on this slide.

There was a small increase in the percentage of subjects with gestational diabetes in the 17-

hydroxyprogesterone arm in the principal study.

In the initial formulation study, there were eight cases of gestational diabetes in the 17-hydroxyprogesterone arm compared to no cases in the vehicle arm.

This difference approached statistical significance.

In terms of oligohydramnios, there was almost a three-fold increase in the percentage of subjects with oligohydramnios in the 17-hydroxyprogesterone arm of the principal study.

The percentage of subjects with pre-eclampsia in the 17-hydroxyprogesterone arm in the principal study was almost twice that in the vehicle arm.

The percentage of subjects with pre-eclampsia in the 17-hydroxyprogesterone arm in the initial formulation study was also higher.

Although the initial formulation study was terminated prematurely, I will briefly describe some of the findings from this study.

The design of this study was identical to that of the principal efficacy and safety study;

namely, double-blind, vehicle controlled, and randomized 2-to-1, 17-alpha- hydroxyprogesterone caproate to vehicle.

This study was terminated prematurely because of a recall of the study drug.

150 subjects were randomized prior to the recall; 104 subjects either completed treatment or withdrew for reasons other than recall of the study drug.

Of these 104 subjects, 65 subjects were in the 17-hydroxyprogesterone arm, and 39 subjects were in the vehicle arm.

Key findings from this study are presented in the next slide.

The top of this slide shows the proportion of subjects who delivered at less than 37 weeks gestation, among those subjects not affected by the study drug recall.

These are the subjects who either completed treatment or terminated for reasons unrelated to the recall.

The percentage of pre-term births in the 17-

hydroxyprogesterone arm was slightly higher than that in the vehicle arm, 43.1 percent versus 38.5 percent.

The lower portion of the slide lists all fetal and neonatal deaths from all enrolled and treated subjects.

The increased miscarriage or stillbirth rate that was observed in the principal study was not seen in this study.

There was only one case of miscarriage in each treatment arm.

In terms of stillbirths, there were two cases in the vehicle arm compared to one case in the 17-hydroxyprogesterone arm.

There were two neonatal deaths in the 17-hydroxyprogesterone arm, and none in the vehicle arm.

The next slide provides an overview of the follow-up study of children born in the principal study.

The objective of this study was to evaluate the long-term health and development of children who were born in the principal study.

Only 14 of the original 19 sites were remaining in the Maternal Fetal Medicine Network at the time this follow-up study was conducted; therefore, approximately 80 percent of the children were eligible to participate.

Of these eligible children, 278 enrolled, 194 from the 17-hydroxyprogesterone arm and 84 from the vehicle arm.

Some demographic information for the children in the follow-up study are listed in this slide.

The mean gestational age of the children who participated in the follow-up of each treatment arm was one week greater than that in the principal study.

As such, the follow-up children may represent a slightly lower risk subset of the total group of children from the principal study.

The mean age of the children in the follow-up study at the time of evaluation was 47.2 months from the children from the 17-hydroxyprogesterone arm, and 48 months in children from the vehicle arm.

As stated previously, the primary objective of the follow-up study was to determine if there were differences in achievement of developmental milestones between children whose mothers received 17-hydroxyprogesterone, and those whose mothers received vehicle, in the principal study, as measured by the Ages and Stages Questionnaire, otherwise known as the ASQ.

This primary endpoint of the follow-up study measured the proportion of children from each treatment arm who fell below a specified cutoff, at least one of the five developmental areas listed -- communications, gross motor, fine motor, problem solving, or personal/social.

A positive screen was defined as a score which was two standard deviations below the mean in any of these five areas.

The secondary objective of the study was to determine if differences existed between children whose mothers received 17-hydroxyprogesterone and those whose mothers received vehicle in the principal study in any of the following factors:

activity motor control, vision/hearing, height/weight, head circumference, gender specific play, or diagnosis by a physician.

These children also received a physical exam.

The results of the ASQ, the primary endpoint assessing developmental milestones, will be shown on the next two slides.

This slide lists the number of children whose ASQ scores were screened positive or two standard deviations below the mean.

The proportion of children below the cutoff in each developmental domain was similar for each treatment arm.

The area with the highest percentage of children with low scores was fine motor skills with approximately one in five children scoring below the cutoff.

Approximately one in ten children had scores below the cutoff in communication or problem solving.

Few children had low scores for gross motor, or personal social skills.

Overall, approximately 28 percent of children from each treatment arm, shown by the numbers in yellow at the bottom of the slide, scored below the cutoff in at least one domain.

The absence of an apparent difference between the treatment arms should be interpreted with caution because the number of children in this study is relatively small.

A second integrated evaluation concerned identification of the true positives among those children identified as potentially at risk for developmental delay based on their ASQ scores.

As stated previously, the purpose of the ASQ was to identify children who may require further evaluation by a physician.

Those children with at least one score below cutoff and who had a parental report of a diagnosis of developmental delay, made independently by a physician, were reviewed in more detail.

13, or 6.7 percent, of the children from the 17-hydroxyprogesterone arm, and 8, or 9.8 percent, of the children from the vehicle arm had an ASQ score below cutoff in at least one developmental area and a reported diagnosis of developmental delay.

Of the 21 children, total, meeting both criteria, the most common ASQ domains falling below the cutoff were: Fine motor and communication for the 17-hydroxyprogesterone exposed children, and communication and problem-solving for the vehicle exposed children.

The results of the follow-up study revealed no substantial difference in the outcome of the children exposed to 17-hydroxyprogesterone compared to vehicle.

To summarize, the applicant is seeking approval for 17- alpha-hydroxyprogesterone caproate based on findings from a single clinical trial and a surrogate endpoint for infant mortality and morbidity, pre-term birth less than 37 weeks gestation.

We are concerned that these findings may not be applicable to other populations and that the pre-term birthrate in the vehicle arm is considerably higher than that reported in another large Maternal Fetal Medicine Network study.

We are also concerned that there is a potential safety signal of increased fetal wastage in the 17-hydroxyprogesterone arm.

We are asking the members of the Advisory Committee to consider these issues during your deliberations later today.

Thank you.

(Applause.)

DR. DAVIDSON: I'm sorry. This will cover both the sponsor and the agency presentations.

I think, in fairness, I should start where we left off this morning with our incomplete list of questions.

Dr. Liu.

DR. LIU: I wanted to ask about the first study that was stopped because of the medication.

One was, what was the problem with the medication in terms of the quality in terms of the manufacturer.

And, two, have you had the opportunity to combine the results of the completed datasets from the first and the second study for the outcomes as opposed to just the followup?

DR. HICKOK: Yes. Let me make sure that I have your questions correct.

In the response to the recall of the study drug, as we mentioned before, in the 001 Study, there was a Consent Decree cited; "Significant GMP," Good Manufacturing Practice, you know, violations, and that information is -- that is the only information that we have in the public domain.

So FDA, at that point, and the manufacture, recalled the study drug in the 001 trial.

And we don't have any other information other than that.

NICHD, as I stated, following that, decided that since there had been a recall of the manufacturer, and 17-p was no longer available at that point, basically, to initiate a new study.=

And, at that point, they also found a different manufacturer.

In terms of your second study about, you know, did the sponsor go ahead and give information and integrate the data, even though the 001 Study was not complete, yes, we did go ahead and do that.

And I might remark, though, that it is percentage in the 001 Study to look at the percentage of women who actually went through the whole study; in other words, had an opportunity for a full course of drugs, and that was, between the two groups, only approximately 55 percent.

So for the purpose of efficacy, we chose to present the data from the 002 Study.

If I can present the results to you, though, of, you know, integrating these two studies, which we did for the purpose of efficacy, you will see the following findings here.

For pre-term birth less then 37 weeks of gestation in the integrated data, again, 17-p, 404 versus 209 in the placebo group, we saw the following pre-term birth rates: 38.1 percent versus 49.8 percent.

And, again, this "P" value was significant at the .0052 level.

For birth less than 35 weeks, the difference was 22 percent versus 30.6 percent, again, a "P" value of .02. Birth less than 32 weeks, these differences, with a "P" value of .003067.

And, again, for the primary outcome of birth less than 37 weeks, as we described previously, we did adjust that by logistic regression for the imbalance in the prior pre-term birthrate.

So I guess I would say, in conclusion -- I'm sorry, I'm looking at you over a monitor here.

In conclusion, now, even though we didn't feel that it was completely correct to integrate these two studies for the purpose of efficacy because the 001 Study received less than 60 percent full opportunity to get the full trial drug, nonetheless, we see that, integrating these results, we still see statistically significant endpoints for the primary endpoint of less than 37, but also less than 35, and less than 32.

DR. DAVIDSON: Dr. Simhan.

DR. Simhan: This is a question for Dr. Hickok.

Your intent or proposal is that the trial inclusion and exclusion criteria should apply to clinical use; specifically, the inclusion criteria that I'm speaking of is the history of prior spontaneous pre-term birth of a singleton pregnancy.

And the two exclusion criteria in 002 that I'm asking about are hypertension requiring treatment, and seizure disorder.

DR. HICKOK: Yes, we do, Dr. Simhan. Thank you.

We do propose the same labeling indication because that is all we have information on, and it would be unfair to include people on those labeling that were not studied during the NICHD trial.

Specifically to your question about a single, you know, prior pre-term birth, we do not propose that Gestiva be labeled for anything other than that sole indication, because there are not clinical data supporting other indications.

DR. DAVIDSON: Dr. Harris.

DR. HARRIS: Yes. Thank you.

Could you address the stillbirths in the study, please?

You had, I think, eight in the treatment group and only two in the placebo group.

Percentages weren't statistically significant, but it appeared to be a trend towards an increase in the treatment group. Part of that appeared to be infection.

Does that mean that bacterial vaginosis at the time of entry would be a contraindication, and/or should we look at stillbirth rates in this population a little closer before or as part of the Informed Consent for treatment?

DR. HICKOK: I'm sorry, Dr. Harris. At the very end -- if you would clarify the very end of your question about Informed?

DR. HARRIS: The question is, if there is a towards -- which appears to be a trend towards stillbirths, how do we address that as part of this overall approval process?

Do we need to look at more patients, or do we need to make that part of the drug labeling or Informed Consent? What is your --

DR. HICKOK: I see. Thank you for the -- yes. Thank your for the clarification.

Yes. Let me review the stillbirths with you from the 001 and 002 Studies.

And, again, to give you the overall integrated conclusions from the 17-p and placebo groups, there were seven stillbirths that occurred in the 17-p group, for a frequency of 1.7 percent, and four in the placebo group, for a frequency of 1.9 percent.

Six of these occurred antepartum, and one intrapartum in the 17-p group. Two in the placebo group antepartum and two intrapartum.

And, again, remember, when you compare across columns for raw numbers here, there is a 2-to-1 ratio of 17-p versus placebo patients.

You saw the analysis that I previously presented to you about stillbirths, and we actually took the -- or about miscarriages. I'm sorry, I misspoke.

We took the same approach with stillbirths, in that we know that stillbirth risk varies across populations. There are high-risk and low-risk groups for stillbirth, as described in a couple of very good, large recent surveys.

So we took the approach, and we looked at other information from clinical studies, both Network studies and from the literature, and have summarized this information for you on this slide.

And I want to remark, first, that four of these studies that I'm describing are actually randomized trials of 17-p versus placebo.

And these were the studies by John Hauth that I described to you previously, that used active military duty as a criteria for randomization.

And then a second study, the Johnson study, that we are all aware of from 1975. That's very well known.

Then I've included the 17-p study here with the data that I previously have shown to you.

And then one other study that's received a fair amount of attention because it is a recent study, and this is a study by Carrodo in Italy, that randomized women with 17-hpc versus placebo following a mid-trimester amniocentesis.

So, again, you know, the outcomes for pre-term birth are not presented, but, specifically, these investigators examined that interval following the amniocentesis to see if there was any -- you know, any risk or any benefit from 17-hpc.

But going back to other Network, studies, again, one of the studies that has been performed by the Network that we feel has extremely valuable information is the Factor Five Leiden study, which, again, was an observational study.

Women were enrolled very early in the Factor Five Leiden study, you know, on average of 12 weeks or so.

So they were followed longitudinally throughout pregnancy, and there is good opportunity of, you know, getting very valid data on stillbirths.

And, in addition, the Factor Five Leiden study, again, as a Network study, is likely to comprise patients who are quite similar to other Network studies, like the 17-p study.

So for that reason, we feel that these numbers are quite good.

So when you look across the different columns here, we see the Factor Five Leiden study.

We see that in the three randomized studies of 17-p versus placebo, we have 3.8 percent versus 1.3 percent for stillbirths in the Hauth Study.

We have 4.5 percent versus zero percent in the Johnson Study; 1.1 percent versus 0.6 percent in Corrodo; 1.9 percent versus 1.7 percent.

And our summary conclusions on these are that there is really no apparent association that we can determine from all the available data that we have collected that we feel are valid comparison groups.

So there is no association between 17-p exposure and the risk of stillbirth based on these numbers.

Did you wish for me to go further into the questions about BV and occurrence of bacterial vaginosis during pregnancy?

DR. HARRIS: Not necessarily. I should clarify.

The question I had was really about the antepartum versus the intrapartum. Presumably, unless there is a catastrophe, most intrapartum stillbirths should be preventable.

But it is the unmonitored, supposedly low- risk antepartum stillbirth that I was raising the concern about.

And since you mentioned the thrombophilia area, which is associated with an increase in stillbirths, it raises even more questions about selection criteria for the treatment with progesterone.

DR. DAVIDSON: Dr. Merritt.

DR. MERRITT: I would like to go back to the presentation of the studies on animal data and ask again about the teratogenic effects in two populations.

In the rodent population, as I read the slide, it appeared that the number of animals studied were between 8 and 15 in each study.

When the primate data was presented, I didn't see.

Anc could you please clarify those study numbers for us?

DR. HICKOK: Dr. Singh, will you review these studies again for us, please?

DR. SINGH: I am going to have to tell you that, from my memory, I believe, it was three. An N of 3 for the monkey studies.

But I will have to -- in fact, at lunch, I can verify that. I have the actual references and everything with me.

But -- so for the two -- for the Cynomolgus monkey study -- if you want to bring that slide back up -- and the Rhesus monkey study, which is actually one and the same -- we want the next slide, please.

Okay. So this slide actually represents two different studies.

The Hendricks, et al, paper that was published in 1987 is the one that contains the data from both the Rhesus monkeys and the Cynomolgus monkeys.

And that is the study in which I believe there was an N of 3.

And, I'm sorry, I just need to pull that reference, and I will confirm that with you later on.

So, and then in the second studies, well, I have that reference, actually, in the Boardroom, and, again, I can make that available to you.

If there's any follow-up question for now on content?

DR. MERRITT: Could you go back to the rodent slide, please?

DR. SINGH: That's one slide back.

So you're correct. The C-57 Black Six Mice study. In that study, the N was 8 per group.

And in the Swiss Webster Mulhouse study, that the N was between 11 and 15 per group.

Again, you will notice that the route of exposure is different.

There are sub-dermal pellets or subcutaneous injections, so this is different than the intramuscular route. So there is a bit of extrapolation there.

DR. MERRITT: Thank you for that clarification.

I have one other question, which is why was castor oil included in the vehicle as opposed to some other compound?

DR. HICKOK: Yes. Castor oil has traditionally been included in a vehicle as a depot injection to, again, prolong the duration of action at the 17-hpc.

If given orally, it is rapidly degraded and not bio-available.

DR. DAVIDSON: Dr. Lewis.

DR. LEWIS: Yes. I also was wondering a little bit about the castor oil.

Is Delalutin also in a castor oil? That's one.

And, secondly, it is bothersome that there is such a high background rate of pre-term births in the 002 Study.

And I know that if you compare it to the other Maternal Fetal Medicine Network Unit study, they had a much lower rate.

Were the same centers involved?

And what is the speculation on why the difference is so great?

Were the time periods overlapping at all?

You know, it's just -- that is bothersome.

DR. HICKOK: Thank you, Dr. Lewis.

Let me address each one of your questions separately, as I can.

And the first one I'll go to is, you had a question about Delalutin and the formulation. And let me just show you some data on the comparison between the two.

Here, you see the Adeza-proposed product, or Gestiva. You see the studies 17-p 002, and, here, Delalutin.

And you see, again, the quantity of 17-hpc and the concentrations of benzyl alcohol, benzyl benzoate, and benzyl and castor oil are all identical between the three.

For your second question, I believe you're getting at the question of the pre-term birthrate and the placebo that Dr. Wesley raised.

And I'd like to invite Dr. Anita Dos, our bio-statistician, to address the issue of the pre-term birthrate in the placebo group.

DR. DAS: There are a lot of reasons why the pre-term delivery rate in HUAM which is the Home Uterine Activity Monitoring study, and the Study 002 could be different.

The most quantifiable reason is that Study 002 enrolled the population at higher than the HUAM study.

And this is evidenced by looking at the number of previous pre-term deliveries in the 002 Study.

In the 002 Study, there was 32 percent that had greater than one previous pre-term delivery, and in the HUAM study, there were 22 percent of women.

The gestational age at the worst previous pre-term delivery was also slightly lower, at 29.7 weeks versus 30.2 weeks.

But, also importantly, the gestational age of the qualifying delivery in Study 002 was early, at 30.8 weeks, showing that this is a higher risk population.

There is other non-quantifiable reasons why these two studies might differ.

One would be the temporal reason in that Study 002 was completed in 2002. The HUAM study was completed in 1996.

And the MFMU Network was slightly different, with 19 participating centers in 002, and 11 participating centers in the HUAM study.

But, also, very important is the study design.

The HUAM study was not a randomized trial, it was an observational study.

Study 002 is a randomized trial with very intensive intervention. An injection once a week.

And we know from anecdotes that the women who participated in this trial were extremely motivated.

One: Because of their prior pre-term history and their adverse obstetrical history.

So, again, one of the non-quantifiable differences, truly, is an observational study versus a randomized trial.

I'd also like to have Dr. Savitz come and speak a bit to this point.

DR. HICKOK: And Dr. Savitz, I might add, is a reproductive epidemiologist.

DR. SAVITZ: Thank you.

David Savitz, Mount Sinai School of Medicine.

I can just maybe comment and just add to that that the -- sort of the art of predicting the baseline rates in randomized trials is a challenging one for those who have engaged in trials, and you use the -- of course, the best historical data you have the best estimates.

But, as Dr. Das explained, the constitution of the patient groups will often differ and especially the willingness to participate, is a more subtle, but, I think, can be a very important influence on the baseline risk.

I don't think there has been so much a question about maybe whether the placebo group accurately reflects the baseline risk.

That is an issue of randomization, I think has been well taken care of.

But I think probably the concern is maybe with one of generalize-ability; that is, whether these results would apply to the full spectrum of women who meet the eligibility criteria of one or more prior pre-term births.

And, there, I think the data are clear in the various subgroup analyses, saying that all of the groups of varying background risk seem to share the same benefit.

That is, whether the groups are defined by number of prior pre-term births or other criteria --

bacterial vaginosis, and so on, as Dr. Hickok presented.

There's every reason to think that a different group with a different mix of those attributes would probably have a lower risk of pre-term birth. but there is a consistent pattern that they would be predicted to show the same benefit.

DR. DAVIDSON: Dr. Henderson.

DR. HENDERSON: I, too, am struck by the high background rate of pre-term delivery.

I wonder, from the literature, do you know what the background rate was in any of those publications, the ones that you used to cite in support of what the Maternal Fetal Network did?

DR. HICKOK: Yes. You know, it is quite remarkable about having spent, it seems like over a week looking, for this type of information.

You know, you probably go back to, you know, the quote from Robert Goldenberg that's widely cited, that there's a 20 to 40 percent risk of recurrent pre-term birth kind of period.

And we did look, and we can actually, you know, show you some data from the 002 Study on the risk of recurrent pre-term birth, by the number of prior pre-term births, which is, you know, certainly a big risk.

And that goes up dramatically with each consecutive number of prior pre-term births.

In other words, those women that have one, versus those that have two, then those that have three. And it makes quite a -- it's quite remarkably higher as you move up.

A second variable that's been pointed out by the Network studies, and specifically Dr. Brian Mercer, has been a lower gestational age at the time of, you know, prior pre-term birth.

And I think, as Dr. Das pointed out to you in her presentation, that the average gestational age of the prior pre-term birth was about 30.9 weeks, which really is very low when you consider the data that Dr. Nageotte presented, that 75 percent of pre-term births occur between 34 and 37 weeks of gestation.

So, obviously, the women that entered into the

NICHD clinical study were at high risk. Very high risk, by virtue of number of prior pre-term births, and by the low gestational age at the qualifying pre-term birth.

DR. HENDERSON: One thing that strikes me, the age certainly is getting younger, gestational age.

But part of that is the multiple gestations, and that group was excluded from this trial.

So, in looking at the incidence of pre-term delivery is increasing, the age of gestation is decreasing, and part of that is the contribution of multiple gestations, and so that's not part of what we're looking at.

I'm just still struck by the high incidence of pre-term delivery in the placebo group.

And just other than just saying that the rate has increased over the baseline rate, in general, do you have any thoughts of how or what may be -- I mean, the vehicle or what -- the intervention?

And you would think that women who are in randomized clinical trials because of their history, as was stated, they are very motivated and they're very cooperative, and they show up, and they don't know that they are getting placebo.

So it is very likely that they were really, really good patients, and they did what they were supposed to. So you would think that just the intervention would lower their risk.

So I just -- I can't get my hands around the 50-so odd percent of pre-term delivery.

DR. HICKOK: Yes. The women were certainly motivated, and they had, had, you know, a prior -- at least one prior very bad experience.

And I might even give you a little, you know, flavor for that at the study site by asking Ms. Gwendolyn Norman to talk a little bit about her relationship with patients. And she -- you know, she recruited them, she followed them.

Ms. Norman, would you step forward and just give us a little bit of flavor for the risk status of your patients and their motivations and compliance and all?

MS. NORMAN: Certainly. Gwendolyn Norman from Wayne State University.

In the original trial, the 002, we did find that the women were very willing to participate.

They had had, as you said, a very high risk of exposure. They had had a previous loss, were very compliant, and participating in coming weekly or, if they were on bed rest, for us to come out and do home visits for them.

DR. HICKOK: And I'd also like Dr. Paul Meis, the principal investigator of the study -- we're fortunate to have him here today -- to remark on this subject.

DR. MEIS: Paul Meis, Wake Forest University.

I can only say that, anecdotally, when I would recruit patients for this study, that when we explained the study to women, that they would receive weekly intramuscular injections from 16 to 20 weeks, all the way up to 36 weeks, and that there might be a chance that they're getting the placebo for no benefit, the women who had had a prior pre-term birth at, say, 35 weeks or so and the baby had done very well, they were not very interested in participating in this study.

But if the woman had had a pre-term birth at 28 or 29 weeks and the baby had stayed in the hospital for a long time and had problems, they were very interested in this study.

So I think there was a self-selection process involved.

DR. HICKOK: Thank you, Dr. Meis.

DR. DAVIDSON: Dr. Gillen.

DR. GILLEN: Thank you.

I hate to beat a dead horse here but, clearly, this is a sticking point in terms of the generalize-ability of what we're looking at.

So, it seems like one of the most plausible explanations that's been offered is that there's co-variate imbalances, effectively, with respect to risk factors for pre-term births between the 001 Study and the 002 Study.

And, I guess, I'm just wondering if the Committee can offer us any sorts of -- so, I mean, it begs the question, effectively, to say, which way are the imbalances going in terms of the general population or the target population that you're

going to be targeting here?
     And so, is there any sort of literature or review that we have evidence for that says, you know, the target population currently today is more like the placebo group that was enrolled, or the group that was sampled for the 002 Study versus the 001 study, in order to help us make this distinction between the two?
     DR. HICKOK: Yes. The answer off the top of my head, is, again, these were very motivated women that had had a bad experience.
     And we would expect, you know, going forth, at least -- and, again, this is opinion on my side -- we would expect women who perceive themselves at higher risk to be more likely to engage in a course of treatment that involves something like weekly, you know, injections of a -- you know, of a drug and castor oil then we would people that, as Dr. Meis and Ms. Norman described, as those at 35 or 36 weeks that had had a child, but perhaps had a longer neonatal stay.
     In terms of your -- I think you had almost a

second question about generalize-ability and all, too, and Dr. Savitz addressed that briefly.

But the stratified analysis that we presented to you, we sent to you during the core presentation, I think a very strong argument about the generalize-ability of the benefit of 17-p.

And, again, if we go to the first slide that I showed, this gets at the prior question, also, that was raised about risks by number of prior pre-term deliveries.

Again, we see in a population, with a lot of pre-term deliveries, those baseline risks in the placebo group can be very, very high if you have a large number of pre-term deliveries.

But on the issue of generalize-ability, whenever you start dividing groups into different strata and get consistent effects, it's a very strong argument about generalize-ability of the results.

And what we showed you here, previously, was the effect by number of prior pre-term births.

And then, secondly, we divided the population into African-American versus non-African-American and saw the same general pattern as we did with the benefit of 17-p over placebo.

A third stratification was by bacterial vaginosis, which is a known risk factor, as Dr. Nageotte showed you.

And we would see the same kind of pattern about, you know, an increased risk in people with bacterial vaginosis in the placebo group, which you would expect.

But, similarly, a decrease that paralleled one and another between the "BV" and the no "BV" group.

So, because of those, you know, four ways that we stratified and all, it is a very strong argument that there is generalize-ability of those study results.

Dr. Savitz, would you have any further comments on this regarding our statistician's question here?

DR. SAVITZ: Very briefly.

I think that the best guess about what would happen if you reconstituted a different that had a lower risk distribution is to look at the data that

Dr. Hickok presented, and imagine a group with fewer multiple prior pre-term births or a lower rate of bacterial vaginosis.

Or, if you will, an average -- a more favorable risk factor profile.

The best evidence from the study says that group with a lower risk profile would share the same benefit as was observed in this population, given that the stratum specific results were so consistent.

So if you had a different mix of strata, if you will, you would still predict and anticipate the same kind of benefit.

DR. GILLEN: I certainly agree that there is consistency; I guess, that they're -- and true in terms of the point estimate, all pointing in the correct direction.

But, I mean, you know, there is variability there in terms of pre-gestational or pre-term births of less than one. You only have an 11 percent difference, going up to, you know, what we see as an average of 17 percent differences, and a maximum, I think, 30 percent difference from what I saw on the previous slide.

So, you know, when we're weighing sort of efficacy versus safety, you know, the magnitude of a point estimate is very important; and so, therefore, what constitutes the population later on is going to be very important in terms of how that point estimate is going to fluctuate between, say, a 10 percent improvement and a 30 percent improvement, for example.

And so, I guess, that's my main point in terms of saying, you know, what is the population, or target population, truly going to look like.

And is it what we've seen in the past or what we see now with this 002 trial?

And I understand that is a very difficult question. I'm just trying to raise it and illustrate some of the things.

DR. SAVITZ: I think that, again, the data provide the basis for speculating about a different mix of the known risk factors.

But I think, as Dr. Meis mentioned, I think one of the biggest -- you know, the issues is the self-selection into the study.

And, again, there is no reason to anticipate that a different mix of women with different motivation would experience a different consequence.

I think there is an issue, though, about the challenge of simply -- for this kind of a protocol, of having in a trial situation where there is that placebo arm, obviously, that people are aware of, to generate a group that really is fully representative of the clinical source population.

So there is that nature of generalize-ability always from randomized trials.

DR. DAVIDSON: Okay. Dr. Wenstrom.

DR, WENSTROM: A lot of concern was expressed about the five miscarriages in the 17-p group.

But a miscarriage was defined as a loss between 16 and 20 weeks. And I believe we were told that the average gestational age at the first dose was almost 19 weeks.

So do we even know that those five women got a dose of 17-p or, if they did, if fetal viability was confirmed before they got that dose?

DR. HICKOK: So, Dr. Wenstrom, that has to do with combining the 001 data with the integrating. That's a very -- a very good question on your part.

And we actually did go back and look at, specifically, the number in Study 001 who completed treatment through 20 weeks of gestation.

In other words, we had a full course of treatment through 20 weeks gestation.

That number was 94.5 percent, so we felt very good about combining that with the data from 002, you know, and giving a bigger estimate and more stability of the numbers with, you know, again, almost 95 percent of the women in that 001 study, did complete treatment through 20 weeks.

DR. WENSTROM: Does this mean they had one dose at 19 weeks? The average -- wasn't that correct?

DR. HICKOK: It is possible that they had one dose.

But, again, the average gestational age at the time of randomization was almost identical between the 001 and the 002 Study.

So there was a balance -- I'm sorry, between the 17-p and the placebo groups.

So there was a balance on, you know, when people entered the study and the average number of injections they received by 20 weeks.

DR. WENSTROM: But it's possible that some of those five women hadn't even received a dose; correct? They could have been randomized and counted as a loss?

DR. HICKOK: No. They were all randomized and given an injection of 17-p at the same day.

DR. WENSTROM: Okay.

DR. HICKOK: And that had -- again, that had to occur before 20 weeks, 6 days of gestation.

DR. DAVIDSON: I understand Dr. Kammerman from the FDA may have a question or comment on this.

DR. KAMMERMAN: Yes. One of the concerns I have regarding this discussion of safety, is that we're ignoring the time on study drug that you were getting at.

And if we looked at the distribution of

gestational age at randomization, 25 percent of the subjects were enrolled by 18 weeks, 75 percent by 20 weeks, and there were 25 percent that were enrolled during that last week.

So, right off, there is only 75 percent of the subjects that we're talking about.

And we need to look at the amount of time that they were actually on study drug.

For example, there was one subject who was lost follow up, and I think that person was counted as one day in the study.

So if we account for the exposure to the study drug, the percent of stillbirths -- I'm sorry, miscarriages is actually 3.5 percent. The percentage of deaths at 21 weeks is 6 percent versus just about zero for placebo.

And if the rate of death adds up, fetal death at 24 weeks, is 7 percent for placebo versus 3 percent -- I'm sorry, 7 percent for 17-p, and 3 percent for placebo, and then that's when you start seeing the curves come back together.

So if we do look at the amount of time that patients were on study drug, the rates become elevated when we use the proper denominator.

DR. HICKOK: Should I respond to that, Dr. Davidson, or are you going to take another question? Does that mean that I can respond?

DR. DAVIDSON: I think we will have to cut off for one hour for lunch to stay on schedule.

And, as usual, our list is longer than the time we have.

So we will pick up this afternoon with the discussion in terms of those that did not have an opportunity to raise a question.

Dr. Watkins may have some logistical comments about lunch.

DR. WATKINS: Just two housekeeping issues.

For the Committee, the hotel's restaurant has an area cordoned off so that you can quietly enjoy your lunch.

If so, if you will proceed to the restaurant, I would appreciate that.

For those members who have pre-registered to participate in the Open Public Hearing but have not yet checked in at the registration desk, please do so.

Thank you. And we'll see you after lunch.

(Whereupon, a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

MS. WATKINS: We'd like to call the first open public hearing speaker to the microphone. The first speaker is Senator Connie Lawson.

SENATOR LAWSON: Good afternoon. I am Indiana State Senator Connie Lawson and Vice Chair of Women in Government, a national 501(c)(3) non-profit bipartisan organization of women state legislators providing leadership opportunities, networking, expert forums, and educational resources to address and resolve complex public policy issues.

Women in Government leads the nation with a bold, courageous, and passionate vision that empowers and mobilizes all women legislators to effect sound policy. In the interest of disclosure, my trip today was paid for by Women in Government, and Women in Government does receive unrestricted educational grants from Adeza Biomedical.

As you all know, preterm birth is a burden to the American health care system. According to the March of Dimes, every week in the United States, nearly 9,600 babies are born preterm. In the course of one year, over 12% of all live births are preterm.

Beyond the stress this causes for each family across our country, preterm birth has a lasting financial stress on our states and our nation, with over $18 billion spent nationally each year in hospital charges for babies born with low birth weight or prematurity.

I understand both these stresses on a personal level as a grandmother to two premature babies, one born at 29 weeks, one born at 32 weeks, and as a state legislator for 10 years.

We now understand the science and have the ability to prevent preterm birth. We also know that women who have previously had a premature baby are more likely to deliver prematurely in a subsequent pregnancy.

Progesterone treatments, such as 17P, have been shown in clinical studies, as we've all heard today, to have a positive effect on preventing preterm delivery. In the study conducted by the National Institute of Health, 17P was successful in reducing preterm delivery by 34%.

Furthermore, the American College of Obstetricians and Gynecologists has recommended the use of progesterone in certain high-risk pregnancies, particularly for women who have previously had premature deliveries.

With available medicine and screening technologies, we can save lives, health care dollars, and undue stress on families in our nation. Women in Government has convened several educational forums on the issue of preterm birth, and many women state legislators across the country are addressing this important topic in women's health.

On behalf of my colleagues across the country, I urge the Advisory Committee to make recommendations to the Food and Drug Administration to improve the availability of preventative treatments for preterm delivery and to ensure access to life-saving technologies, such as 17P, for all women.

I thank you for the opportunity to speak to you today, and I look forward to the important decisions you will make for the women of the United States, my family, and the people I represent.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next open public hearing speaker is Barbara Dehn.

MS. DEHN: Good morning. I'm Barbara Dehn. I'm a women's health nurse practitioner, and previously, I was a pediatric ICU nurse at Stanford University Medical Center, so I know first-hand about the long-term issues of prematurity. Next slide.

When children are fortunate enough to survive their stay in the NICU, they go home to mom and dad and then if they become ill, they go back to peds or peds ICU, where I was a nurse. So I saw some of the things that they came in for. Next slide.

One of the things I saw a lot of was broncho-pulmonary dysplasia. This is also known as chronic lung disease. Those babies have very fragile lung tissue, so when they're mechanically ventilated, they can have scarring, and they can develop what's called chronic lung disease, almost like COPD in an elderly person.

These children have a propensity to asthma, and small colds or flus that your child would brush off and be able to go to school with, these children can't, so they'd end up in the PICU with me and sometimes, they'd have to be ventilated. Next slide.

Another thing I saw was necrotizing enterocolitis. We called it NEC in the ICU. This is more common in children who are very low birth weight. If they did survive -- next slide -- this, because the mortality is very high, they often needed surgery, where a small portion of their very small intestine was removed.

So these children had chronic diarrhea and malabsorption syndrome. And so it was very interesting taking care of them in the PICU with chronic diarrhea, especially because they didn't grow very well. Next slide.

The other thing that was particularly difficult for me as a nurse was to see children who had developed intra-ventricular or peri-ventricular hemorrhaging, and this is when their cerebral arteries or cerebral capillaries, excuse me, bleed and it would cause almost like a stroke in an older person.

Now, this is much higher risk in people who are delivered before 32 weeks, and small things that we did routinely in the ICU could trigger this. Just suctioning a child on a ventilator could trigger IVH. Next slide.

Now, the long-term consequences, I also saw. Children who had grade three or grade four IVH had much more serious sequelae and what I saw were children who came in for seizure disorders. So they seized and seized and seized and we couldn't get them under control.

Or their IVH made them more susceptible to hydrocephalus, and that's water on the brain. They needed shunting, and often times, they had to have shunt re-dos or their shunts became infected. And of course, we saw a lot of cerebral palsy, and those poor kids needed a lot of tendon-lengthening surgery. Next slide.

This is a partial list of risks factors. You know that. Next slide. You all know about the study by Meis, but what you may -- we should talk about is that using 17P decreases the rates of NEC, it decreases IVH, and it decreases the need for supplemental O2, or oxygen. Next slide. Next slide.

So what I want to talk about is the difference one week can make. So one extra week can make a huge difference in a child's life for their lifetime. Babies really do need to spend a lot of time in mommy's tummy. That's really where they develop best.

One extra week can mean the difference between reading at grade level and needing special education. It can mean the difference between wearing glasses and not wearing glasses. It can mean the differences between spitting up once in a while and having chronic reflux. It can mean the difference between running with your friends and being able to play soccer or having cerebral palsy, having spasticity, and needing tendon-lengthening surgery.

Now, why don't we use more 17P? I work in the San Francisco Bay area. Stanford is nearby, we have Valley Medical Center. Both of those institutions have very different protocols for 17P. So it's difficult for me, as a women's health nurse practitioner, to initiate this for my patients, and that means limited access, and that also means under-treatment of women at risk. Next slide.

Because we don't have an FDA-approved formulation, it's not on every hospital formulary. It's not on my hospital formulary, and I work at El Camino Hospital in Mountain View, California in Silicone Valley. It's not covered by a lot of insurances. So for me, it makes it more difficult for me to do my job, and my job really is to help ensure healthy babies and healthy moms.

Because it has to be compounded, a lot of us are concerned about the quality assurance, and it is available through some pharmacies, but we're not really sure whether or not we should be using that for our patients. So I want to strongly -- next slide -- I want to strongly encourage you to consider approving 17P, because I think it would help me do a better job of preventing the long-term consequences of prematurity.

I thank you for your time. In the interest of disclosure, a portion of my travel was paid for by Adeza Biomedical. Thank you.

DR. DAVIDSON: Thank you. Let me put this statement in the record. Fortunately, the first two speakers, I think, have complied with this. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making.

To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, the financial information may include the sponsor's payment for your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

MS. WATKINS: Thank you, sir. Our next presenter is Dr. Michael Paidas.

DR. PAIDAS: Dr. Davidson, members of the committee, ladies and gentlemen, thanks for the opportunity for being here. My name is Michael Paidas. I'm Associate Professor and Co-Director of the Yale Blood Center for Women and Children. I have paid for this on my own to attend here today. I've been part of the speakers bureau for the March of Dimes and Adeza Biomedical in the past. Next slide, please. Thanks.

So as you've all heard, preterm delivery is a distressing problem, continues to have major issues for us for a number of different areas, and you've heard about the use of progesterone as a preventative strategy. Next slide, please.

You've heard a lot about the randomized trial completed by Dr. Meis and colleagues which showed that progesterone caproate IM weekly early on in pregnancy significantly reduced the risk of preterm delivery. Next slide. And you've also heard that it's improved the number of neonatal morbidities, as shown here.

You've also seen -- next slide. Thank you. You've also seen that a number of progestational agents have been used in the preterm delivery prevention, and in a recent med analysis that's shown here, you've seen -- and the conclusion was the use of these agents and particularly 17P has been shown to reduce the rate of preterm birth and low birth weight. Next slide.

Recently, also, ACOG has issued a committee opinion, also identifying that progesterone has greatly reduced the risk of preterm delivery, and also stressed, I might add, that much more research is needed in these areas for patients with other high risk factors. Next slide. Thanks.

So I just want to highlight a bit about some of progesterone's actions and show you a little bit of the work that may have relevance to this topic. As you can see, progesterone has a number of actions. It relaxes the myometrial smooth muscle, it blocks the action of oxytocin, it inhibits the formation of gap junctions.

It also inhibits uterine prostaglandin production. It also inhibits T-lymphocyte mediated processes. It also seems to create a barrier to the entry of pathogens into the uterus, which is very important in terms of prevention of infection.

More recently, we've identified a number of issues of progesterone regarding the regulation of decidual cell homeostasis, those cells that come in direct contact with the placenta, and it seems to be that one of its effects is to block the effects of thrombin, which is involved in the clotting cascade. Next slide.

So we know that hemorrhage is one of the discrete pathogenic mechanisms involved in preterm delivery. In this cartoon here, you see the diagram where hemorrhage has occurred. When that does occur, there's an extravasation of a number of clotting factors, and that sets off the cascade to create thrombin.

Now, thrombin is one of the most potent uterine contractile agents that we're aware of. It's also involved in clot formation, certainly, but also, it's very much involved in the degradation of the extracellular matrix through the activation of a number of MMPs that you see on the right-hand side of the screen, which we think is important for involvement in preterm delivery. Next slide.

Recently now, we understand that thrombin induces decidual interleukin-8 expression, and interleukin-8 is very important in terms of recruiting neutrophils in the area. The panel on the right are two slides demonstrating a number of neutrophils in cases where you have abruption occurring, and in other cases on the top panel, preterm delivery unassociated with abruption.

So now, we have a clear mechanism of thrombin being important in extracellular matrix degradation, and we've shown at least one compound of progesterone to reduce the risk of thrombin. So we have a potential mechanism of its effect. Next slide.

So as you know, there are a number of different candidates in various trials, but what we're talking about here today is women with a risk of preterm delivery based on a prior history. You've already heard already about the candidates for therapy. Next slide.

You've heard a lot about safety today, and a number of reviews have come out really attesting to the safety of progesterone. Next slide. So the main problem that we have right now is that we can't get doctors to access this drug, and having an entity that might be helpful for physicians nationwide to access the drug would be of great benefit.

So I would urge the committee to consider seriously approving this drug for the treatment of -- prevention of preterm delivery. Thank you very much.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next presenter is Nancy Green.

DR. GREEN: Thank you. My name is Nancy Green. I'm the Medical Director at the March of Dimes, and I'll be representing the foundation. First, in terms of the conflict of interest, I have no personal conflict to reveal. The March of Dimes has accepted donations from Adeza, and I can just say we've never discussed the topic of prevention of preterm birth or this application or progesterone with them.

So as many of you probably know, the mission of the March of Dimes is to prevent birth defects, prematurity, and infant mortality. On behalf of the over three million volunteers and 1,300 staff members of the March of Dimes nationwide, I will provide the foundation's perspective on this application for 17-alpha-hydroxyprogesterone caproate.

The March of Dimes offers the following recommendations to the committee based upon the promising results, and we've heard about it now several times already today from the Meis et al study through the (inaudible). It is our recommendation that: (1) the FDA approve the application to license 17- hydroxyprogesterone; (2) to direct that the FDA direct the product labeling to clearly be for the specific indications during pregnancy; i.e, prevention of recurrent preterm birth; and (3) that the FDA require a structured post-marketing evaluation of 17-hydroxyprogesterone by its proposed manufacturer.

Well, we've heard about the IOM (phonetic) report as well, so I won't mention that, but I would like to point out that based on the Meis et al study, the March of Dimes did an analysis based on 2002 birth data to estimate the impact of hydroxyprogesterone on prevention of recurrent preterm birth. This paper is published in Obstetrics and Gynecology in 2005, and we -- noting the historic rate of recurrent preterm birth reported by Brian Mercer of 22%.

We looked at actually retrospective longitudinal data from two state health departments, maternal linkage, data sets that represent the ethnic distribution of the U.S., and actually, also found a recurrent preterm birth rate of 22%.

So all of those women who were eligible for progesterone as outlined by Meis et al, there would be 30,000 -- this is a estimate extrapolating from the Meis data -- approximately 30,000 recurrent singleton preterm births would occur, for which -- so those women would be eligible for progesterone. And if they had -- if all these women had received prenatal treatment with the drug, nearly 10,000 spontaneous preterm births would have been prevented; again, using 2002 data.

Widespread use of 17-hydroxyprogesterone for pregnant women has already been demonstrated amongst perinatal medicine specialists, maternal-fetal medicine specialists. A 2005 survey by Dr. Vince Bergella (phonetic), who's here in the audience, demonstrated that of those members surveyed -- or responded, actually, to the survey -- that 67% -- that's two-thirds of the respondents already prescribed progesterone to their pregnant patients who are at risk of preterm birth. And that's data that was published as an abstract in 2005, and it's currently in press.

Interestingly, despite a lack of support of clinical data, one-third of the respondents -- these are maternal-fetal medicine specialists -- one-third of those who responded to the survey recommend progesterone for indications in addition to recurrent preterm birth, such things as effaced cervix and even tocolysis and other indications -- or other clinical situations.

Certainly, we've heard today that there's a paucity of published data around the safety issues on infants and children, although the datas appear to be favorable, but the March of Dimes continues to be cautious, of course, about the use of this drug, given the target population of pregnant women.

Certainly, the studies were not designed -- the clinical studies were not designed to provide assurance of the drug's safety. Again, this is really why we encourage careful monitoring of the prescription use of 17-hydroxyprogesterone, including long-term data, as well as short-term potential manifestations, so we can best inform women and their prescribing providers around costs -- risks and benefits of 17P.

So therefore, given the common and serious problem of prematurity, as you've heard about, the unique property of 17- hydroxyprogesterone for reducing risk of preterm birth, the intended target user, pregnant women, and the documented widespread and broad prescription of the drug amongst perinatal specialists, the March of Dimes recommends that the FDA approve the licensing application for 17-hydroxyprogesterone.

If approved, that would mean that this drug would be available, if medically appropriate, to all pregnant women, including women who rely on Medicaid for health insurance and are risk of preterm birth. As you probably know, federal law prohibits Medicaid reimbursement unless the pharmaceutical or therapy has received FDA approval and the manufacturer participates in a drug rebate agreement.

In fact, a number of states have already been working for Medicaid coverage for 17-hydroxyprogesterone. For example, the North Carolina legislature recently passed a bill in May of this year to provide funds from the Department of Health to cover the cost of purchasing the drug for low income women until "the medication becomes readily available through the Medicaid program."

MS. WATKINS: Ma'am? Your time is up.

DR. GREEN: Thank you very much.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next presenter is Joseph Hwang.

DR. HWANG: Good afternoon. My name is Joseph Hwang. And thank you for allowing me the opportunity to participate in this meeting. My name is Joseph Hwang. I'm a practicing maternal-fetal medicine specialist in Des Moines, Iowa. As a -- for disclosure, my trip was sponsored by Adeza Biomedical.

Prematurity is by far the leading cause of perinatal mortality in my area, as well. As a practicing physician, this is quite frustrating to know that there's no effective treatment that I can offer to my patient.

As I look through literature, literature is flooded with negative studies of things that we do and offer to our patients, including tocolytics, antibiotics, home uterine activity monitoring, and cerclage. None of that seems to have any efficacy when it comes to prematurity. All I could offer is, as a clinician, maybe watchful eyes and give steroids.

The aforementioned NIH study by Meis gave a practicing physician like myself a glimpse of hope. I was excited to see such well-designed studies sponsored by NIH, conducted by our own network, with a positive result for once. The protocol that they used was simple and easy to follow, and it would be very easy to apply in a busy clinical setting.

As a clinician, Gestiva will ensure at-risk patients will receive a uniform and consistent drug delivery, and protocol is easy to follow for our patients.

Unfortunately, 17P is not widely available, especially in rural settings. When the NIH trial was first published in 2003, I was trying to find 17P in the local pharmacy and I was not able to do so for many months. And compounding pharmacy is a luxury in a lot of rural area.

So having Gestiva on the market approved by FDA will ensure at-risk patients in all areas will have access to this drug with proven safe records, and the clinician can follow the high fidelity protocols and feel confident that they're doing the right thing for our patient. Thank you very much.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next presenter is Terry Grossklaus.

MS. GROSSKLAUS: Good afternoon. Thank you. I paid for this trip myself. I live in Idaho and we do have family in Sunnyvale, but I don't think we know anyone here today from Adeza, and we don't own stock in Adeza.

I'm a graduate student at Gonzaga University in Washington. I'd like to specifically recommend that patients be warned to avoid all alcohol consumption while they're pregnant and under treatment with this drug. Next.

Let's learn some lessons from my previous use of Delalutin. Next. I used Delalutin during three of my pregnancies in the 1980s for treatment of a different condition and during different gestation weeks. Next. There's the product insert. Next.

The condition I was treated for suspected corpus luteum insufficiency and the progesterone was thought to supplement the endogenous production of that hormone.

Next. The protocol that was used required a combination of progesterone vaginal suppositories and weekly injections. The protocol was for gestation weeks five through nine or five through 12, and my obstetrician modified it to extend to 17 weeks or 18 weeks. It's a little bit different for each pregnancy. Next slide. It was very successful. We have three wonderful children who are all in their 20s now, all full-term. Next.

The concerns I have -- actually, I was very well-informed when I used this medication and I appreciate that from my obstetrician.

Next. The -- what I would like to comment on is a possible adverse interaction between alcohol and 17P when it's used for this particular treatment during those gestation weeks five through 18. Next. My son had a congenital cardiac condition, primary microcephaly, intrauterine growth retardation, that I experienced.

I actually developed what I thought was alcoholism during my pregnancy, but I do not have a history of that, and nor do I drink now. So I just had a drinking problem during my pregnancy. And those of you that have a handout can see the -- I have a graph of estimated ounces -- absolute ounces of alcohol per week on the Y axis and then on the X axis is gestation weeks.

Next. There's our son, and that was the pregnancy that was effected. On the left, he's about a year old and he's just a little bit hypotonic and he was very delayed in his development. On the right, he's six years old. Next slide.

In 1991, when he was six years old, I decided to conduct my own literature review on all these topics: alcohol use during pregnancy, congenital heart conditions, microcephaly, teratology, intrauterine growth retardation, all of these things, and I figured something out that made sense to me for about eight months, and then I filed all my literature away.

Next slide. The subjective experience I had is that I was addicted by 15 to 17 weeks. I was never intoxicated. In fact, when I went back and calculated my approximate blood alcohol content, it would've been about .02. I felt fetal growth restriction.

The symptoms actually diminished when I stopped my progesterone injections at 17 or 18 weeks, and then they accelerated, and then at 26 weeks, a compulsive drinking problem just completely erupted. The sensation I had is that it was all my fault for drinking in the third trimester. Next slide.

A very over simplified explanation. Alcohol, you know, is a two-tiered psychotropic drug. It's actually ethanol and acetaldehyde. I think the first portion of the chemical is metabolized, but then the metabolism is stuck at the acetaldehyde level. Next slide.

The acetaldehyde then accumulates in the mother's brain, liver, and serum, and it can serve as a teratogen, fetal growth inhibitor, disruptor of steroid hormone biosynthesis, it's addicting, and inhibits the fetal brain growth. So I think 17P is actually what restricts the metabolism of the acetaldehyde. Next.

I finally wrote my literature review up. It's over 600 pages. I need a medical researcher to take a look at it. I filed the MedWatch report with the FDA and the drug company. It's incomplete. I made some additions, and this, too, is incomplete. It's -- becoming addicted during pregnancy is just a phenomenal experience, and I'm not sure even this captures everything. Next slide.

I think that a decision on this drug maybe needs to be delayed until I can have someone review this manuscript or at least have a very specific warning to avoid alcohol while a woman is using 17P during her pregnancy. This information needs to be communicated ahead of time. If you refer to your graph again --

MS. WATKINS: Ma'am, your allotted time has expired.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next presenter is Jackie Duda.

MS. DUDA: Good afternoon. My name is Jackie Duda. I'm a Sidelines volunteer, health writer, and a mom who's experienced two high-risk pregnancies. Sidelines National Support Network is a 501(c)(3) nonprofit organization supporting women with high-risk pregnancy and their families. In the interest of disclosure, Sidelines does receive private funding from various volunteers, patients, private individuals, and industry.

I'm here to speak today on behalf of Candace

Hurley, Sidelines founder and director, in her words. In 1991, Candace founded Sidelines National Support Network after her own battle with infertility, miscarriage, and high-risk pregnancy. Eighteen years ago, she benefitted from the use of progesterone during two successful pregnancies.

Fifteen years later, Sidelines is still thriving, supporting thousands of moms around the world, having served approximately 100,000 women with education, support, and encouragement through a vast network of 7,500 volunteers who were all at one time high-risk moms themselves.

Sidelines takes an interest in treatments and technologies that will help with the devastation of pregnancy loss and preterm birth, because these are the things we deal with first-hand. If you visit our web site or read our magazine, you will see that one of our goals is to educate moms about treatments and medications used during pregnancy. We also have the responsibility of training our volunteers who support moms and speak nationally on behalf of this organization.

We have been following the use and anticipated approval of progesterone, as detailed in our 2005 publication of Left Sidelines, where we featured an article about 17P, the history of progesterone, and its use in the treatment of preterm labor.

As a representative of Sidelines and on behalf of Candace and other high-risk moms, I would encourage this panel for approval of this drug, but as a generic, not as an exclusive drug as is currently proposed. As you know, there are no FDA-approved drugs for the treatment of preterm labor, so all drugs are used off-label.

I do want to take this opportunity to express our concerns about the approval of this drug to this panel. Our understanding is that this drug is being positioned as qualifying for orphan drug status, or another form of approval that would grant one company the exclusive rights to advertise, manufacture, and distribute 17P for several years.

The concern here is that this will limit the availability of this drug, as well as drive up the price. Over the past 20 years, this drug has been widely available and used in the treatment of recurrent preterm labor as a reasonably-priced compound within a market of free competition.

From a consumer point of view, it concerns us that pregnant moms will be the ones to pay a substantially higher price for something many pharmacies have been providing to their physicians for between $7 and $10 per dose. Allowing one company using NIH research data from the public domain to have full control over this product will create a monopoly and most certainly drive up the price for a group of people who need solutions to this problem of preterm labor.

We urge this panel to approve this drug, but as a generic drug without any exclusivity, so that the under-served and often under-insured population of pregnant moms will not be the ones to pay for the high price of approval.

One loop hole in the Orphan Drug Act states that this program is developed to encourage companies to study off-label or new drugs for small populations of under 200,000 people.

As the director and founder of Sidelines, Candace would like to state for the record that the problem of preterm labor and premature delivery is a national crisis that according to national vital statistics, affects half a million women each year, more than double the number required to give a drug the qualification of Orphan Drug status.

One in three pregnant women develop a pregnancy complication, and of over four million births in 2003, the rate of preterm births increased to an astounding 12.3% of all births.

Another important concern is the impact an exclusive approval may have on jeopardizing further research into the safety aspects of this promising drug. The American College of Obstetricans and Gynecologists recommends further studies to determine the long-term effects of multiple doses and the potential for embryo toxicity on the developing fetus. We strongly support the completion of these studies.

Our main concern is for expectant families. Sidelines, in coalition with the national March of

Dimes campaign, looks to help solve this puzzle and reduce the rate of preterm babies. This first step in the approval of this drug is one in the right direction if it is as a generic, not in the proposed form of an orphan drug or one that will grant exclusivity to one entity and thereby restrict availability, drive up price, and stifle further research.

We thank you for your time and the opportunity to speak on behalf of the families who will benefit from this approval.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next presentation is a group presentation from Howard University: Davene White, Carrie Lewis, and Mikel Young.

MS. WHITE: Good afternoon. My name is Davene White. Dr. Young and Dr. Lewis had an emergency at Howard and weren't able to attend. I represent Howard University. I am not aware of any problems with my presentation. I have not had any contact with this drug agent before.

I am a clinical instructor in the Department of

Pediatrics and Child Health at Howard University's College of Medicine, and I direct our family-centered public health services at Howard University Hospital.

I am speaking to you as a result of my 30 years of experience in reproductive services at Howard University Hospital and as a neonatal nurse practitioner, where I specialized in the care of preterm infants and the support services for mothers and families.

I have particular concerns about this particular substance. Number one, pregnancy is a life-altering event for women and families, particularly when a previous outcome was less than desirable. Pregnancy is also a period during which women need and seek attention. I am interested in the continued monitoring of the effects of 17-hydroxyprogesterone and when it is no longer an intervention and what will become of this routine treatment -- what will become of it when it becomes a routine treatment.

During this study, the women were given very special attention and I know that that does have an effect and can reduce preterm pregnancy, because women need attention during pregnancy.

So I'm very concerned about the education and training that was implemented for the study staff and whether or not this will be replicated in the OB/GYN community and other participants that would be using this drug.

I'm also concerned about studies that may be available to determine the effect of progesterone on women who experience severe emotional or economic stress, since that is a very significant factor that we have identified at Howard.

We're also concerned about the extensive issue of and painful injection sites and whether or not additional investigation is needed to determine methods that should become available to reduce this discomfort and negative effects. We do know that one issue that will deter women from treatment is pain.

My greatest concern, because I am a pediatric nurse, is the potential impact of 17-hydroxy on developmental outcomes of children. As Dr. Wesley elegantly presented, there is some concern about communication, fine motor and problem-solving scores of these infants.

Because these infants will no longer be preterm, they will not be eligible for early intervention services in states around the country, so these families may not have these children evaluated as early as would be available for a child that was born premature.

We recognize that the benefit of reducing prematurity is wonderful. We support any and all efforts that will go to this cause. We do, however, recommend that further study is required of this medication and that the participants, persons who use this medication should receive adequate training. Thank you very much.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our last open public hearing speaker is Cynthia Pearson.

MS. PEARSON: Thank you. I'm Cynthia Pearson, Executive Director of the National Women's Health

Network. We're an independent women's health consumer group. We've been around for 30 years. We take no money from industry. We weren't contacted by the sponsor about this. We prepared our position based on the open literature, the documents on the FDA's web site yesterday, and the presentations this morning.

And from all that, what we take is that we understand the panel -- the committee has been brought together today and asked to advise the FDA on formal approval for a product, the use for which has been accepted by the profession, at least in main part, a few years ago.

So this meeting may be something of a formality from the committee's position, or maybe you've even gotten the message that this is your opportunity to clean up kind of a mess outside, that women are getting this product, but they're getting it from who knows where, in what sort of dose, and is the education really good.

And if you take this step forward, give the -- advise the FDA to give the seal of approval, then women will get neat and tidy 17 progesterone from a source that's inspected, that has good manufacturing practices, and all will be well with the world.

However, out in the public, we don't take your meeting today as a formality or a rubber stamp, nor, I know, do you. Because I know many of you have been on this committee for many years and struggled through some pretty tough meetings and finally, your advice is starting to be taken, albeit a little belatedly.

But we appreciate the role you play, because with you, the public gets its one and only chance to have an open discussion and viewing of the real data that underly the papers that are published which lead to the committee recommendations and other guidelines.

And what you've been asked to do by the FDA today, or to advise them about what they should do, is whether or not you should go against the typical approach of the FDA and recommend approval of a new product on one pivotal trial.

And the trial that was designed uses what, in some sense, is a surrogate endpoint. It does not have as its primary endpoint more babies alive. It has as its primary endpoint more babies who make it inside their mom's uterus for a longer time.

Now, that surrogate endpoint has meaning and value in and of itself. The nurse who spoke earlier described some really vivid and important ways, and the moms who would speak about how important it is for them to have their baby home with them as soon as possible.

All of that leads to say that that surrogate endpoint isn't like a cholesterol reading that has no meaning in the life of people who experience it. But when you look then at the data that shows some interesting back and forth underneath that no net benefit in live babies, you start to wonder, is the surrogate endpoint important as it is in itself and robust as it seems to be in this study, where it's statistically significant on its own and it's statistically significant and all in the same direction when looked at in subgroups?

But when you look then at who's living and who's dying, where were the deaths in this one trial, it starts to seem a little worrisome that there's an increased rate of miscarriage in women who were randomized to the active intervention. It also seems worrisome that that seems to appear in other studies.

So although the data are encouraging and the sponsor is to be tremendously complimented for doing a follow-up study in babies, having data on kids that are over two years old is wonderful. You're meeting the demands and the requests and the prayers of mothers, of consumer activists, and of the people who remember DES.

And no sponsor should have to do a prospective trial of children born -- do prospective follow-up of children born in the pivotal trial all the way out to puberty, but boy, it sure would be nice to have those data.

One piece of advice we'd like to make to the committee is to consider asking that the sponsor go back to some of the existing observational data sets where kids were followed or checked into at around age 11 and update them. Now, we know that's an effort and it's an expensive effort, but it can be done. So that's one thing we'd like to know, what happens to kids after puberty.

The other thing we'd like to know is really more about this apparent increase in miscarriage. So overall, I think our comments to the committee are for you to act very cautiously, to consider a recommendation of delay, even though that seems to fly in the face of common practice and the results of the trial, and give us all the time that it seems like we're going to need, the extra time to get the answers to these important questions. Thank you.

DR. DAVIDSON: Thank you. Is that the end of the list?

MS. WATKINS: Yes.

DR. DAVIDSON: Okay. The committee can go back to work. One of the committee members, Dr. Gillen. Do you want to do it from there? It's your choice.

DR. GILLEN: Before the committee started open discussion, I thought as the only statistician named on the committee, I wanted to present a couple of views of how some in the statistical community view using a single confirmatory trial and the role of probability in that versus two independent trials, and state some corrections -- or adjustments, anyway, as I should say -- to the statistics that has been presented to this time just quickly.

It's probably more formal than it needs to be, but I'm going to quote some numbers, so I just thought it would be a little easier if they were up on the screen here.

So again, we've heard already that typical criteria for approval requires the submission of two independent well-controlled clinical trials as substantial evidence for effectiveness. Of course, from a statistician's point of view, our goal is to quantify uncertainty in samples in order to make inference and to generalize to a larger population. That's what we're trying to do with these trials, in particular.

So obviously, our primary reason for requiring this consistent results on two independent trial is really to broaden the generalize-ability of our observed results, be it through clinical centers, different clinical centers, an array of them, different training that may take place over time or learning experiences of those involved in the trial, and also, different patient pools and possibly cohort effects.

One of the things that we focus on often for at least one evidence or one criteria of evidence in a trial obviously is the P value, and so we've seen a lot of them presented today. Sorry about presenting some more to you, but I'm going to need to.

Just to define it again, it's the probability of observing our results as are more extreme than those actually observed if the no hypothesis were true; in this case, our no hypothesis being equal rates in the two treatment arms. We've all heard the magic .05 for a two-sided test or a standard for a single trial that has a one-sided P value, it would be .025; cut that in half.

So the way some in the statistical community view a single trial as posing for two independent trials is to say, well, if we were to do two independent trials and we were to achieve our level .025 on both of those trials, then the probabilities would just multiply together. So one single criteria of evidence might be .000625, would be your new type one error level. Okay?

So this has been proposed, and there is some precedence to this being used at times. I'm not speaking for the FDA here, but this is a criteria that has been proposed in a single trial. So again, this corresponds to a threshold for two independent level .025 trials.

So the reason I kind of wanted to present this is because this is the way I'm thinking about things from a statistical perspective at times as I'm reading through the report, and if I'm going to talk about P values, I wanted to note, and I brought up earlier, that there were some interim analyses that were going on in the study.

Now, the committee should be aware that there are some adjustments that can be made -- taken into account, at least -- with having those interim analyses there. So I reformed them so that we can view those P values, as well, and you can take them into consideration as you will.

So the sponsor reported in this study, for their 37-week endpoint, their primary endpoint, observed proportions of .371 in the active arm and .549 in the placebo arm, so we had a difference of minus 17.8%, and the reported 95% confidence interval being minus 28% to 7%, with a corresponding P value of .0003.

In reading the FDA's report, they did note that there was an interim analysis that was done. In fact, there were two interim analysis and the final analysis. They used an O'Brien-Fleming rule, two-sided again, with level .05, so splitting that between the two sides, .025 on each arm.

And we have our adjusted results presented by the FDA's report of, again, 17.8% difference in favor of active control, and our adjusted confidence interval, which again didn't change. But I went ahead and adjusted the P values because we actually never got to observe adjusted P values that take into account the interim analyses, and so I thought it would be at least useful to see what those looked like and take that into consideration.

So my assumption is not having the full protocol at hand, but just the description given in the text, was that if we used our two-sided level .025 -- our level .05 O'Brien-Fleming boundary, the one that was used in the trial, I assumed three equally spaced analyses. I was informed today, actually, that it was 15.2% and 70% (phonetic) of the final samples size which was used.

That would make a very slight difference in the calculations that I'm using, very slight. But for -- just so you know, I'm assuming three equally-spaced analyses. And then again, our final sample size is 310 and 153, which is what we observed in the trial, and then a baseline event rate of .549.

So our adjusted P value -- and this was quoted earlier, actually, -- is .0035. This is using the sample mean ordering, so there are many ways that you can adjust P values given interim analyses, but this is what we have. So .0035 is actually with the adjustment for the interim analyses.

It turns out that when you're performing group sequential tests, where you can stop early, in fact, your observed estimates can be slightly biased. It's usually biased away from the null, so there's some attenuation that takes place. So if we adjust for that bias in the difference proportions, it's truly 16.5%, using a bias-adjusted estimate.

Again, just for completeness so that you have this, if we talked about adjusting for the interim analyses on the 35-week, 32-week, and 28-week endpoints, we can again see some adjustments in terms of the bias towards the null, attenuation towards the null, in some of these estimates, getting lower and lower as we go down. The adjusted P values, again, are slightly higher than those that were reported in the initial analysis, so just take that into consideration, as well.

Just a final note. Again, I wanted to present these because they're things that I'm looking at and I thought it should -- it would be nice for the rest of the committee to see. My own personal belief is that P values really only represent one criteria for evidence.

We need to consider also obviously clinical significance of observed point estimates. That, of course, goes into our questions of the observed rate and the preterm risk (phonetic) in the placebo arms, and we might think about other things, as well. Since we've got these divisions up by different gestational time periods, we could think about mean time to birth, as well. So these have been presented in some of the other analyses, but haven't been talked about so far today.

And then obviously, we need to consider generalize-ability of our findings, safety profile, and the urgency of clinical need. But I just wanted to present those P values for you so that you had them at your disposal. Thanks.

DR. DAVIDSON: Okay, thank you. Dr. Hickok, you may feel compelled to respond to that presentation.

DR. HICKOK: Thank you very much, Dr. Davidson. Could I move this computer off the top of the desktop here, if you don't mind? First, I think I'd like to invite Dr. Anita Das to address a couple of these statistical questions that were raised in the last presentation. Dr. Das?

DR. DAS: Yes. Regarding the adjustment for the interim analysis, the primary endpoint of preterm delivery at less than 37 weeks was the outcome that was monitored by the data and safety monitoring committee. The outcomes of less than 35, less than 32, and less than 30 were not monitored by the data and safety monitoring committee. In fact, the less than 32 outcome and the less than 30 outcomes were not even in the study protocol.

So our position is that these outcomes do not need to be adjusted for the interim analysis look. The only ones that would need to be adjusted would be the one for the primary endpoint. As we have stated, is that the alpha level for that comparison would be .035 using a .05 original alpha level.

But regardless of that, if you look at the outcomes of less than 35 and less than 32, that you could do an adjustment for these based on multiple testing procedures, and considering that these are very highly correlated endpoints, an appropriate adjustment might be something as a Hochberg method, a step-down type of method.

If you do that type of adjustment, even given a .035 as your alpha level, the outcomes of less than 32 and less than 35 would remain statistically significant with adjusted P values of .027 for both.

With that said, I would also like to agree with the panel statistician that you just can't just look at the P values when you're determining significance of these endpoints. It's the generalize-ability, it's the consistency that you're seeing across of all of our subgroups. It's the consistency that you're seeing with the neonatal outcomes, also showing benefit. So these all have to be taken in together when determining if there is a benefit.

DR. DAVIDSON: Okay, thank you. We can go -- unless you have some special introductory remarks, we can go back to questions.

DR. HICKOK: Thank you, Dr. Davidson. I don't, but I'm pleased to entertain more questions.

DR. DAVIDSON: Okay. If the interest persists, on our list here, we have Dr. Viscardi.

DR. VISCARDI: My only question was related to, again, this difference between the rates of -- higher than expected rate of preterm delivery in the control group. One of the analyses that wasn't discussed earlier, I believe, was looking at the actual indication for preterm delivery.

As Dr. Romero eloquently presented at the beginning of the day, there actually are some subgroups, and particularly indicated delivery, preterm labor versus preterm rupture of the membranes, and I think there were some differences between the groups, as far as the type of preterm delivery.

DR. HICKOK: If we go back to the efficacy analysis from our core presentation, we provided you with preterm birth rates less than 37 weeks, and I believe on that same slide was less than 35. But in addition, we have indicated preterm delivery rates in the two groups, which we'll share with you in just a second here.

Forgive me. I'm not getting exactly the data I want up yet, but let me tell you when we do find that exact number that's going to come up, we did find a very similar and not statistically different rate between the 17P and placebo groups in terms of indicated preterm deliveries. And it's very important, as you pointed out, to take a look at that because if you have an imbalance of that, you could result in bias towards one group or another by your indicated preterm deliveries.

I apologize that we don't have this up on the screen yet, but I'll give you those numbers very shortly.

DR. VISCARDI: The other reason I bring that up is that one of the things that really hasn't been addressed, and again, Dr. Romero brought this up, is a very important cause of preterm delivery, which is intrauterine infection.

And again, trying to get some idea of what might be mechanism, as I remember looking at that data, there -- it was about the same rate of indicated delivery between the two groups, but there was a higher rate of preterm labor in the control group, but no difference for the preterm premature rupture of membranes. So it looked like the effect was primarily in the preterm rupture group. Am I remembering that correctly?

DR. HICKOK: Yes. Let's first look and address your first question, if we can, about the indicated preterm delivery rate in the two groups. As you can see here, if you can see around the bottom of the podium, the indicated preterm delivery at less than 37 weeks for the 17P group was 8.1%, as opposed to 9.8% for the placebo group. So this rate was very similar and obviously not statistically significant, and we didn't do any adjustments beyond that.

We do have rates, for example, that we can share with you about rates of BV in each one of the groups, which some people could say would be a potential prognostic factor, and we would be glad to share those data with you also, if you would like.

Right? Okay. I think if we can turn to Slide 614, I believe. We have information about bacterial vaginosis and trichomonas that was collected at two different time periods on the case report forms, first at baseline, by patient report and by record review, and then during the study on the case report form, that was for record of antibiotic use that was taken at each visit, if it was appropriate. This included not only the antibiotic use, but also, the reason for the administration of the antibiotic.

Secondly, there is information on clinical chorioamnionitis, which was an outcome that was collected at the time of labor and delivery, and it can be found on the delivery summary case report form.

I might add that in this study, as again, it was a preterm birth prevention study examining the influence of 17P, that infections were diagnosed by the treating physicians based on their methods and their customs at their own individual site. So, for example, again, there wasn't routine collecting -- or routine testing of patients for bacterial vaginitis in a standardized form throughout.

If we first look at the outcome of confirmed clinical chorioamnionitis in the 17P versus the placebo mothers, we see at the time of delivery, this occurred in 3.3% of 17P mothers, 2.4% of mothers in the placebo group. Again, a value that was not significantly significant.

Turning to the incidence of BV, I said before that we had information prior to randomization, and prior to randomization, 13.2% of 17P mothers had bacterial vaginosis reported, as opposed to 13.1 in the placebo group. In the time period from randomization through delivery, the total was 8.7 in the 17P group and 5.2 in the placebo group. If you express that as any time during pregnancy, it was 20.7% in the 17P group and 15.7 in the placebo group.

One might wonder what antibiotics did women receive during pregnancy and for what reasons, in terms of vaginal infections. If we look here at the patients with bacterial vaginosis, we see that 10% were treated with metronidazole in the 17P group, as opposed to 5.2% in the placebo group. There were low rates of vaginal administration of metronidazole and again, any rate was 10.7% versus

5.9%. Again, this reflects I think clearly the slightly higher rate of bacterial vaginosis in the 17P treated group.

The next logical question is how does this reflect in terms of outcomes? We examined preterm birth less than 37 weeks in mothers that did not have bacterial vaginosis and those that did. Again, in the mothers with no bacterial vaginosis, the preterm delivery rate 35.8% in the 17P group and 51.9% in the placebo group. Again, in the 17P group, this was 42.2% in the 17P group and 70.8% in the placebo group.

This, in general, kind of reinforces what we've seen of the epidemiology of bacterial vaginosis and that it indeed is a risk factor for preterm delivery. I think one of the panelists pointed out earlier, however, that there really is no current evidence at this time that treatment of bacterial vaginosis, if it's identified during pregnancy, has an impact on pregnancy outcome.

Nonetheless, we did another analysis and we looked at bacterial vaginosis during pregnancy and the outcome of that pregnancy, and these numbers are fairly small because again, we just had 64 women with BV in the 17P group and 24 in the placebo group. But as you see here, there is low rates of miscarriage, stillbirth. The rate was elevated in the preterm -- for preterm PROM in the placebo group, but low rates of neonatal sepsis, and then no cases of cerebral palsy, as we determined from the actual follow-up study.

DR. DAVIDSON: Dr. Burnett?

DR. BURNETT: You just answered some of my questions with that last one, so I'll pass at this moment.

DR. DAVIDSON: Okay. Dr. Merritt?

DR. MERRITT: Could you please go to your Slide 42, Dr. Hickok?

DR. HICKOK: I'm sorry, Slide 42, did you say?

DR. MERRITT: Please.

DR. HICKOK: Yes. Slide 42.

DR. MERRITT: I think we've dwelt on this before, but could you attempt to justify again for me the imbalance in your treatment versus placebo population when it comes to risk factors?

DR. HICKOK: I'm sorry, I was having trouble understanding you. To talk about the adjustment that was performed in this? Is that what you --

DR. MERRITT: There's apparent risk factor difference, and you were going to discuss something about an adjustment, but I didn't catch that in the subsequent discussion.

DR. HICKOK: I'm sorry. We did not do a formal adjustment for these risk factors, but have chosen to, instead, give you that qualitative assessment. Again, there's a limit to the kind of adjustments that can be done for this. But Dr. Das, would you like to address this just briefly? It's more of a statistical question.

DR. DAS: Yes, we did do an adjustment for the number of previous preterm births, so we adjusted the primary outcome of using the logistic regression. The results remained highly statistically significant. They had a P value, I believe, of .001.

DR. MERRITT: So is that Slide 45, please?

DR. DAS: Yes. Slide 44, I believe. Here, I've got it up on the screen for you. So it's the second P value on the row, so for the intent to treat analysis, the logistic regression adjustment resulted in a P value of .001, and in the all available data, it was adjusted to .0006.

DR. MERRITT: That's not what I am addressing. My concern is that the placebo group had a larger number of patients at risk in Slide 42, at greater risk.

DR. DAS: Yes, that adjustment takes care of or adjusts for the fact that there's an imbalance between the placebo group and the active group with the number of previous preterm deliveries. So that's the standard adjustment for when there are treatment imbalances on a prognostic factor.

DR. DAVIDSON: Okay, Dr. Wenstrom? Dr. Carson? Oh. Dr. Lewis?

DR. LEWIS: All right. I would just like to pick up briefly on a point raised by Dr. Carson earlier on about the pharmacokinetic data in -- for sort of rates -- absorption rates of this compound.

I wonder if you've looked at -- stratified your results in any way according to the mother's BMI? Because you have very few data on the pharmacokinetics of this compound, period, let alone adjusted for such a wide range of BMI as was apparently reported in the 2003 study.

DR. DAVIDSON: Let me introduce another variable. You know, the maternal blood volume increases about 50% during pregnancy, and the larger the woman is, the larger that volume increase. So if you looking at the pharmacokinetics, it may be very different than what it is in a non-pregnant woman.

DR. HICKOK: Yes. Give me one second. We did look at -- over the noon hour, we pulled out information on body mass index, and I may have left it on my chair right here. We did stratify by BMI in terms of safety, but not efficacy, so we don't have an answer for you in terms of efficacy. But when we looked at safety outcomes, we did not see a difference based on body mass index.

DR. DAVIDSON: Dr. Nelson?

DR. NELSON: Dr. Wesley raised the point about gestational diabetes and preeclampsia being more frequent in both studies in the treatment arm, and I wondered if there's been any -- since -- or one of the open hearing comments was -- written comments, anyway -- was about caution with carbohydrate metabolism. What I wonder is since both of those conditions might have implications for the mother's future health, whether there's anything further known about those complications in pregnancy in the two arms?

DR. HICKOK: Yes. Let me take both of those issues separately, if I might, and first turn to the rate of diabetes. What we observed in terms of the rate of diabetes -- and I might add that this is slightly different than the data that you have seen, but it does not make the 17P group look better, let's say, so I'm not trying to bias you towards a better result.

Again, in women with no history of diabetes in the Study 002, we found a rate of gestational diabetes -- and again, this was described on the labor and delivery form. There was a check box that said does the mother have gestational diabetes? That rate was 5.8% in the 17P group and 4.7% in the placebo group.

If we look at this and then go to the 001 study, the prematurely terminated study, we see some curious, curious numbers in this, in that we see 9% in the 17P group, but none of the 52 women in the placebo group were recorded who delivered as having a history of gestational diabetes, which is clearly lower than what we would believe should be there.

So if we look at the integrated data, then, between the two studies, we see that the rate of gestational diabetes -- this is in women without previous insulin-dependent diabetes, for example -- is 6.5% in the 17P group and 3.5% in the placebo group.

So naturally, we asked ourselves the question also, what could account for these kinds of differences? So first, with the observed differences, although they are different, again, they weren't statistically significant in their differences, but we went to the American Diabetes Association, which compiles rates on this, and found again that the standard rate that's quoted by the American Diabetes Association is a 7% rate of gestational diabetes during pregnancy.

We also looked into the literature, which you know is quite voluminous in terms of non-pregnant women with various progestins having various different influences on the rate of type one -- or the rate of type two diabetes, depending on the type of progestin.

But I'd like to say just two points to this first. There really isn't any information to date on gestational diabetes during pregnancy -- well, really, three points. The second point being that the rates in this study were very similar to that of the American Diabetes Association, so we don't think that we're way offline. There is a differential that's been seen, but again, not a large differential.

The reproductive endocrinology people can probably tell you also that although there can be differences by progestins, and especially, the progestin-only pills, on the rate of glucose intolerance, in many cases, those observations that come from the laboratory don't make a big difference on clinical rates of type two diabetes.

DR. DAVIDSON: Dr. Steers?

DR. STEERS: I know I'm treading on thin ice as a urologist, trying to comment on preterm delivery, but I'll take a shot at this. On one hand, if I was a patient with high risk, I'd be reassured by the generalize-ability that's being argued in addition to statistics for approval of this drug.

On the other hand, with regard to efficacy, generalize- ability, in my view, is for a very defined population, and we seem to have a heterogeneous population, based on one clinical trial that's being examined based on race, vaginosis, birth weights, which leads me to think that this drug is being proposed to work fairly equally on all mechanisms which, in my view, would be highly unlikely, that if you propose a shotgun effect, I've not seen data with any of these analyses that there's a subset, nor intent to define a subset, where this drug would be indicated and it leads, again, with the high-risk placebo group, how you can say, this is working equally.

If it was just -- do we have data, for example, on the miscarried fetuses, on the vascular abnormalities of the placenta? Do you have any other data that suggest either a mechanism of some specificity with this agent, rather than it's working equally in all groups and it's generalizable with everybody? That isn't reassuring to me as a mechanism of action, and --

DR. HICKOK: Thank you, Dr. Steers. Let me say that, in terms of all different mechanisms, we are first proposing that that mechanism being fairly narrowly defined as those women who have had one or more prior preterm births.

If we go back to Dr. Romero's talk this morning, I think he described how there were a lot of different mechanisms that go into -- whether it's thrombosis, infection, hemorrhage, things like that.

We are proposing that this is a very narrow indication for women with one or more prior pre-term births.

I will, for example, also, if you'd like, talk about -- a little bit about proposed mechanisms of action, if that would more directly address your question.

DR. STEERS: I guess I'm confused. Mechanism, you're looking at a risk group where it's not an independent mechanism, and I guess if there's -- these women continue to have preterm -- you're always saying this is due to one mechanism, but isn't it possible that the immunologic abnormality, their socioeconomic, racial (inaudible), environment, infection, put all these women in different mechanisms; they just happened to have expressed it as multiple preterm deliveries.

I mean, it just -- I just don't understand that -- preterm delivery in that -- yes, that is just one mechanism for that.

DR. HICKOK: Yes, there's a joke that when somebody discovers the true mechanism of preterm labor, they're going to win a Nobel Prize for it. But your question is a good one, because a lot of preterm deliveries are unknown as to what their etiology are.

If you take other mechanisms, like women with multiple pregnancies, it's presumed due to uterine over-distension and stress. And for example, the one study that we know on 17P that looked at women with multiple pregnancies, the Harketene (phonetic) and Sorrey (phonetic) study, 17P was not successful in those women.

So we know that at least for that other indication, with the data that we know right now, that 17P may not be successful in that group, and hence, Adeza will very narrow in our labeling to limit this to a subset of women that, again, have one or more prior preterm births.

DR. STEERS: Did I hear there's a study ongoing with greater than two -- twin and triplet births, as well, that's not being reported yet?

DR. HICKOK: There is an NICHD maternal-fetal medicine network study ongoing with multiple pregnancies, and we don't have any data on that study to date from my knowledge today on that.

DR. DAVIDSON: Okay. Dr. Wesley?

DR. WESLEY: Yes. I just would -- something we had begun addressing in our impromptu question and answer session, the question about whether there is any availability of meaningful long-term data? It would seem as though with the 44-year experience with Delalutin, that there would be some information, although it may be difficult to interpret.

However, Dr. Hickok had previously, in response to Dr. Steers, said that there was some information, long-term information from the manufacturer. I don't know whether that consists of some sort of voluntary registry or what form that takes.

Could you please comment on the quantity and the quality of that information? And then, secondarily, has the FDA had an opportunity to review that and are there any observations or conclusions that can be drawn from that information?

DR. HICKOK: Yes. As I mentioned previously, there is a long-term safety database that's managed called the AERS and ADRs databases, and I'd like to call on Dr. Dove to briefly discuss that. We have obtained that database, and we'll -- I'm sorry. I'm going to call on Dr. Meis, actually, to give a kind of broader view of the safety issues. Not only has he been the P.I. of the NICHD study, but Dr. Meis, as you know, has also published information on safety data, and he's going to share with us some long-term safety data.

DR. MEIS: First, before we -- I address that, we have examined the results of our study according to BMI, and these -- treatment was effective against broad ranges of BMI in the participants. A high BMI was somewhat protective in the placebo group, but the treatment did have efficacy across the broad ranges of BMI.

I'd like to just talk about what information is available about longer-term effects of treatment in teenaged and older individuals. There are a few studies that have been published, as it was remarked, that Delalutin is a drug that has been around for a long time.

I would just like to mention some of the studies that have been published. A study by Kester (phonetic) in 1984 examined a group of adolescent males exposed in utero to Delalutin and performed a battery of psychological tests on the patients and on matched control subjects. The mean age of the subjects was 15 years, and the two groups were comparable in demographic and baseline characteristics.

Prenatal exposure of a male to 17P had no significant effect on type and direction of aggression expressed, the need to conform to group norms of social behavior, the gender identity, interest in sports, games, and rough and tumble play, visual spatial ability, interest in reading and type of books selected, and selection of television programs.

The only significant difference that Kester found was that the males who had been treated with 17P watched more television.

Dalton has published several studies. Dalton, in the '50s, performed some trials of prophylactic use of progesterone in prevention of pre-eclampsia, which seems to us a strange concept, but at any rate, she then had the opportunity to do follow-up on the children who were in her trials.

They reported no case of masculinization of the girls observed, and compared with controls, the children exposed to progesterone in utero had earlier attainment of standing and walking, greater attainment of above average school grades at nine to 10, and later, she found that the children who were exposed attained higher levels on national examinations and were more likely to enter a university.

Renish (phonetic) studied children aged five to 18 years exposed to progestins and estrogen in utero and compared the subjects to their unexposed siblings. There were a number of agents that they were exposed to, but basically, the progestin-exposed children had significant higher scores for independence, individualism, and self-sufficiency compared with their unexposed siblings, and lower scores for insecurity.

The personality profile has been associated with having a significant relationship with school achievement and success. So at any rate, they didn't really find any deleterious results in these studies of the teenaged children.

DR. DAVIDSON: Okay. Dr. Tulman?

DR. TULMAN: Yes, thank you. I was wondering if you could show us the -- I'm still troubled about the high rate of prematurity in the control group. Were there any differences by site?

DR. HICKOK: Let me address this, Dr. Das. We don't have a slide prepared for you on this. We can probably look this up fairly quickly for you on prematurity rates by site. Oh, we do have -- I'm sorry, we do have a slide.

DR. DAS: Yes, we -- I'm sorry. We have looked at preterm less than 37 weeks by site, and you'll see a relatively consistent treatment effect across sites. Some of the sites with lower enrollment won't have as stable estimates, and so there may be some differences there.

We also did do a site by treatment interaction analysis, and there was no significance on this analysis, except for the top site, which is Pittsburgh, where that was significant interaction, but you'll see that the number of patients enrolled there is not that high and would not be driving the overall treatment effect.

DR. TULMAN: Could I ask a follow-up question on that?

DR. HICKOK: Yes.

DR. TULMAN: Were there differences in the -- because it does -- there is quite a variation there. Do you have data on the other management of the patients who are at risk -- they all were at risk -- for premature delivery, in terms of other interventions that were done during the pregnancy, whether it was things such as cerclage or bedrest or hospitalization or some such other things? Were there differences in how they were managed?

DR. HICKOK: We do have information, for example, that directly addresses your question on the use of tocolytics and corticosteroids and would that help you? First, we do have a limitation on the information on tocolytic use because the way the case report forms were created, we have information only on tocolytic use prior to the birth hospitalization; so, for example, as information on tocolytic use, if a mother got admitted one or more times and then discharged, but not for her ultimate hospitalization that led to the birth.

I might add though, too, that this was difficult to summarize because there were no specific guidelines given to the site investigators regarding tocolytic use, and just -- there's various opinions amongst the maternal-fetal medicine unit centers regarding how you should use that. For example, one site used no tocolytic agents whatsoever, and they do that by policy at that institution.

But in terms of giving you the rates of tocolytic use between the 17P and the placebo group, these are very similar at 12.9% in the 17P group and 11.8% in the placebo group.

If we can turn now, though, and talk about corticosteroids -- that should be Slide 544 -- I can give you more information on corticosteroid use. Again, corticosteroids were -- that information was taken at several times during the course of the pregnancy, first at baseline, did you use corticosteroids and for what reason, then weekly during the prenatal visits, and then also, for preterm labor admissions.

But once again, corticosteroid use was collected only prior to the final birth hospitalization.

Again, regarding the same comment that I used about tocolytics, is that there wasn't any guidelines given by the network on that, and people did, just, I'm sure, as people do in the room here, use corticosteroids in various different ways in terms of when to stop administering it, what the dose is, and things like that.

But if we actually turn to the corticosteroid use during the 17P study itself, we can first look at information on any corticosteroid use before randomization, and in the 17P group, there were five women, or 1.6%; in the placebo group, eight women, or 5.2%.

If we look at that in terms of the type of steroid that was used, we see that inhaled corticosteroids accounted for the great proportion of this 1.6 and -- or at least of the 5.2. The great proportion in the placebo group was due to inhaled corticosteroids, which were presumably because of asthma.

So the difference in corticosteroid use between the 17P and the placebo group was primarily due to the use of -- the lower use of corticosteroids in the 17P group and the higher use of corticosteroids in the placebo is likely due to a high rate of asthma. So in other words, of this difference that we observe, it's most likely due primarily to a high use of an inhaled corticosteroid use for asthma.

We didn't make an adjustment for this in the analysis because recently, there's been two large studies that have failed to identify asthma as a prognostic risk factor for preterm birth. Another network study by Dembrasky (phonetic) and another study out of the epidemiology literature by Bracken (phonetic) failed to identify asthma as a predictor of preterm birth. Therefore, we felt justified not to adjust for this in the analysis.

DR. DAVIDSON: Dr. Scott?

DR. SCOTT: I guess the efficacy really comes down to are the two groups truly comparable, and we've spent a lot of time on that and the statistics and so on. But aside from that, I just wonder about the biologic plausibility. 17- hydroxyprogesterone is a pretty week progestin, and the endocrinology of pregnancy, of course, is very complicated, but the last half of pregnancy, there are tremendous amounts of hormones being produced by the placenta, including progesterone.

So how do you -- what is the mechanism of action? Why would it work to give a small amount -- 250 milligrams of Delalutin, or 17-hydroxyprogesterone IM, that diffuses into the maternal circulation at a low rate, when you have all these high levels of progesterone and other hormones -- why would it prevent premature labor?

DR. HICKOK: Your point is a very good one, Dr. Scott, as 20 or 30 years ago, the progesterone supplementation theory was the predominant one. We knew that progesterone levels fell preceding the onset of parturition; hence, if we give progesterone, we prevent -- we supplement with progesterone and prevent preterm birth.

That clearly is not the case, as we know now, and there are mechanisms of action that have been proposed, and I'd like to ask Dr. Singh to again give us brief presentation on some of the mechanisms that have been proposed so far.

DR. DAVIDSON: Dr. Henderson?

DR. HENDERSON: I'd just like to explore -- we talked a little bit earlier about using the animal data, looking -- talking about the effect on the neonate when -- after exposure. And looking at the sexual function and how mature the offspring is, could we talk a little bit about the animal data again? How long did these animals live? I mean, did they have a normal life after they were born?

Did they do all the normal things that they would be expected to do as lab animals, or -- I mean, how can we look at what happened to them after they were exposed to this in utero?

DR. HICKOK: Yes. Mr. Chairman, I'm sorry to ask the question, should we -- I felt like we didn't complete the last answer on mechanism of action, but I'd be pleased to go on to animals and sexual function, if you feel that's most appropriate now. I'm sorry, Dr. Davidson, at your preference, whether you'd like me to finish up the question on mechanism of action or to go on to animal studies and sexual function.

DR. DAVIDSON: Which one would you rather do?

DR. SCOTT: I'd rather the answer to my questions.

DR. HICKOK: Let's defer to Dr. Scott, then -- you're putting me on the spot here -- and have Dr. Singh give us a very brief rundown of some of the proposed mechanisms of action.

DR. SINGH: Actually, Dr. Hickok, since I'm going to be answering both of those questions, it doesn't really matter which order I take them in. Okay, I'll start with mechanisms of action. Thank you.

Several today have already discussed the proposed mechanisms of action of progesterone, and so forgive me for being repetitive here, but the mechanism of action of 17HPC is unknown. Multiple pathways are possible, if not likely.

The pharmacological activity of 17HPC is similar to that of progesterone; however, their mechanisms of action may be distinct. There are proposed mechanisms of action of progesterone and I'll summarize them briefly on the next slide. They've been generally categorized into non-genomic and genomic mechanisms.

So on this next slide, which briefly summarizes these proposed mechanisms that are out in the open literature, it's been shown that progesterone modulates progesterone receptor activity. It also reduces estrogen receptor activity by either direct interaction with the estrogen receptor or potentially proposed genomic type mechanism.

Also, it's been shown to inhibit oxytocin-induced uterine contractility, most likely through inhibition of prostaglandin synthesis. It's been shown to enhance tocolytic responses associated with adrenergic receptor responses, and specifically, the beta adrenergic preceptor.

Also, it's been shown to have local anti-inflammatory effects that touch on some of the mechanisms that were mentioned earlier today, such as the -- perhaps the interference with NF kappa beta, transcription of various genes that lead to pro-inflammatory effects. Also, it's been shown to inhibit myometrial gap junctions, and again, leading to uterine quiescence.

So these, again, are the proposed mechanisms, a summary of them that are out and available open literature for progesterone. However, as I mentioned in the beginning, 17HPC, there's very little known on that. Recently, at the SGI conference back in March of this year, it was shown on two different abstracts a couple of in vitro binding assays with 17HPC that kind of bring to light a little bit of the mechanistic activity of this compound in particular, and how it may be different from progesterone itself.

First, Zaleznic (phonetic) and colleagues presented that actually 17HPC is better at inducing progesterone-responsive genes than progesterone itself or 17 alpha-hydroxyprogesterone. Secondly, Atardi (phonetic) and colleagues showed, in the same conference, that the 17HPC actually exhibits selectivity for the beta isoform of the progesterone receptor, which is associated with transcriptional activity, as opposed to the alpha isoform, which is associated with repressor effects.

So that sort of brings to light some selectivity and differences with respect to 17HPC and how the activity might be different from progesterone, even though they may be very similar, in general.

DR. SCOTT: Are those in vivo studies or in vitro studies?

DR. SINGH: No, those two that were presented, these abstracts are in vitro receptor binding studies.

DR. SCOTT: Do you have any hard data in the actual patients? Any differences in anything; serum levels or --

DR. SINGH: Dr. Meis will respond.

DR. Yes, Dr. Meis will address that, if we can, Dr. Scott.

DR. MEIS: Dr. Scott, one of this is very recent information which we intend to present at the SMFM next year. We collected salivary samples weekly on these women throughout their gestation, and the early results from a serial sampling of a group of women, both in the 17P and the placebo group who delivered at term and who delivered preterm, basically showed that the treatment did not alter salivary levels of progesterone.

However, it did alter salivary levels of estriol. It lowered salivary levels of estriol and in fact, shifted the estrogen -- the progesterone ratio. Now, we don't know what the mechanism of that is, but it clearly had some effect.

DR. DAVIDSON: Satisfied, Dr. Scott?

DR. SCOTT: Yes.

DR. DAVIDSON: Dr. Carson?

DR. CARSON: Did any of your side effects -- I'm glad that it had such low side effects --

DR. DAVIDSON: Just one he had two questions to answer.

DR. HICKOK: Oh, Dr. Scott asked about -- I'm sorry -- about sexual functions later on in life. Now --

DR. HENDERSON: I asked -- we started when Dr. Steers asked about sexual function, and as adolescents, would you expect or have we noticed that there was any change in puberty. Did fetuses who were exposed to this, when they got to be in puberty age, were they different? And we don't have the answers to that.

So I was asking about the -- and you then suggested looking at the animal studies. The animals -- as the animals went into puberty, or adolescence, what ever the phase would be comparable -- were there -- one, was it any different, and then two, their length of life, did -- throughout life, were the animals any different after having been exposed to the progesterone in utero?

DR. HICKOK: Yes. I'm sorry we got interspersed questions, and Dr. Singh was ready to address that question.

DR. SINGH: Yes. Unfortunately, I don't have a study to cite for you because that was not actually looked at in the broad range of animal data that is out there and published on 17HPC. The studies that were done only looked at the fetuses upon caesarean section, upon removal from the mother. So they did not look at -- apart from that one study that I mentioned earlier in rats where an F-1 generation was looked at, and the males actually exhibited a suppression in spermatogenesis.

A follow-up study was done by the same team, and it was felt that this might be due to inhibition of testosterone production in those males. And I can tell you that on that subject, though, as far as -- there have been sort of sex-specific differences to your question, as far as what's been seen in the animal data.

There is no evidence whatsoever of verilization due to the exposures to 17HPC. So in terms of androgenic effects in females, there's nothing, there's no activity there. However, the only signal that there has been in all of the animal data that I have seen is this one study. It was the follow-up study in rats that showed an effect on spermatogenesis.

DR. HICKOK: If I can perhaps turn this a little bit to the molecular level to try to answer your question, it may be helpful. I'd like to remind everybody that the length of exposure to 17P is fairly limited during the pregnancy time. But we have Dr. Frank Stanczyk here, who is a progesterone chemist, who I think could give us some very interesting and worthwhile information on 17HPC as a chemical entity and what its steroid hormone effects are and what we might anticipate in that.

DR. STANCZYK: Frank Stanczyk, University of Southern California in Los Angeles.

DR.HICKOK: Bare with us here as we get a slide ready. We're pretty close

DR. STANCZYK: I'd like to point out that the 17HPC molecule is very different from the progesterone molecule, and it's the caproic acid side chain that makes it very different.

There is no evidence at all that 17HPC is converted to 17-hydroxyprogesterone. That's what would happen if you had hydrolysis of the caproic acid group. Nor is there any evidence that it's converted to progesterone. Both the 17-hydroxyprogesterone and progesterone assays are readily available. They've been around for many years now, and there is not one study that has shown the conversion of 17HPC to either of these molecules, and this is using both radio-amino assay methodology and mass spectrometry methodology.

Since 17-hydroxyprogesterone, and progesterone, of course, are important precursors for the formation of androgens, estrogens, and corticosteroids, you don't have any conversion of 17HPC to these compounds.

DR. DAVIDSON: Thank you. Dr. Carson?

DR. CARSON: But does 17HPC displace those from albumin or SHBG, to then make them more biologically available?

DR. STANCZYK: 17HPC does not bind to SHBG, but it would bind weakly to albumin. So it would be just like all steroids. It would bind very loosely and would be available to target cells and for metabolism.

DR. CARSON: So it would make those -- the endogenous steroids available then? You would have -- it could --

DR. STANCZYK: The endogenous? Yes.

DR. CARSON: You could, in effect, increase your endogenous bioavailable androgens, estrogens, and progestins.

DR. STANCZYK: You mean by displacing --

DR. CARSON: By --

DR. STANCZYK: From albumin? Well, albumin is a -- like a sponge. It carries all steroids. So it's possible that you would because you get that differentiation between, for example, the sulfates and the glucaronites (phonetic), where the albumin likes the sulfates a little better than the glucaronites. So this is why you see mostly glucaronites in urine, in addition to the faster glomerular filtration rate. But albumin prefers the sulfates, so -- a little bit, so --

DR. BUSTILLO: But that would also explain the elevated salivary estrogen.

DR. STANCZYK: Yes, that, I don't know how to explain. Of course, it wouldn't be by conversion to estrogens, but it could be that some enzyme is induced somehow, and I think that would be interesting to find out how this occurs.

DR. DAVIDSON: Okay. Dr. Wenstrom?

DR. WENSTROM: I had a comment about an earlier issue and that's the high rate of preterm delivery in the placebo group, which still seems to still be a concern for people around the table. I would think it would be possible to figure out exactly what that preterm delivery rate should have been based on the women's previous preterm delivery, using the data from Brian Mercer that I believe that Dr. Romero presented earlier.

So, for example, a previous delivery between 24 and 28 weeks has, I think, a 50% recurrence risk. If half the patients in this study had a preterm delivery in that range, that would indicate a higher risk of recurrence.

And so couldn't we go back and look at the previous -- what proportion of women were in each of those categories of gestational age at preterm birth, and sort of use that to predict what the preterm birth rate should have been in the placebo group? Because I'm guessing if we did that, we'd find out that it is pretty close to what we'd expect, based on the fact that they were very early -- many of the women had very early preterm births in their previous pregnancies.

DR. HICKOK: Dr. Savitz, can you -- I believe Dr. Wenstrom may be referring to maybe direct standardization technique or something like that. Would you comment to that, Dr. Savitz?

DR. SAVITZ: The sort of -- the general comment is that when we took a look at that, the question was whether -- and specifically comparing the rate in the placebos in the 17P trial with some of the previous maternal and fetal medicine network trials. In other words, that's the comparison to make. And we're not talking about -- we're not worried at this point about the placebo arm versus the treatment arm; we're worried about why is that baseline rate so high?

That fact alone accounts for a fraction -- I don't remember the exact figure, but it's not by any means the complete explanation. It doesn't go from 37 to 51% when you make that adjustment. It goes up some in that direction.

I think -- I'm afraid that when you look at the results across the centers and so on, I think what we are probably getting is an accurate reflection of the population served in the network centers. In other words, this is the baseline risk in the calendar years of the study, and again, one of the reasons in this case was their recruitment that seemed to more effectively or preferentially recruit those with a more severe history of adverse outcome.

But I really think it's this combination of medically indicated preterm deliveries, of course, are going up fairly rapidly. If the demographic constitution of the MFM centers changes over time -- and I know I've done work at North Carolina over 10 years. With nothing else changing, we would watch the preterm rates go up. Nothing else changed, the same institution and just over calendar time, not accounted for by demographics.

So this combination of who you're recruiting, clinician inclination, in terms of medically indicated preterm delivery, and I think also just the recruitment into the trial, all of those are part of it. It is also part of it, the most severe adverse outcome history, but not all of it.

DR. DAVIDSON: Dr. Bustillo?

DR. BUSTILLO: I had a question about this last slide that was just handed again, which I think is sort of an amplification of a previous slide that was shown by Dr. Wesley, which was Slide 9, about the graphs of the patients that were still pregnant at certain gestational ages.

MS. WATKINS: For clarification, was that an open public hearing statement submission?

DR. BUSTILLO: I'm sorry?

MS. WATKINS: For clarification purposes, the slide you are referring to, is it an open public hearing statement submission?

DR. BUSTILLO: No, I'm talking about Dr. Wesley's presentation this morning with the two live table analyses --

MS. WATKINS: Okay. Thank you.

DR. BUSTILLO: -- of the patients that are still pregnant between 20 weeks and 24 weeks being much lower in the treatment group versus the placebo group. So I don't understand that, but my question relevant to that actually is, how was it decided to give drug prior to 20 weeks? Was there any data on -- for the initial trial? Was there a reason that we thought might be more efficacious starting it earlier than 20 weeks, as opposed to 20 weeks? Because the --

DR. HICKOK: Dr. Meis? I'm sorry. Dr. Meis, would you comment on the rationale, as the principal investigator?

DR. MEIS: It seemed that some of the trials of progesterone which had not shown efficacious started the drug rather late in gestation, and we felt that the efficacy would -- may be enhanced by starting it at an earlier time.

We wanted to wait until after 16 weeks to reduce any possible teratogenic effects. We felt that we might prejudice the outcome if we waited until after 21 weeks, that it may not be as effective after that time. The slide presented here shows that the -- I'm sorry, this doesn't really help. That's -- the study in Finland that studied women with the twin gestation started their drug at 28 weeks, and it was totally ineffective, and we thought that might be part of it.

DR. KAMMERMAN: Oh, excuse me. I just had a comment on that. I actually did that analysis for this dataset, and I stratified -- I looked at women who started studies beyond 20 weeks, and the two curves pretty much are identical and they overlap.

It would appear that most of the effect is coming from women who are started on study drug prior to 20 weeks gestational age, so that would be pretty much consistent with what you were saying.

DR. DAVIDSON: Okay. Dr. Johnson?

DR. JOHNSON: Actually, don't sit down, Dr. Meis. I was going to ask you another question. Addressing back to my original question this morning, when you looked at the Delalutin data, did you find anything in regards to examining children for genital abnormalities? Now, you talked about the effect on their cognitive and behavioral changes, but did you look at any effect on their reproductive tracts?

DR. MEIS: There were no effects found on their reproductive tracts. I didn't go into that, but there was nothing there compared with controls.

DR. JOHNSON: So they did do exams and compare controls to the children that got the 17-hydroxyprogesterone?

DR. HICKOK: Yes.

DR. JOHNSON: Thanks.

DR. HICKOK: And again, that was reinforced by the three large trials that I showed you this morning that looked specifically at 17HPC, exposed infants with controls for the most part, and then FDA's -- also the FDA assessment in 1999 on the progestin class here that I showed you also.

Again, the FDA has done this periodically over time in assessing risks of progestins being -- and estrogens being given during pregnancy.

DR. DAVIDSON: Dr. Nelson, did you have a question?

DR. NELSON: I was -- had been going to comment on the issue that has been raised repeatedly about the high rate of preterm birth in the control arm, and the answer that was given was why there was a high rate of preterm birth in all the entrants to the study. I think the answer to why that's different in the placebo and the active drug recipients had to be -- just has to be the randomization failed, and given -- and that certainly can happen.

I think if we're going to do this study again, one would lock randomize it at admission for number of preterm births.

While I have the microphone, may I make one other comment? That is that the justification for studying an agent to prevent preterm birth has been significantly for the prevention of long-term disabilities, and we have been shown no evidence whatever that that was achieved here. The one week of benefit in gestational age was not in the data we've seen on follow-up associated with any benefit in any of the categories examined.

In fact, it doesn't rule out that there could've been a sharp increase in cerebral palsy, for example, in the children who received active drug, because so few children were examined.

DR. DAVIDSON: Just to comment. Dr. Carson?

DR. CARSON: It's reassuring to see there weren't very many side effects to the drug, and I'm glad about that. But I wonder if you looked at any of the side effects that did occur and see if they were a predictor of preterm labor, particularly like the local site reaction and the GI side effects.

DR. HICKOK: We looked at the timing of the injection site reactions and found interestingly that they were fairly unpredictable. They would happen in some cases early on and in some cases later on. But it wasn't really an indication that it was a true allergic reaction, with somebody receiving an injection and then later -- or subsequently, getting a more severe reaction.

We don't -- I -- we looked at the relationship between -- I believe we looked at the relationship between onset of premature labor and did not find a result, but I don't have those data to give to you.

DR. CARSON: So you're saying that if they had a reaction, they were not more likely to have preterm labor? Or do you --

DR. HICKOK: I don't believe our -- we had such a low rate of adverse reactions also --

DR. CARSON: I realize --

DR. HICKOK: -- that those -- now, those -- the women -- and I don't have it to show you, but the women that had injection site reactions, no, were not more likely to have preterm delivery.

DR. CARSON: How about GI side effects?

DR. HICKOK: Gastrointestinal side effects?

DR. CARSON: Yes.

DR. HICKOK: We had very low rates of those also, and that's generally confounded by the pregnancy condition itself and when the -- and a lot of gastrointestinal complications also.

Dr. Davison, could I address -- there's one question of Dr. Nelson's -- she had a two-part question -- that I did not get a chance to answer, which was regarding pre-eclampsia, and then I think she just raised another issue about the value of prolonging pregnancy one week and what might that result.

Because again, the follow-up study was designed as a safety study. It wasn't designed as an efficacy study to say that 17P babies did better than placebo babies. It was really just looking for safety signals up until five years of age. So I wanted to make that point clear. But we do have other data about the value of prolonging pregnancy. And if I can, we have a neonatologist with us, Dr. Michael O'Shea, that can speak to that issue, and he's trained in public health and epidemiology also, in addition to being a professor and a person who cares for sick neonates.

DR. O'SHEA: I'm going to pull up a slide to try to tie together a number of concepts that several people have spoken about, and it relates to the issue of the surrogate outcome measure. As Dr. Nelson mentioned, there seemed to have been an average prolongation of gestation. Excuse me just a minute. Well, to give you some framework of --

DR. DAVIDSON: How long do you think this is going to take?

DR. O'SHEA: One minute.

DR. DAVIDSON: Okay.

DR. O'SHEA: We can think in terms of the sequela of prematurity as being very prevalent short-terms effects, such as an admission to the neonatal intensive care unit. We can think in terms of somewhat less prevalent, but more severe problems as one of the -- several of the speakers have spoken about; necrotizing enterocolitis, for example.

Even less prevalent, but more important, would be long-term effects like cerebral palsy. And most important, but least prevalent, would be mortality.

I think the data that were provided to you from the study show an effect on necrotizing enterocolitis and NICU admission. In terms of the latter two events, which are much less prevalent, cerebral palsy and mortality, we would have to use external data which indicate that there is a gradient of risk that extends all the way from 23 to 37 weeks.

DR. DAVIDSON: Okay. Dr. Simhan, you have the last shot at this.

DR. Simhan: Thanks. That's a big responsibility. I have a caution regarding the value of prolonging pregnancy in this setting of what might be a pathological process. If infection is, in fact, the etiology of preterm labor, preterm PROM, that having the fetus remain in utero may, in fact, have undesired long-term consequences, whether those are neuron-inflammatory or otherwise.

However, with respect to these data, I was -- am I correct in being reassured that the chorioamnionitis frequency in the 17P treated population and the placebo treated population was in fact similar?

DR. HICKOK: That's correct. We were -- it was -- the rate of confirmed clinical chorioamnionitis was very similar between the two groups, and again, that also reassured us, because as you know, you certainly don't want to prolong a gestation where there's an active infection going. But again, this rate was 3.3% in the 17P group, 2.4% in the placebo group, and investigators didn't know which group women were in, so there shouldn't be any biases introduced by that.

DR. DAVIDSON: Let's take -- I know it's impossible, but let's do it. Let's take a 10-minute break, and when we return, we will go over the list of questions from the standpoint of making sure that the committee has clarity about each one of these questions before we go to the voting at the end of the day, so that if we need to find out additional information from the agency or et cetera so that we're all on the same page when we get ready to vote. Let's take a short break.

(Off the record at 3:05 p.m.)

(On the record at 3:15 p.m.)

DR. DAVIDSON: Okay. Let's reassemble, please. Let's turn our attention to the page -- do you have a -- in your folder a sheet of questions for the Advisory Committee for Reproductive Health Drugs that are numbered? Everyone has this sheet? Is there anyone without a sheet? Okay.

This is not for voting; this is for clarity and making sure we understand the questions. So why don't we just go through these in order and see whether or not any clarification is requested by anyone? I have been advised that maybe I should read the introductory paragraph that's at the top of this page.

In general, the FDA requires an applicant for a new drug product to submit two adequate and well-controlled clinical trials as substantial evidence of effectiveness. One of the circumstances in which a single clinical trial may be used as substantial evidence of effectiveness is a trial that has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome, and confirmation of the result in a second trial would be logistically impossible or ethically unacceptable.

The applicant is seeking marketing approval for 17HP based primarily on: (1) the findings from a single clinical trial and (2) a surrogate endpoint for neonatal infant morbidity and mortality; i.e., reduction of the incidence of preterm birth at less than 37 weeks gestation. Any questions or comments about that?

Question 1-A. Is the primary endpoint for 17P CT002 prevention of preterm birth prior to 37 weeks gestation an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity? Understandable? Any questions about that?

DR. VISCARDI: Actually, I guess I have a comment. Again, as a neonatologist, I'm a little concerned about that being a surrogate for fetal and neonatal mortality and morbidity, because when you actually look at the mortality data and the morbidity data, both -- at least the short-term NICU morbidity, there really were not any important differences, yet there was a reduction in the incidence of preterm birth less than 37 weeks.

But the more important outcome is how do those pregnancies do, and I think that I'm not entirely convinced that that is an appropriate surrogate.

DR. DAVIDSON: Let me get this. You understand the question, but you are questioning its appropriateness?

DR. VISCARDI: Well, the question is, is it an adequate surrogate? And I would state that it is not an adequate surrogate.

DR. DAVIDSON: Yes, we are now just clarifying the question. All of those other things may go into how you answer it --

DR. VISCARDI: Okay.

DR. DAVIDSON: -- but you do understand the question?

DR. VISCARDI: I do understand the question. I was --

DR. DAVIDSON: Okay.

PARTICIPANT: She was answering it for us.

DR. DAVIDSON: Yes.

PARTICIPANT: As a neonatologist, she answered the question.

DR. VISCARDI: Jumped ahead there.

DR. DAVIDSON: Dr. Hankins?

DR. HANKINS: Is it and, or is it or? Fetal and neonatal, or fetal or neonatal? I hate to be picky, but which is it? The same thing is going to come up in (inaudible).

DR. DAVIDSON: Okay. An adequate surrogate for a reduction in fetal and neonatal mortality. I'll ask the FDA. They put the and here. I can't hear you.

DR. MONROE: Can you hear me?

DR. DAVIDSON: Yes.

DR. MONROE: Yes, we would prefer that to be an and, because we're looking at the whole pregnancy as a continuum. So if, for instance, you had a negative impact on fetal outcomes, but you had a gain on neonatal, and the outcome was zero, we wouldn't consider that a benefit. So I think we would like it to be fetal and neonatal as a continuum. Is that hopefully clear?

DR. DAVIDSON: 1-B. If not, would prevention of preterm birth prior to 35 weeks or prior to 32 weeks gestation be an adequate surrogate? Any questions? Like -- yes?

DR. JOHNSON: Yes. When answering that, would it be -- if we need to answer that question, should we state 35 or 32? I presume we should let you know which of those two is acceptable.

DR. MONROE: Yes, we would like to know which of those two, or if both are acceptable.

DR. DAVIDSON: Now, I have a list -- the Chair would like a clarification. I have a list of yes, no, or abstain as an answer to all of these questions. You're telling me that there is another option here in 1-B, that if one votes one way or the other, they say both or 35 or 32 weeks?

DR. MONROE: I guess in retrospect, that should be a B and a C, perhaps. We would like the differentiation. That would helpful in our deliberations.

DR. DAVIDSON: Okay. Any questions about that? Question 2. Do the differences in the incidence of preterm birth in Study -- I'm just -- 002 prior to 37 weeks in the vehicle control group, 55% compared to those in the control arms of another maternal-fetal medicine unit network trial, approximately 37%, and (b) Study 1701, 36%, evaluating similar high-risk populations, indicate the need to replicate the Study 002 in a confirmatory trial? Any questions about that? Understandable and clear?

Question 3-A. Do the data reviewed by the committee provide substantial evidence that 17PC prevents preterm birth prior to 35 weeks or 32 weeks gestation age? Do you want a specific week after this question?

DR. MONROE: Yes. Once again, the differentiation between 35 and 32 is important.

DR. DAVIDSON: Okay. Any question about that? You answer with either both, or a differentiation between these weeks of gestation.

Question 3-B. No, no, we're not voting. No. I will ask you to vote, and your vote will be public and we are -- we're just going through to make sure when we do this when you're voting, that there is understanding of the questions. If you leave the starting blocks before the gun, it's a foul.

3-B. Do the data reviewed by the committee provide substantial evidence that 17HPC reduces fetal and neonatal mortality or morbidity? Any question about that? Potential safety concerns and adequacy of safety data, there was a numeric increase in the percentage of second trimester miscarriages, pregnancy loss prior to week 20 of gestation, and stillbirths in the 17HPC group.

Overall, 11 of 306 subjects, 3.6% 17HPC group, and two of 153 subjects, 1.3 in the vehicle or control group, had a second trimester miscarriage or stillbirth.

Question 4-A. Is further study needed to evaluate the potential association of 17HPC with increased risk of second trimester miscarriage and stillbirth?

DR. WESTNEY: Sorry, I just had a question, and I hate to subdivide things unnecessarily, but the question is, when you're speaking about morbidity or mortality, it's conceivable that you might say there's a different threshold, depending on whether you're talking about morbidity versus mortality.

DR. DAVIDSON: Would you say that over again?

DR. WESTNEY: I'm saying you may say, for instance, for morbidity, that would be sufficient 35 weeks -- less than 35 weeks, and in mortality, you may say that it's 32 weeks.

DR. DAVIDSON: Dr. Monroe, did you understand that?

DR. WESTNEY: Or just group them together, but I just want a clarification.

DR. MONROE: I understand the concept. Are you referring to a specific question, and which subpart?

DR. WESTNEY: I'm sorry?

DR. MONROE: I understand the concept of your question --

DR. WESTNEY: Right.

DR. MONROE: -- but are you referring to a specific question, and --

DR. WESTNEY: Yes, either 1B or 3B. Where you were asking for either 32 or 35 weeks, is it just both together, morbidity and mortality, or one or the other, or is there a specific week that you should look at for mortality versus morbidity, if that's different to you? And that maybe something that's more critical to the people who are actually MFM. I mean, we're all --

DR. MONROE: We were not really differentiating between that. If you wish to comment, that would be up to you. I guess you could discuss that during your discussion about it.

DR. WESTNEY: Okay.

DR. DAVIDSON: Are you clear? Any other questions? Speak now, or -- I'll read Question B, anyway, although it's been discussed. If so, should this information be obtained prior to approval for marketing or post-approval? So that's kind of two parts to that question. I guess you want specific help in that regard?

DR. Simhan: So again, just to clarify, that's -- if the three options are yes, no, or abstain, there's actually two options there that -- so prior to approval for marketing would be one option, and then post-approval would be option two?

DR. DAVIDSON: Right, right. Any further questions? I know some of you thought this was unnecessary. Question 5. Are the overall safety data obtained in studies 17PCT02 and 01 and studies 17PFU long-term follow-up adequate and sufficiently reassuring to support marketing approval of 17HPC without the need for additional pre-approval safety data? Any question about that? No?

Post-approval clinical studies. Question 6-A. If 17HPC were to be approved for marketing without additional pre-approval clinical studies, would you recommend that the applicant conduct a post- approval clinical trials to investigate further safety or effectiveness? Any question about that and its options? Yes?

DR. TULMAN: There might be an overlap of potential conflicting results that can lead to some ambiguity here. For example, if we were to say that we think we need some more -- if we were to say that we don't believe that we need more second trimester miscarriage and stillbirth info post-approval, but we still might want post-approval studies for long-term effects after the child is born alive.

So I think we could get into a situation of having an -- of not being able to vote on what we wanted to vote on because of the way it's phrased. I'm not sure how to fix it, so --

DR. DAVIDSON: I -- okay, let me read 6-B and see if that helps. If so, what would be the primary objective of the trials? What unanswered questions would this study investigate?

DR. TULMAN: Okay. So then you could -- okay.

DR. DAVIDSON: Does that help?

DR. TULMAN: Probably.

DR. DAVIDSON: I've been assured these questions have been gone over carefully in the Agency, and if there are internal issues to resolve, they will have to resolve them. Yes, sir?

DR. MONROE: To perhaps reduce some of the ambiguity and make voting easier, where you correctly identified that we didn't fully differentiate between weeks 35 and 32, would it be helpful if, for Question 1-B, we make it a B, as far as 35 weeks, and then call that C for 32, just to keep track of bookkeeping.

So it would be -- for instance, 1-B would read, "If not, would prevention of preterm birth prior to (B) 35 weeks or prior to (C) 32 weeks," just for the purposes of answering and keeping track of this score?

DR. DAVIDSON: Wait a minute.

DR. MONROE: I'm going back to 1-B, where you had identified --

DR. DAVIDSON: You're going back to 1-B?

DR. MONROE: Yes. I thought you had finished everything, and I just wanted to clarify before you go on to voting, to make that perhaps --

DR. DAVIDSON: Well, okay. Well, then go over that again?

DR. MONROE: Yes. For Question 1-B, says, would prevention of preterm birth prior to 35 weeks or prior to 32 weeks gestation be an adequate surrogate? Perhaps it would just be easier to call that a B and a C, or I don't know how you will keep track of the vote. I just --

DR. DAVIDSON: You want to make a C and put 35 weeks, B; 32 weeks, C?

DR. MONROE: yes. I think it would just allow people to answer yes or no very simply. If you feel that will further confound everybody, I'll defer to your judgment. And then the same would apply to Question 3, Dr. Davidson. A would have to be -- A would apply up through 35 weeks, then B could apply through 32 weeks, and then what is now B would become a C. If that hasn't confused everybody, I'll --

DR. DAVIDSON: So you want to make B, C?

DR. MONROE: Yes. And I think then it'll be very easy to keep track of the votes.

DR. DAVIDSON: Okay.

DR. MONROE: All right.

DR. DAVIDSON: You're challenging our bookkeeper here. A would be 35 weeks, Question 3-B would be 32 weeks, and C stands as it is, and --

DR. NELSON: To help us in answering that first question, we all know that the risk per baby is much greater in under 32-weekers. On the other hand, there are a lot more babies in the less severely preterm children. Is any information available about attributable risks in those groups that would help us answer that question; that is, how much of the morbidity and mortality come from these different niches, or is such data available?

DR. DAVIDSON: Well, I think, unless someone wants to answer that, you'll have to go from whatever available information that's been provided.

DR. HANKINS: Well, Karin asks a very interesting question, and the NIH convened a task force on the late preterm infant, and that data is generally available --

DR. DAVIDSON: Would you speak a little closer into the microphone?

DR. HANKINS: The question that Karin asked is very, very important, and the NIH, within the last few months, convened a task force on the late preterm delivery. And it was alluded to earlier, ACOG has a practice bulletin that's coming out. One of the astounding things that would probably surprise very people is there are more ventilator days in America between 34 and 37 weeks than in all the rest of the babies going into units.

Now, I'm in a tertiary care center and I'm biased. I would've never believed that if I hadn't seen the data that came from the pediatrics group, etc. So the data is available, the task force met, and I think that is important information, perhaps, that people that are just giving input might need to look at to give the best-informed input.

DR. HENDERSON: It's also available on the March of Dimes web site. They do a very nice graph for each gestational age and what the contribution is to the preterm delivery population.

DR. DAVIDSON: Dr. Steers?

DR. STEERS: Yes, clarification for Question 6. If you don't believe that the mechanism for any concerned safety is a clinical trial, but let's say a registry, are we allowed to kind of have that trial registry, or is it strictly within the confines that the FDA wants us to specify a clinical trial, which may not actually answer or be impractical?

DR. MONROE: We would like it answered in the broader context, where -- a trial we would lump under the general request to you, yes. I mean, a registry could be considered a trial in the context of the question.

DR. DAVIDSON: Dr. Monroe, did you have any answer for Dr. Hankins and Dr. Nelson?

DR. MONROE: No, I don't have a specific answer. I think if I understood their comments is that there is new information that would be nice if everybody, I guess, on the panel had access to, to help them in their answering our questions, but I think the reality of the moment is that everyone will have to go with whatever information they have, and I guess those individuals that have access to that data, in terms of their response to the questions, it's up to your prerogative, Dr. Davidson, but frequently, an individual has the opportunity to explain their vote, and perhaps in that context, they might explain something that which to some people, may not appear to be -- the logical answer be based on some new information that have privy to. Does that perhaps help?

DR. DAVIDSON: I am -- I have been advised -- I don't know if this answers it -- that if you wanted to make a comment or a statement at the time of your vote, I guess that also will be registered on the -- so that may help.

I think I see a collective nod from the Agency. So that -- if that provides any comfort to yes or no and then making a statement about it, it will be a part of the record that they will have for review. Is that acceptable? Any other questions? Are there any other questions? Oh, you do? Okay.

Well, let's see if we can go through this and keep all of the new Bs and Cs separated, so let's be careful about that. So let's begin at Question 1. I will not start with the same person on each question, so that there will be no bias here, at least as much as possible.

I think Dr. Hankins is the first voting member on this side. Is that correct? We'll start with you, Gary, with the first question.

DR. WATKINS: Just -- I'm sorry, just a reminder to the committee members. Please identify yourself prior to casting your vote so that the transcriber is able to easily identify you.

DR. DAVIDSON: Is the -- I won't read this question each time for each person, so we're going on Question 1-A. Is the primary input for Study 02, prevention of preterm birth prior to 37 weeks gestation, an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity?

DR. HANKINS: Gary Hankins. No.

DR. DAVIDSON: Next?

DR. NELSON: Karin Nelson. No.

DR. DAVIDSON: Speak -- was that --

DR. NELSON: No.

DR. BURNETT: Arthur Burnett. No.

DR. BUSTILLO: Maria Bustillo. No.

DR. MERRITT: Diane Merritt. No.

DR. JOHNSON: Julia Johnson. Yes.

DR. DAVIDSON: Yes?

DR. JOHNSON: Yes.

DR. STEERS: William Steers. No.

DR. LIU: James Liu. No.

DR. Simhan: Hy Simhan. Yes.

DR. DAVIDSON: Yes?

DR. LEWIS: Vivian Lewis. No.

DR. DAVIDSON: I've been advised not to vote until the end.

DR. WENSTROM: Katharine Wenstrom. Yes.

DR. HARRIS: Joseph Harris. No.

DR. GILLEN: Daniel Gillen. No.

DR. VISCARDI: Rose Viscardi. No.

DR. SCOTT: Jim Scott. Yes.

DR. HENDERSON: Cassandra Henderson. Yes.

DR. CARSON: Sandra Carson. No.

DR. WESTNEY: Lenaine Westney. No.

DR. SHANKLIN-SELBY: Elizabeth Shanklin-Selby. No.

DR. DAVIDSON: No?

DR. SHANKLIN-SELBY: No.

DR. TULMAN: Lorraine Tulman. No.

DR. DAVIDSON: Ezra Davidson. No.

MS. WATKINS: If the committee members will kindly turn their mikes off after voting. Thank you.

DR. DAVIDSON: Thank you. The next question has a B and a C, B being 35 weeks and C being 32 weeks. Let's start with Dr. Tulman on B. If not, would prevention of preterm birth prior to 35 weeks gestation be an adequate surrogate?

DR. TULMAN: Yes.

DR. SELBY: No.

DR. DAVIDSON: No?

DR. SELBY: No.

DR. WESTNEY: Lenaine Westney. No.

DR. CARSON: Sandra Carson. Yes.

DR. HENDERSON: Cassandra Henderson. I said yes for 37, so --

DR. DAVIDSON: Hold just a second. That's not an option. This is yes. Selby is no. And Westney is no? Is that right? Two yes. That's -- Tulman is no.

MS. WATKINS: Dr. Tulman?

DR. DAVIDSON: Tulman is yes.

MS. WATKINS: Dr. Tulman, please restate your vote.

DR. TULMAN: Yes.

MS. WATKINS: Yes.

DR. DAVIDSON: Okay. And Shanklin-Selby is no, and Westney is no, and Carson is yes. Okay.

DR. HENDERSON: I voted yes for 37 weeks, and I think either -- I think 37, 35, 32 --

DR. DAVIDSON: You can't change the question now.

DR. HENDERSON: Well, but I'm -- yes, but -- okay. Yes for both.

DR. SCOTT: What do we do if we voted yes the first time?

DR. HENDERSON: Then say yes the second time too.

DR. DAVIDSON: You can say yes both times.

DR. SCOTT: 35 weeks better, yes.

DR. DAVIDSON: Dr. Henderson, would you restate your vote?

DR. HENDERSON: Yes.

DR. VISCARDI: No.

DR. GILLEN: Daniel Gillen. No.

DR. HARRIS: Joseph Harris. No.

DR. WENSTROM: Kathy Wenstrom. Yes.

DR. LEWIS: Vivian Lewis. Yes.

DR. SIMHAN: Hy Simhan. Yes.

DR. LIU: James Liu. Yes.

DR. STEERS: William Steers. No.

DR. JOHNSON: Julia Johnson. Yes.

DR. MERRITT: Diane Merritt. No.

DR. BUSTILLO: Maria Bustillo. Yes.

DR. BURNETT: Arthur Burnett. No.

DR. NELSON: Karin Nelson. Yes.

DR. HANKINS: Gary Hankins. Yes.

DR. DAVIDSON: What are the totals? Oh, 21? Well, we didn't -- maybe we should read the totals for the first one. For the record, we are reading the totals -- I'm going -- you've already done this. This is 1-A. The yes votes are -- I'm doing the first one now. The yes voted are five and the no votes -- it couldn't be. Have to be 16. The no votes are 16.

DR. DAVIDSON: On Question 1-B, Ezra Davidson votes yes. So 1-B, the yes votes are 13, the no votes, eight. Question 1-C, if not, would prevention of preterm births prior to 32 weeks gestation be an adequate surrogate? Let's start with Dr. Harris and go back around. Oh, I'm sorry. I intended to do the first one here, Dr. Wenstrom.

DR. WENSTROM: Kathy Wenstrom. Yes.

DR. LEWIS: Vivian Lewis. Yes.

DR. Simhan: Hy Simhan. Yes.

DR. LIU: Jim Liu. Yes.

DR. STEERS: William Steers --

DR. DAVIDSON: Wait, hold, hold -- hold just a minute. Hold just a minute. My multi-tasking here isn't -- what do you have for Harris? I mean, so far, all yeses. Okay. Dr. Liu? Yes?

DR. LIU: Yes.
DR. DAVIDSON: Okay.
DR. STEERS: William Steers. Yes.
DR. JOHNSON: Julia Johnson. Yes.
DR. MERRITT: Diane Merritt. Yes.
DR. BUSTILLO: Maria Bustillo. Yes.
DR. BURNETT: Arthur Burnett. No.
DR. DAVIDSON: No?
DR. BURNETT: No. No.
DR. DAVIDSON: Okay.
DR. NELSON: Karin Nelson. Yes.
DR. HANKINS: Gary Hankins. Yes.
DR. DAVIDSON: Tulman?
DR. TULMAN: Lorraine Tulman. Yes.
DR. SHANKLIN-SELBY: Elizabeth SHANKLIN-SELBY. Yes.
DR. WESTNEY: Lenaine Westney. Yes.
DR. CARSON: Sandra Carson. Yes.
DR. HENDERSON: Sandra Henderson. Yes.
DR. SCOTT: Jim Scott. Yes.
DR. VISCARDI: Rose Viscardi. Yes.
DR. GILLEN: Daniel Gillen. Yes.

DR. HARRIS: Joseph Harris. Yes.

DR. DAVIDSON: Ezra Davidson. Yes. So there is 20 yes and one no. Question 2. Do the differences in the incidence of preterm birth in Study 02 prior to 37 weeks in the vehicle control group, 55%, compared to those in the control arms of another maternal-fetal medicine unit network trial, approximately 37%, in Study 17IF01, 36%, evaluating similar high-risk populations, indicate the need to replicate the findings of Study 17B02 in a confirmatory trial? Dr. Lewis, why don't we start with you and go around the table?

DR. LEWIS: No. Vivian Lewis.

DR. Simhan: Dr. Davidson, can I append my vote with a little comment? Was I allowed to do that?

DR. DAVIDSON: Sure.

DR. Simhan: Okay. Hy Simhan, no. I'm reassured that the frequency of preterm birth in the control arm, in fact, represents an expected frequency of preterm birth in a population with a risk profile that was actually enrolled in the study.

DR. LIU: I also vote no. Jim Liu.

DR. STEERS: William Steers. No.

DR. JOHNSON: Julia Johnson. No.

DR. MERRITT: Diane Merritt. Yes.

DR. DAVIDSON: Yes?

DR. BUSTILLO: Maria Bustillo. Yes.

DR. BURNETT: Arthur Burnett. Yes.

DR. NELSON: Karin Nelson. No.

DR. HANKINS: Gary Hankins. No. And I would like to also note that if you drop down to the 35-week and lower categories, those huge changes disappear and look much more close to the other trial data that exists.

DR. DAVIDSON: Tulman?

DR. TULMAN: Lorraine Tulman. No.

DR. SHANKLIN-SELBY: Elizabeth SHANKLIN-SELBY. Yes.

DR. WESTNEY: Lenaine Westney. No.

DR. CARSON: Sandra Carson. Yes.

DR. HENDERSON: Cassandra Henderson. No.

DR. SCOTT: Jim Scott. No.

DR. VISCARDI: Rose Viscardi. Yes.

DR. GILLEN: Daniel Gillen. Yes.

DR. HARRIS: Joseph Harris. Yes.

DR. WENSTROM: Kathy Wenstrom. No.

DR. DAVIDSON: Ezra Davidson. Yes. I have nine yes and 12 no. Question 3-A. Now remember, again, we have a 3-B and C, so A and B are separated, A being 35 weeks and B being 32 weeks.

Okay. Why don't we start with you again, Dr. Hankins? And the question is, do the data reviewed by the committee provide substantial evidence that 17HPC prevents preterm birth prior to 35 weeks gestation age?

DR. HANKINS: Yes.

DR. DAVIDSON: Yes, this way.

DR. NELSON: Karin Nelson. Yes.

DR. BURNETT: Arthur Burnett. No.

DR. BUSTILLO: Maria Bustillo. Yes.

DR. MERRITT: Diane Merritt. No.

DR. DAVIDSON: No?

DR. JOHNSON: Julia Johnson. Yes.

DR. STEERS: William Steers. No.

DR. LIU: James Liu. Yes.

DR. Simhan: Hy Simhan. Yes.

DR. LEWIS: Vivian Lewis. Yes.

DR. WENSTROM: Kathy Wenstrom. Yes.

DR. HARRIS: Joseph Harris. No.

DR. GILLEN: Daniel Gillen. No.

DR. VISCARDI: Rose Viscardi. No.

DR. SCOTT: Jim Scott. Yes.

DR. HENDERSON: Cassandra Henderson. Yes.

DR. CARSON: Sandy Carson. No.

DR. WESTNEY: Lenaine Westney. No.

DR. SHANKLIN-SELBY: Elizabeth Shanklin-Selby. Yes.

DR. TULMAN: Lorraine Tulman. No.

DR. DAVIDSON: Ezra Davidson. Yes. And the tally: yes, 12; no, nine. Question 3-B. Do the data reviewed by the committee provide substantial evidence that 17HPC prevents preterm birth prior to 32 weeks gestation? Let's start with Dr. Tulman.

DR. TULMAN: No.

DR. SELBY: Yes.

DR. WESTNEY: Lenaine Westney. No.

DR. CARSON: Sandy Carson. No.

DR. HENDERSON: Cassandra Henderson. Yes.

DR. SCOTT: Jim Scott. Yes.

DR. VISCARDI: Rose Viscardi. No.

DR. GILLEN: Daniel Gillen. No.

DR. HARRIS: Joseph Harris. No.

DR. WENSTROM: Kathy Wenstrom. Yes.

DR. LEWIS: Vivian Lewis. No.

DR. Simhan: Hy Simhan. Yes.

DR. LIU: Yes.

DR. DAVIDSON: Wait a minute, I think I have -- let me just confirm. Okay.

DR. LIU: Jim Liu. Yes.

DR. STEERS: William Steers. No.

DR. JOHNSON: Julia Johnson. No.

DR. MERRITT: Diane Merritt. No.

DR. BUSTILLO: Maria Bustillo. No.

DR. BURNETT: Arthur Burnett. No.

DR. NELSON: Karin Nelson. No.

DR. HANKINS: Gary Hankins. Yes.

DR. DAVIDSON: That it? Ezra Davidson. No. Okay, what's your tally? Yes, six; 15 no. Question

-- which is now 3-C. Do the data reviewed by the committee provide substantial evidence that 17HPC reduces fetal and neonatal mortality or morbidity? Start with Dr. Wenstrom.

DR. WENSTROM: Kathy Wenstrom. Yes.

DR. DAVIDSON: And let's go around.

DR. HARRIS: Joseph Harris. No.

DR. GILLEN: Daniel Gillen. No.

DR. VISCARDI: Rose Viscardi. No.

DR. SCOTT: Jim Scott. No.

DR. HENDERSON: Cassandra Henderson. No.

DR. CARSON: Sandy Carson. No.

DR. WESTNEY: Lenaine Westney. Yes, but an addendum; only in relation to morbidity, not mortality.

DR. SHANKLIN-SELBY: Liz Selby. No.

DR. TULMAN: Lorraine Tulman. No.

DR. HANKINS: Gary Hankins. No. And I would again like to state that's why I asked for if it's either/or versus both, and it was clarified, so the answer is no.

DR. NELSON: Karin Nelson. No.

DR. DAVIDSON: That was no, Dr. Nelson?

DR. NELSON: Correct.

DR. BURNETT: Arthur Burnett. No.

DR. BUSTILLO: Maria Bustillo. No.

DR. MERRITT: Diane Merritt. No.

DR. JOHNSON: Julia Johnson. No.

DR. STEERS: William Steers. No.

DR. LIU: Jim Liu. No.

DR. Simhan: Hy Simhan. No.

DR. LEWIS: Vivian Lewis. No.

DR. DAVIDSON: Ezra Davidson. No. I have two yes, 19 no. Question 4. Well, let me read the preface. There was a numeric increase in the percentage of second trimester miscarriages, pregnancy loss prior to week 20 of gestation, and stillbirths in the 17HPC group. Overall, 11 of 306 subjects, 3.6 in 17HPC group, and two of 153 subjects, 1.3 in the vehicle group, had a second trimester miscarriage or stillbirth.

Question 4-A. Is further study needed to evaluate the potential association of 17HPC with increased risks of second trimester miscarriage and stillbirth? Dr. Lewis, why don't we start with you and go around?

DR. LEWIS: Vivian Lewis. Yes.

DR. Simhan: Hy Simhan. Yes.

DR. LIU: James Liu. Yes.

DR. STEERS: William Steers. Yes.

DR. JOHNSON: Julia Johnson. Yes.

DR. MERRITT: Diane Merritt. Yes.

DR. BUSTILLO: Maria Bustillo. Yes.

DR. BURNETT: Arthur Burnett. Yes.

DR. NELSON: Karin Nelson. Yes.

DR. HANKINS: Gary Hankins. Yes.

DR. TULMAN: Lorraine Tulman. Yes.

DR. SHANKLIN-SELBY: Liz Selby. Yes.

DR. WESTNEY: Lenaine Westney. Yes.

DR. CARSON: Sandy Carson. Yes.

DR. HENDERSON: Cassandra Henderson. Yes.

DR. SCOTT: Jim Scott. Yes.

DR. VISCARDI: Rose Viscardi. Yes.

DR. GILLEN: Daniel Gillen. Yes.

DR. HARRIS: Joseph Harris. Yes.

DR. WENSTROM: Kathy Wenstrom. Yes

DR. DAVIDSON: Ezra Davidson. Yes. Twenty-one yes, zero no. Question 4-B. If so, should this information be obtained prior to approval for marketing or post-approval? Dr. Tulman, let's start with you.

DR. TULMAN: Clarification, so the vote is either pre or post; is that the two choices?

DR. DAVIDSON: Your vote is to be pre or post.

DR. TULMAN: Okay. Pre.

DR. SHANKLIN-SELBY: Liz Selby. Pre.

DR. WESTNEY: Lenaine Westney. Post.

DR. CARSON: Sandy Carson. Post.

DR. HENDERSON: Cassandra Henderson. Post.

DR. SCOTT: Jim Scott. Post.

DR. VISCARDI: Rose Viscardi. Pre.

DR. GILLEN: Daniel Gillen. Post.

DR. HARRIS: Joseph Harris. Pre.

DR. WENSTROM: Kathy Wenstrom. Post.

DR. LEWIS: Vivian Lewis. Pre.

DR. Simhan: Hy Simhan. Post.

DR. LIU: Jim Liu. Post.

DR. STEERS: William Steers. Post.

DR. DAVIDSON: Post?
DR. STEERS: William is post.
DR. DAVIDSON: I'm sorry?
DR. STEERS: Post.
DR. DAVIDSON: Post? Okay.
DR. JOHNSON: Julia Johnson. Pre.
DR. MERRITT: Diane Merritt. Post-approval.
DR. BUSTILLO: Maria Bustillo. Pre.
DR. BURNETT: Arthur Burnett. Pre.
DR. NELSON: Karin Nelson. Post.
DR. HANKINS: Gary Hankins. Post.
DR. DAVIDSON: Ezra Davidson. Post. Eight yes -- I mean, eight pre-approval, 13 post-approval.
Question 5, yes or no. Are the overall safety data obtained in Study 1701, 02, and long-term follow-up adequate and sufficiently reassuring to support marketing approval of 17HPC without need for additional pre-approval safety data? Dr. Hankins, why don't we start with you?
DR. HANKINS: Yes. Gary Hankins. Yes.
DR. DAVIDSON: Let's go this way.
DR. NELSON: Karin Nelson. Yes.

DR. BURNETT: Arthur Burnett. No.

DR. BUSTILLO: Maria Bustillo. Yes.

DR. MERRITT: Diane Merritt. No.

DR. JOHNSON: Julia Johnson. No.

DR. STEERS: William Steers. Yes.

DR. LIU: Jim Liu. Yes.

DR. Simhan: Hy Simhan. Yes.

DR. LEWIS: Vivian Lewis. No.

DR. WENSTROM: Kathy Wenstrom. Yes.

DR. HARRIS: Joseph Harris. Yes.

DR. GILLEN: Daniel Gillen. No.

DR. VISCARDI: Rose Viscardi. No. And I would just comment that the follow-up study was inadequate because of the methods used to identify all children with disabilities.

DR. SCOTT: Jim Scott. Yes.

DR. HENDERSON: Cassandra Henderson. Yes.

DR. CARSON: Sandy Carson. Yes.

DR. WESTNEY: Lenaine Westney. Yes.

DR. SHANKLIN-SELBY: Liz Selby. No.

DR. TULMAN: Lorraine Tulman. No.

DR. DAVIDSON: Ezra Davidson. Yes. Thirteen yes, eight no. Post-approval clinical studies. Question 6-A. If 17HPC were to be approved for marketing without additional pre-approval clinical studies, would you recommend that the applicant conduct a post-approval clinical trial to investigate further safety or effectiveness? Dr. Lewis, why don't we start with you?

DR. LEWIS: Yes.

DR. Simhan: Hy Simhan. Yes.

DR. STEERS: William Steers. Yes.

DR. JOHNSON: Julia Johnson. Yes.

DR. MERRITT: Diane Merritt. Yes.

DR. BUSTILLO: Maria Bustillo. Yes.

DR. BURNETT: Arthur Burnett. Yes.

DR. NELSON: Karin Nelson. Yes.

DR. HANKINS: Gary Hankins. Yes.

DR. TULMAN: Lorraine Tulman. Yes.

DR. SHANKLIN-SELBY: Liz Selby. Yes.

DR. WESTNEY: Lenaine Westney. Yes.

DR. CARSON: Sandy Carson. Yes.

DR. HENDERSON: Cassandra Henderson. Yes.

DR. SCOTT: Jim Scott. Yes.

DR. VISCARDI: Rose Viscardi. Yes.

DR. GILLEN: Daniel Gillen. Yes.

DR. HARRIS: Joseph Harris. Yes.

DR. WENSTROM: Kathy Wenstrom. Yes

DR. DAVIDSON: Ezra Davidson. Yes. Twenty-one yes, zero -- oh, I'm sorry.

DR. LIU: Jim Liu. Yes.

DR. DAVIDSON: Oh. Twenty-one yes, zero no. Okay. I hear you have a chance at a narrative. Should we put a time limit on these? If so, what would be the primary objective of the trials? What unanswered questions would the study investigate? Since we started with you, Gary, let's end with you.

DR. HANKINS: Since I think every one of us voted that the issue of stillbirth and early loss needs to be looked at, I think that's certainly a part of the surveillance that we would hope, even post-marketing of the drug. That's one issue.

The second issue is I would like to see more long-term follow-up of the children in a more formalized testing fashion. I understand how this study was conducted, that was never the goal of it, etc., but post-marketing, I think there should be a leveled requirement to follow at least a cohort of these children in a prospective fashion for neural development.

DR. NELSON: Karin Nelson. Maternal gestational diabetes, fetal death, neonatal death, days in hospital, days on ventilator, abnormal neonatal neuron-imaging, I'd love to see a lengthy late testing, but I think the numbers -- unless you get really -- it just doesn't seem clearly realistic.

DR. BURNETT: This is going to sound a little bit like a broken record, but I echo their comments. I think we need long-term follow-up on the children, and I do think that there are some concerns raised in the mother with regard to gestational diabetes and some of the other co-morbidities, and I think follow-up on that side is required, as well.

DR. BUSTILLO: Being an endocrinologist, I'm very interested in pubertal development, so I certainly would like long-term studies looking at the children in terms of their genital development and their internal general structures, etc.

DR. MERRITT: Being a pediatric gynecologist, internal structures on children are very difficult to assess, short ultrasound. So I would vote for more immediate neonatal data that is already being -- started to be looked at, as well as maternal data, and post-marketing stillbirth and first trimester data, second trimester -- the post-marketing is second trimester pregnancy loss data, sorry.

DR. JOHNSON: Yes, Julia Johnson. I hear Dr. Nelson's argument about not following patients long-term, but I would like to see the effect on reproductive health, fertility, because of the issue about sperm production, on reproductive health for both men and women who were exposed to this in utero.

DR. STEERS: William Steers. Based on the spermatogenesis, or sperm count data, and the lack of long-term data, I'd like to recommend a more practical approach, and not necessarily a study, but a registry of all children exposed to this with fertility, rather than a strict study, per say, but at least they're registered and they can be tracked.

DR. LIU: I haven't expressed my views on this, but judging from the way that this compound is handled in the body, I think we should consider this a new type of progestogen as opposed to thinking that this is progesterone or 17-hydroxyprogesterone, because the caproate moiety is not broken down.

I am concerned that we may be dealing with a different steroidal exposure, even though it does bind to progesterone receptors, and I think a registry is the minimum I would recommend, if nothing else, as well as long-term pubertal development follow-up. Because I'm afraid that we may be forced to use this compound for preterm labor prevention, but yet, we don't know what the downstream side effects are.

DR. Simhan: I echo the support for surveillance for mid trimester loss, whether that be stillbirth or birth prior to 24 weeks. I think a practical methodology for surveying some of these other issues is a registry, so I echo support for that, as well.

DR. LEWIS: I concur with a registry. That's certainly a good idea. It's true that there are -- I think valid concerns have been raised about potential pubertal or reproductive effects downstream in both sexes. As well, of course, I'm concerned about the incidence of very early stillbirth and/or second trimester loss.

Some of these questions can be answered through a registry. Also, I would wonder whether there aren't data available by studying European populations which are easier to track the -- after all, this compound has been available for many, many years and in wide use, and perhaps a study, even a case control study, could be designed on populations who are already out there, rather than thinking that we have to wait another 20 years to get some of this information.

DR. WENSTROM: I would like to see all future losses evaluated by a fetal pathologist with a complete protocol. Several studies have shown that with a complete evaluation, you can determine the cause of a loss in over 90% of cases. And then, because this drug is already being used for all sorts of perceived or imagined risk factors, I think we should start looking at it in other kinds of high-risk women.

DR. HARRIS: Yes, I'd like to agree with the increased examination of second trimester miscarriages and stillbirths that's already been mentioned on the safety side, and on the efficacy and effective side, better data on neonatal outcome.

And under maternal complications, perhaps at least screening women for depression to make sure that this drug is not increasing their risk of depression in the postpartum period for this population. And maybe be more user-specific, since we now have described at least four etiologies or four pathways for preterm labor, some which are contraindications to even preventative therapy, to look at that to see how that holds up in a post-marketing evaluation.

DR. GILLEN: I think it's pretty hard to argue with days in the hospital following birth and long-term follow-up being clinically relevant, and so I would like to see both of those evaluated, with penalties taken for some sort of penalization for miscarriages and stillbirths in that way.

DR. VISCARDI: I second that about hospital days as being probably an appropriate thing to track, as well as, for long-term follow-up, probably an appropriate comparison would be comparing these children that were exposed to the progesterone to their siblings who were born preterm, since the indication is going to be a prior preterm birth, to see whether, in fact, there is any difference as a result of being exposed to that drug.

DR. SCOTT: Even though I voted for it, I'm still skeptical. I think that premature labor and preterm birth is such a huge and devastating problem that the potential benefits way outweigh the risks of non-approval, but I still think that there are potential problems with the control group that was presented.

And so I'd like to see longer and additional studies that really do prove the efficacy. I think that that's necessary. I think that it should be possible to get much better data on the exact risk of premature labor in the next pregnancy by week of gestation, and I think that's a crucial thing.

I'd like to see more biologic data to prove that it really works. In other words, why not just even do simple 17-hydroxyprogesterone levels in mothers in which it worked -- in other words, premature labor was prevented -- versus those that were a failure? In other words, I think that those things are important.

I pretty much second the March of Dimes' recommendations, in which they outlined how this ought to be done and followed up.

DR. HENDERSON: I'd like to see investigation for the losses, the stillbirths and the spontaneous abortions, looking for infectious etiologies that could potentially be treated. And I'd also like to -- well, I think a clinical trial to really prove that this works would be useful.

I think it would also be helpful to just even go back and survey all the networks to see what their rate of preterm delivery has been, understanding that this drug is so widespread now -- urologists are using it if they have a complicated pregnancy; they don't tell the GYN to give it.

So, I mean, understanding that it's out there and people are using it, that it would be nice to know what the networks preterm delivery rates were now. Because if they were approaching 50%, then it would make sense that the control group had a 50% incidence of preterm delivery.

DR. CARSON: Well, I'm very concerned about how much we don't know about just regular pharmacokinetics and dynamics of this drug. The studies that we've read in preparation to this gave 25 milligrams to a rodent model. That's about -- it seems to me, doing the math, that that's probably, on a per-kilogram basis, about 25 times larger than the dose that was administered.

The axle (phonetic) study gave 1000 milligrams to squirrel monkeys. I don't know how big they are, but I guess they're about like this. And so I would think you're getting four times the dose in that model at -- which is maybe about a fifth the size of an adult non-pregnant woman. And we don't have -- and in those studies, it's very variable about efficacy and drug levels are not that high.

We don't have any idea about what kind of drug levels we have in women who have BMIs all over the board who have at least a 30% increase in their blood volume. I'm very concerned about exactly whether any of these women really did have an effective drug in their circulation. And when one -- so I think that we need to ask for, (1) some dose ranging studies and (2) some concentrations of drugs.

I did ask for a repeat study because I think when you look at the data, again, not -- at least as presented, not controlled to BMI -- you see that one site had a huge efficacy, but every other site had maybe five patients. I'm not at all sure that this is -- that we can really say it's efficacious.

And along those lines, the -- when -- it would be nice to have larger numbers at what sites. If you really look at the data and rather than call it drug and placebo, call it Drug A and Drug B, you can actually say B was a very potent stimulator of labor, because the Drug A, which was the 17-hydroxy B, has the same background risk of preterm delivery as the population studies presented by Dr. Romero, and Drug B, which we call placebo, has a higher than background risk. So I'm quite concerned about efficacy and I think we need to have at least those parameters.

DR. WESTNEY: I would agree in whole with what Dr. Carson said. I think we really should have some rigorous pharmacokinetic studies to allow for dose adjustment and in addition to that, I would advocate also an extension of the current follow-up, and that would decrease the -- that would give us a lead time in those children to really evaluate them in the late teen and early adult years.

DR. SELBY: Yes. I'm a preemie mom and I had delivered my son at 30 weeks, and he died five months later due to complications of sepsis. That said, I still don't feel that the efficacy data is strong enough to me. I would not want to be -- I would not want to trade -- I would not be ready, based on this data, to trade one set of problems for another. I don't feel comfortable enough with the efficacy data.

Because I would be afraid, looking down the road -- some of the -- I would be concerned about long-term, about a possible -- that 17P might have a potential carcinogenic potential in the adult children of these moms who have been treated with Delalutin, and I was -- I didn't hear anything about whether they had looked at that or there was any increased incidence of reproductive cancers. So I would be concerned about that.

I didn't see enough to convince me that -- I mean, gaining a week didn't seem to make any difference, as far as the long-term neuro-developmental outcomes, and that would be something that would be very important to me, but I didn't see enough proof with that to take the risk with 17P.

I would also want them to evaluate more studies on mortality and morbidity and repeat studies on stillbirth and miscarriage. And I was also wondering if they've been looking at these patients who are being treated currently, if there's any data coming in from those patients, as far as efficacy and safety. They said that, what, 67% of maternal-fetal specialists were using this -- using the compound, and I was wondering if any data had come in from them. So I would want that looked at, too.

DR. TULMAN: Lorraine Tulman. I agree, it seems like there's two types of things that have been proposed. One is a registry for follow-up on mothers and infants who would be getting the medication in terms of stillbirth, miscarriages, gestational diabetes for the mother, neonatal morbidity, pubertal development, reproductive health problems in the generation of children born. And I agree with the notion of a registry.

No one has addressed -- and I don't know if this is a procedural matter that should be addressed or not -- but exactly who is going to keep that registry. If it is the pharmaceutical company, they have a -- if the drug is approved, they have a patent on the drug, the patent runs out, what is their responsibility after that? Does that revert to the FDA or some other government agency? How does that work exactly?

And I think we need the mechanisms for that registry spelled out very clearly. And I think we need the notion of -- rather than just saying we need a registry, but I think we need the mechanisms put in place; otherwise, it won't get done.

The other things that have been proposed that I'm in agreement with is we know very little about how this thing actually works, in terms of the basic biology, and some of the pharmacokinetics, and what does it mean in women of different weights and how exactly is it working?

And again, I'm concerned about the mechanism for getting that done. Are we saying this is what the sponsor should be doing? Is that what other drug companies should be doing? But if so, they don't have the incentive if we have a patent -- they have a patent on it.

Is it something that the NIH would pose as an

RFA request for applications and proposals? Would it be contract work? My concern is that's not the FDA's purview, but it becomes an NIH, perhaps, purview.

So I'm very concerned that we can voice all these concerns, but it won't happen. So I'd like that sort of for the record, that -- I'd like to hear more from, I guess, the FDA on how this works.

DR. SHAMES: Well, we can facilitate these issues. I mean, we can't -- we don't have the appropriate funds or -- to address the monetary issues, but we can facilitate and bring together partners to come up with a group of ideas or partners that will allow us to do some of these things, once we go back and decide exactly what we want to do.

So we can sort of leverage and facilitate with the company, with NIH, with we talked about epi studies, things like that, so -- we see ourselves as having a more facilitative role more than just a regulatory body. So we can -- we do try to be more aggressive in this area in more recent years, I would say.

DR. SHAMES: We would try to stimulate the appropriate studies, if that's what we decide, what we decide to do. Okay?

DR. DAVIDSON: I tend to agree with the recommendations about post-marketing studies that's in the March of Dimes testimony. I think it is very important in the short term to answer this miscarriage/stillbirth question, because that has -- and it probably could be answered in the shorter term.

I don't have very much faith, I think, in the long-term follow-up being done by a pharmaceutical company, but I hope that NICHD understands that all of the definitive work around this has not been completed, and they probably would be in the best position to either do or fund long-term studies into the reproductive lives of these kids.

Because if there are some adverse effects, it ought to be found as soon as possible. And I think those are two of the really large things that ought to be done and encouraged, one on the shorter term and one on the longer term.

Well, did anybody miss saying or proposing something?

DR. LEWIS: Adjournment.

DR. DAVIDSON: There is a motion and a second to adjourn. All in favor, say I. Oppose? Well, you've done a lot of work. Thank you for everybody.

(Off the record and adjourned at 4:40 p.m.)

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Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Advisory Committee for Reproductive Health Drugs
August 29, 2006
620 Perry Parkway, Gaithersburg, Maryland

Advisory Committee for Reproductive Health Drugs Members Present (Voting):
Arthur L. Burnett, II, M.D.
Diane Merritt, M.D.
James R. Scott, M.D.
William D. Steers, M.D.
Lorraine J. Tulman, DNSc, RN, FAAN
O. Lenaine Westney, M.D.

Advisory Committee for Reproductive Health Drugs Consultants (voting):
Maria Bustillo, M.D.
Sandra Carson, M.D.
Daniel Gillen, Ph.D.
Julia V. Johnson, M.D.
James Liu, M.D.
Elizabeth Shanklin-Selby (Patient Representative)
Ezra Davidson, M.D.
Karin B. Nelson, M.D.
Joseph Harris, M.D.
Cassandra Henderson, M.D.
Katharine Wenstrom, M.D.
Gary B. Hankins, M.D.
Hyagriv Simhan, M.D.
Vivian Lewis, M.D.
Rose Viscardi, M.D.

Industry Representative (non-voting):
Steven Ryder, M.D. – Acting Industry Representative

Advisory Committee for Reproductive Health Drugs Members Absent:
Charles Lockwood, M.D.
Ronald S. Gibbs, M.D.
Jonathan Tobert (Industry Representative)

FDA Participants:
Julie Beitz, M.D.
Dan Shames, M.D.
Scott Monroe, M.D.
Lisa Kammerman, Ph.D.
Barbara Wesley, M.D.

Open Public Hearing Speakers:
Barbara Dehn
Jackie Duda
Nancy Green
Terri Grossklaus
Joseph Hwang
Senator Connie Lawson (Indiana)
Michael Paidas
Davene White
Cynthia Pearson

Designated Federal Official
Teresa A. Watkins

I certify that I attended the August 29, 2006 meeting of the Advisory Committee for Reproductive Health Drugs and that these minutes accurately reflect what transpired.

_____________/S/_______________
Teresa A. Watkins
Designated Federal Official

_____________/S/____________________
Ezra Davidson, M.D.
Acting Chair, ACRHD

FINAL Minutes
Advisory Committee for Reproductive Health Drugs Meeting
August 29, 2006

A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at: http://www.fda.gov/ohrms/dockets/ac/cder06.html#rhdac

<u>All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.</u>

Prior to the meeting, the members and the invited consultants were provided the background material from the FDA. The meeting was called to order by Ezra Davidson, M.D. (Acting Chair, ACRHD); the conflict of interest statement was read into the record by Teresa Watkins (Designated Federal Official). There were approximately 175 persons in attendance. There were 9 speakers for the Open Public Hearing Session (see below for a listing of the speakers).

Attendance:
Advisory Committee for Reproductive Health Drugs Members Present (voting)
Arthur L. Burnett, II, M.D., Diane Merritt, M.D., James R. Scott, M.D., William D. Steers, M.D., Lorraine J. Tulman, DNSc, RN, FAAN, O. Lenaine Westney, M.D.

Advisory Committee for Reproductive Health Drugs Consultants (voting):
Maria Bustillo, M.D., Sandra Carson, M.D., Daniel Gillen, Ph.D., Julia V. Johnson, M.D., James Liu, M.D., Elizabeth Shanklin-Selby (Patient Representative), Ezra Davidson, M.D., Karin B. Nelson, M.D., Joseph Harris, M.D., Cassandra Henderson, M.D., Katharine Wenstrom, M.D., Gary B. Hankins, M.D., Hyagriv Simhan, M.D. Vivian Lewis, M.D., Rose Viscardi, M.D.

Industry Representative (non-voting):
Steven Ryder, M.D. – Acting Industry Representative

Advisory Committee for Reproductive Health Drugs Members Absent:
Charles Lockwood, M.D., Ronald S. Gibbs, M.D., Jonathan Tobert (Industry Representative)

Consultant (Government Employee) (non-voting)
Roberto Romero, M.D.

FDA Participants:
Julie Beitz, M.D., Dan Shames, M.D., Scott Monroe, M.D., Lisa Kammerman, Ph.D., Barbara Wesley, M.D.

Open Public Hearing Speakers:
Connie Lawson, Barbara Dehn, Michael Paidas, Nancy Green, Joseph Hwang, Terri Grossklaus, Jackie Duda, Davene White, and Cynthia Pearson

Issue:
The Committee discussed the safety and efficacy of New Drug Application (NDA) 21-945), proposed trade name Gestiva, 17 alpha-hydroxyprogesterone caproate injection, 250 mg/mL, Adeza Biomedical, for the proposed indication prevention of preterm delivery in women with a history of a prior preterm delivery.

The agenda proceeded as follows:

Call to Order and Introductions	Ezra Davidson, M.D. Acting Chair, Advisory Committee for Reproductive Health Drugs (ACRHD)
Conflict of Interest Statement	Teresa Watkins, PharmD. Designated Federal Official (ACRHD)
Welcome and Comments	Scott Monroe, M.D. Acting Director, Division of Reproductive and Urologic Drugs
<u>FDA Invited Speaker</u>	
Causes of Premature Birth: The Preterm Parturition Syndrome	Roberto Romero, M.D. Chief, Perinatology Research Branch Intramural Division, NICHD, NIH, DHHS
<u>Sponsor Presentation</u>	
17P for the Prevention of Recurrent Preterm Birth	Durlin E. Hickok, MD, MPH Vice President, Medical Affairs Adeza Biomedical
The Unmet Medical Need to Reduce Preterm Birth	Michael P Nageotte, MD Professor, Obstetrics and Gynecology University of California, Irvine

FDA Presentation

Efficacy and Safety Findings and Issues — Barbara Wesley, MD, MPH
Medical Officer
Division of Reproductive and Urologic Products

Clarifying questions from the committee to either FDA or Adeza

Open Public Hearing

Statistical Presentation — Daniel Gillen, Ph.D.
Assistant Professor,
Department of Statistics
University of California, Irvine

Committee Discussion

Committee vote

Questions to the Committee:

Adequacy of Clinical Data to Support Effectiveness

In general, the FDA requires an Applicant for a new drug product to submit two adequate and well-controlled clinical trials as substantial evidence of effectiveness. One of the circumstances in which a single clinical trial may be used as substantial evidence of effectiveness is a trial that has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome, and confirmation of the result in a second trial would be logistically impossible or ethically unacceptable. The Applicant is seeking marketing approval for 17-hydroxyprogesterone caproate (17OHP-C) based primarily on (1) the findings from a single clinical trial and (2) a surrogate endpoint for neonatal/infant morbidity and mortality (i.e., reduction in the incidence of preterm births at less than 37 weeks gestation).

Question 1 (The original Question 1b was split into 1b and 1c.)

a. Is the primary endpoint of Study 17P-CT-002 ─ prevention of preterm birth prior to 37 weeks gestation ─ an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity?

YES = 5
NO = 16
ABSTAIN = 0
TOTAL = 21

b. If not, would prevention of preterm birth prior to 35 weeks gestation be an adequate surrogate?

YES = 13
NO = 8
ABSTAIN = 0
TOTAL = 21

c. If not, would prevention of preterm birth prior to 32 weeks gestation be an adequate surrogate?

YES = 20
NO = 1
ABSTAIN = 0
TOTAL = 21

Question 2. Do the differences in the incidence of preterm birth in Study 17P-CT-002 prior to 37 weeks in the vehicle (control) group (**55%**) compared to those in the control arms of (a) another Maternal Fetal Medicine Units Network trial (approximately **37%**) and (b) Study 17P-IF-001 (**36%**) evaluating similar high risk populations indicate the need to replicate the findings of Study 17P-CT-002 in a confirmatory trial?

YES = 9
NO = 12
ABSTAIN = 0
TOTAL = 21

Question 3 (The original Question 3a was split into 3a and 3b. The original Question 3b was changed to 3c.)

a. Do the data reviewed by the Committee provide substantial evidence that 17OHP-C prevents preterm birth prior to 35 weeks gestational age?

YES = 12
NO = 9
ABSTAIN = 0
TOTAL = 21

b. Do the data reviewed by the Committee provide substantial evidence that 17OHP-C prevents preterm birth prior to 32 weeks gestational age?

YES = 7
NO = 14
ABSTAIN = 0
TOTAL = 21

NOTE: The tally was announced incorrectly at the meeting as 6 Yes, 15 No, 0 abstain.

c. Do the data reviewed by the Committee provide substantial evidence that 17OHP-C reduces fetal and neonatal mortality or morbidity?

YES = 2
NO = 19
ABSTAIN = 0
TOTAL = 21

Potential Safety Concern and Adequacy of Safety Data
There was a numeric increase in the percentage of second trimester miscarriages (pregnancy loss prior to Week 20 of gestation) and stillbirths in the 17-hydroxyprogesterone caproate group. Overall, 11 of 306 subjects (3.6%, 17OHP-C group) and 2 of 153 subjects (1.3%, vehicle group) had a second trimester miscarriage or stillbirth.

Question 4

a. Is further study needed to evaluate the potential association of 17OHP-C with increased risk of second trimester miscarriage and stillbirth?

YES = 21
NO = 0
ABSTAIN = 0
TOTAL = 21

b. If so, should this information be obtained prior to approval for marketing or post-approval?

PRE-APPROVAL = 8
POST-APPROVAL = 13
ABSTAIN = 0
TOTAL = 21

Question 5. Are the overall safety data obtained in Studies 17P-CT-002 and 17P-IF-001 and Study 17P-FU (long-term follow-up) adequate and sufficiently reassuring to support marketing approval of 17OHP-C without the need for additional pre-approval safety data?

YES = 13
NO = 8
ABSTAIN = 0
TOTAL = 21

Post-Approval Clinical Study(s)
Question 6

a. If 17-hydroxyprogesterone caproate were to be approved for marketing without additional pre-approval clinical studies, would you recommend that the Applicant conduct a post approval clinical trial(s) to investigate further safety or effectiveness?

YES = 21
NO = 0
ABSTAIN = 0
TOTAL = 21

b. If so, what would be the primary objective of the trial(s) (i.e., what unanswered question(s) would the study investigate)?

Although the following list is not all inclusive, it is representative of the committee participant responses. A full transcript will be posted to the FDA website in approximately 2 weeks.

-Further evaluation of mid-trimester loss and still births
-Further elucidation of the pharmacokinetic and pharmacodynamic properties of 17-hydroxyprogesterone caproate (17P).
-Exploration and optimization of mg/kg dosing
-Evaluation of the impact of increased blood volume on drug levels
-Further evaluation of carcinogenic potential
-Long term follow up studies of children exposed to 17P, including evaluation of reproductive health, fertility, and genital development
-Long term comparative studies of 17P exposed and non-exposed siblings.
-Evaluation of the effect of 17P on the development of gestational diabetes in the mother, as well as other maternal complications.
-Evaluation of the effect of 17P on length of hospital stay for the neonate.
-Evaluation of 17P potential to cause or exacerbate depression in the mother.
-Explore creating a registry to track events.
-Further efficacy studies.
-Exploration of 17P use for other indications

Adjournment at approximately 4:40 p.m.

Dockets Management

Food and Drug Administration

Reproductive Health Drugs Advisory Committee

August 29, 2006

Briefing Information

Adeza Biomedical

Disclaimer

The statements contained in this document(s) are those of the product's sponsor, not FDA, and FDA does not necessarily agree with the sponsor's statements. FDA has not made a final determination about the safety or effectiveness of the product described in this document.

NDA 21-945 (17 a-Hydroxyprogesterone Caproate Injection, 250 mg/mL) (pdf)

Bibliography (pdf)

Addendum/Errata (pdf)

FDA

Disclaimer

Portions of this document have been determined to be exempt from disclosure under the Freedom of Information Act (the FOIA) (5 U.S.C. §552).
These redacted portions will appear as white space on the screen or on the printed page.

Background Document (pdf)

Appendix 1 (pdf)

Bibliography (pdf)

Page last updated August 25, 2006 kk

Appendix 2

BRUDAC Meeting on Makena October 29, 2019

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

Bone, Reproductive, and Urologic Drugs Advisory Committee Meeting October 29, 2019

MAKENA® (hydroxyprogesterone caproate injection)

NDA 021945 / S-023

AMAG Pharmaceuticals, Inc.
1100 Winter Street
Waltham, MA 02451

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LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviation	Definition
17P	Hydroxyprogesterone caproate injection, 250 mg/mL
ACOG	American College of Obstetricians and Gynecologists
AE	Adverse event
API	Active pharmaceutical ingredient
ASQ	Ages and Stages Questionnaire
BMI	Body mass index
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
FDA	Food and Drug Administration
GA	Gestational age
GMP	Good Manufacturing Practices
HPC	Hydroxyprogesterone caproate
IM	Intramuscular
ITT	Intent-to-Treat
IVH	Intraventricular hemorrhage
LMP	Last menstrual period
MFMU	Maternal Fetal Medicine Unit
MPC	Maternal pregnancy complication
NDA	New Drug Application
NEC	Necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
PK	Pharmacokinetic
PP	Per Protocol
pPROM	Preterm premature rupture of membranes
PROLONG	Progestin's Role in Optimizing Neonatal Gestation (PROLONG)
PTB	Preterm birth
PT	Preferred term
RDS	Respiratory Distress Syndrome
RRR	Relative risk reduction
SAE	Serious adverse event
SD	Standard deviation
SMFM	Society for Maternal-Fetal Medicine
SPTB	Spontaneous preterm birth
TEAE	Treatment emergent adverse event
US	United States

1. EXECUTIVE SUMMARY

1.1. Overview

Preterm birth (PTB) is a major public health concern in the United States (US). 17P (a synthetic progestin containing the active pharmaceutical ingredient 17α-hydroxyprogesterone caproate), which includes Makena and the recently approved generic formulations, is FDA-approved therapy to reduce recurrent PTB.

The purpose of this Advisory Committee meeting is to discuss the findings from the post-approval confirmatory trial for Makena, which failed to meet its co-primary endpoint. The discussion will focus on better understanding two studies with similar study designs, yet conflicting results.

Study 002 (hereafter referred to as the Meis Study) was the basis for FDA conditional approval of 17P in 2011, and demonstrated consistent and statistically significant efficacy across multiple endpoints. This landmark study was conducted by the National Institute of Child Health and Human Development, Maternal-Fetal Medicine Unit, and enrolled patients entirely in the US.

As part of the conditional approval of Makena, a confirmatory study (Study 003, or "PROLONG") was required. The PROLONG study, conducted predominantly outside the US, as previously mentioned, did not meet its co-primary efficacy objective. However a favorable maternal and fetal safety profile of 17P was reaffirmed, as there were no new or unexpected safety findings, and no clinically meaningful differences in the safety profile across treatment groups.

Key differences in baseline levels of risk for recurrent PTB between the PROLONG and Meis studies limit the applicability of the PROLONG efficacy data to the US population. Nevertheless, the strong efficacy data from the Meis study, previous supporting clinical trial data in the US, and trends favoring treatment benefit for 17P in post-hoc analyses focused on patients enrolled in the US, coupled with a favorable safety profile, support the continued use of 17P.

1.2. Preterm Birth Prevalence and Prevention

PTB, defined as birth before the 37th week of gestation, is a serious health concern, and is recognized as the leading cause of neonatal mortality and morbidity in the US [ACOG 2012]. One of the most significant risk factors for spontaneous singleton PTB is a patient's history of PTB. Women who have had a prior PTB have a 2.5-fold greater risk for subsequent PTB than women without a prior history of PTB [Iams et al 1998; Mercer et al 1999]. Approximately 3.3% of pregnant women, or 130,000 annually, have a history of prior singleton spontaneous PTB.

Infants born prematurely have increased risks of mortality and morbidity throughout childhood, especially during the first year of life. Premature birth is the number one cause of death of children under 5 years old worldwide. Infants who do survive premature birth often suffer long-term health problems and potential for long-term physical and cognitive disabilities.

According to the Centers for Disease Control and Prevention, ~10% of liveborn births, or nearly 400,000, each year are born prematurely. Rates of PTB are highest in the areas of the country with the greatest disparities in health care, particularly in minorities and poor communities.

Approximately 30% of women who deliver preterm had a history of a prior singleton spontaneous PTB [Gallagher et al 2018].In addition to prior PTB, there are additional known risk factors. Studies have reported that Black women are twice as likely as White women to have preterm deliveries and three times as likely to have very preterm deliveries (<32 weeks), which are the most vulnerable to mortality and long-term morbidities [Carmichael et al 2014; McKinnon et al 2016]. While the rate of PTB in the US is lower than the estimated global rate, the US ranked among the top ten countries in total number of PTBs, and remains among the highest in developed countries. In 2010, the World Health Organization ranked the US as 131st out of 184 countries in regard to rates of PTB.

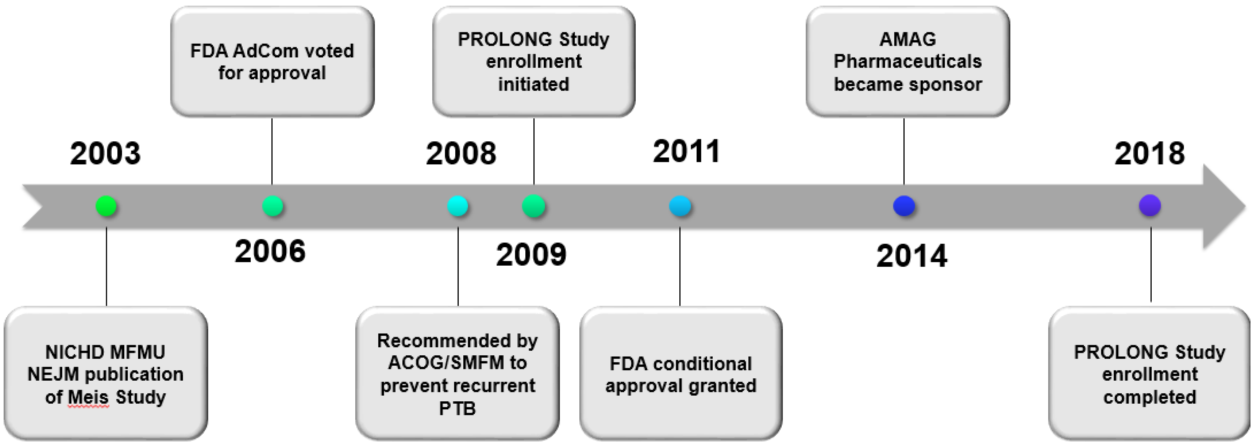
Progesterone agents have demonstrated effectiveness in the prevention PTB in randomized trials [Keirse 1990; Meis and Aleman 2004] which are thought to support gestation by reducing inflammation and inhibiting uterine activity. Hydroxyprogesterone caproate (HPC), or “17P”, has demonstrated efficacy in randomized clinical trials to prevent pre-term birth in women with a prior spontaneous singleton pregnancy. In addition, a number of controlled studies support the use of 17P for this same patient population [Levine 1964; Papiernik-Berkhauser 1970; Johnson et al 1975; Yemini et al 1985; Suvonnakote 1986, Meis et al 2003, Saghafi et al 2011]. Vaginal progesterone has also been studied for the reduction of PTB in women with a history of spontaneous PTB, however, vaginal progesterone is not FDA-approved to prevent PTB in women with a prior spontaneous PTB or an incidental short cervix.

Progestogens, including 17P, have been recommended for use in treatment guidelines issued by professional societies. In 2008, the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice and Society for Maternal-Fetal Medicine (SMFM) issued a joint opinion that progesterone be used to prevent recurrent preterm birth [ACOG 2008]. In 2012, ACOG and the Society for Maternal-Fetal Medicine (SMFM) issued separate guidelines regarding the management of women at risk for PTB. In the SMFM guideline, an algorithm recommends the use of vaginal progesterone for women with an incidental short cervix and the use of 17P for women with histories of spontaneous PTB. The ACOG guideline was more general and stated only that “progesterone supplementation should be offered” to women with histories of spontaneous PTB [Practice Bulletin 2012].

1.3. Makena

A summary of the regulatory history for Makena is depicted in Figure 1 .

Figure 1: Regulatory Timeline



Abbreviations: NEJM=New England Journal of Medicine

1.3.1. Approval

Makena® was approved by FDA under the accelerated approval provisions of Subpart H of 21 CFR Part 314 in February 2011 (New Drug Application [NDA] 21945). Under Subpart H, FDA may grant approval based on an effect on a surrogate endpoint that is reasonably likely to predict a drug's clinical benefit.

"Makena is a progestin indicated to reduce the risk of PTB in women with a singleton pregnancy who have a history of singleton spontaneous PTB. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity."

The Meis study was the pivotal study that served as the basis for approval. As part of the accelerated approval (granted based large unmet need for condition with no other treatment option), FDA required a confirmatory efficacy study be performed in order to demonstrate neonatal benefit as a primary outcome. During the review process, FDA recognized the difficulty of conducting a study once the drug was approved and adopted based on the recommendations of clinical guidelines supporting its use in this patient population. As a result FDA required that at least 5% of the patients be enrolled prior to approval of Makena, and that at least 10% of the patients be enrolled from North America. As such, the confirmatory study began in 2009, and once the North America enrollment requirement was met in 2011, Makena received FDA approval.

The confirmatory trial (PROLONG) was designed in conjunction with the FDA. FDA required that clinical efficacy be confirmed using the co- primary endpoints of PTB rates at less than 35 weeks and and rates of incident cases of neonatal morbidity/mortality with predefined criteria. FDA also wanted additional safety data to better understand the incidence of early fetal loss.

1.3.2. Availability of 17P

Prior to the approval of Makena, 17P was available to patients only through pharmacy compounding. Unlike pharmaceutical manufacturers, compounding pharmacies do not have to demonstrate the safety and efficacy of compounded products or adhere to FDA Good Manufacturing Practices (GMPs). In 2011, the original sponsor of Makena (KV Pharmaceuticals) obtained samples of compounded 17P and the active pharmaceutical ingredient used by pharmacists to compound 17P, and identified that compounded versions of 17P did not meet the purity and potency specifications designated for Makena [Chollet and Jozwiakowski 2012].

In addition to lack of comparability, there are significant potential risks associated with pharmacy compounding products. A stark reminder of these potential safety concerns that can arise from the lack of regulation around purity, potency and sterility of drug products, occurred in the Fall of 2012 when a fungal meningitis outbreak was traced to contaminated compounded drugs formulated and distributed by the New England Compounding Center (NECC). There were 76 deaths were attributed to these substandard sterile injectable drugs produced by the NECC, with over 700 patients being gravely sickened [FDA 2017; Raymond 2017].

The key issue is the lack of standard quality oversight of compounded products from a GMP perspective. Whenever this process is lacking or deficient, there is the potential for untoward effects and unnecessary harm to patients. Without FDA-approved forms of 17P (Makena, plus the four generic products available), pharmacy compounding may be the only available source of this injectable drug for pregnant women.

1.4. Overview of Clinical Studies

An overview of the key adequate and well-controlled safety and efficacy studies comprising the Makena clinical development program is provided in Table 1.

Table 1: Overview of Key Clinical Studies

	Meis	PROLONG
Year	1999 to 2002	2009 to 2018
Sites	19 sites, US Only	93 sites, 9 countries
Randomization	2:1	2:1
Study Drug	17P 250 mg/mL or vehicle	17P 250 mg/mL or vehicle
Dose	1 dose/week through 36^6 weeks gestation or delivery	1 dose/week through 36^6 weeks gestation or delivery
Study Population	Women 16 to 20 weeks gestation with history of spontaneous preterm delivery	Women 16 to 20 weeks gestation with history of spontaneous preterm delivery
Sample Size	17P: N=310 Vehicle: N=153	17P: N=1130 Vehicle: N=578
Primary Endpoint(s)	• PTB <37 weeks	• PTB <35 weeks • Neonatal Composite Index
Key Secondary Endpoints	• PTB <35 and <32 weeks • Neonatal morbidity/mortality	• PTB <37 and <32 weeks • Fetal/early infant death

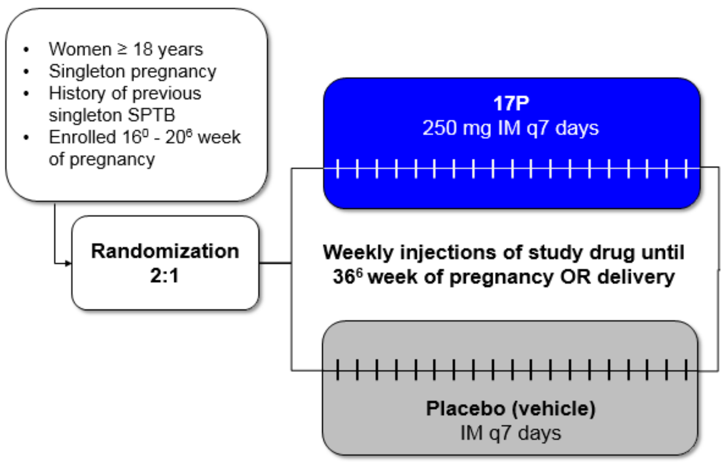
1.5. Meis: Pivotal Trial Results

The Meis study was conducted from 1999 to 2002 by the National Institutes of Child Health and Human Development (NICHD) through the Maternal Fetal Medicine Units Network (MFMU). The study was a US-only, double-blind, randomized placebo-controlled trial in pregnant women with a documented history of spontaneous preterm delivery. Women were enrolled at 19 clinical centers in the US, primarily located in inner city academic institutions with a high proportion of minorities.

A dose of 250 mg IM was selected based on earlier clinical trials designed to determine if 17P could prevent premature delivery [LeVine 1964; Johnson et al 1975; Yemini et al 1985].

The design of Meis is provided in Figure 2**.**

Figure 2: Meis Study Schematic



In 2002, the prespecified stopping criterion (p=0.015) for efficacy was met at the second interim analysis and the Data Monitoring Committee recommended stopping the trial prior to enrolling the proposed 500 patients. Stopping criteria were in place to assure that once efficacy was established the drug could be made available to all appropriate patients.

1.5.1. Efficacy

Patients randomized to the two treatment groups were comparable in mean age, race, body mass index (BMI) prior to pregnancy, marital status, years of education, and substance use during pregnancy. The majority of patients were Black (approximately 59%), with a mean age of 26.2 years. The mean pre-pregnancy BMI was approximately 26.6 kg/m^2. Approximately 50% of patients in the study were married, and approximately 22% smoked, approximately 8% consumed alcohol, and 3% used illicit drugs during the study pregnancy. Compared to the vehicle group, the 17P patients had significantly fewer previous preterm deliveries, fewer previous spontaneous preterm deliveries, and a lower percentage of patients with >1 previous preterm delivery.

1.5.1.1. Primary Efficacy Endpoint Analysis: Recurrent Preterm Birth

The risk of delivering prior to 37^0 weeks gestation in the Meis study was significantly reduced in the 17P group (37.1% vs 54.9%; p=0.0003) (Table 2).

Table 2: Percentage of Patients with Delivery <37^0 Weeks of Gestation (Meis)

Data Source	17P n (%)	Vehicle n (%)	Nominal p-value[a]	Treatment difference [95% CI[b]]
ITT Population	115 (37.1)	84 (54.9)	0.0003	-17.8% [-28%, -7%]
Only available data	111 (36.3)	84 (54.9)	0.0000	-18.6% [-29%, -8%]

Source: FDA Background Gestiva (August 2, 2006), Table 4.
Note: ITT population was all randomized patients (17P N=310; Vehicle N=153). The 4 patients with missing outcome data were classified as having a preterm birth of <37^0 weeks (i.e., treatment failure). "Only available data" does not include the 4 patients in the 17P group with missing outcome data.
[a] Chi-square test. Adjusting for interim analyses, p-values should be compared to 0.035 rather than the usual 0.05.
[b] CI adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, a p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

1.5.1.2. Secondary Endpoint Analyses

1.5.1.2.1. Preterm Birth <35 and <32 Weeks Gestational Age

Despite the fact that the study was not powered to determine statistically significant differences in births at <35^0 and <32^0 weeks gestation, 17P demonstrated clinically important reductions in the number of births before 35^0 weeks (p=0.032) and before 32^0 weeks gestation (p=0.046) (Table 3).

Table 3: Percentage of Patients with Delivery <35^0 and <32^0 Weeks of Gestation (Meis)

Pregnancy Outcome	17P (N=310) n (%)	Vehicle (N=153) n (%)	Nominal p-value[a]
Delivery <35^0	67 (21.6)	47 (30.7)	0.032
Delivery <32^0	39 (12.6)	30 (19.6)	0.046

Source: FDA Background Gestiva (August 2, 2006), Table 6.
Data presented are from the ITT population (i.e., all randomized patients). The 4 patients with missing outcome data were classified as having a preterm birth <37^0 weeks (i.e., treatment failure).
[a] Adjusting for interim analyses, p-values should be compared to 0.035 rather than the usual 0.05.

At the <37^0, <35^0, and <32^0 weeks gestation, the percentage of deliveries was numerically lower in the 17P treatment arm (Table 4). There was no difference between treatment groups for the percentages of deliveries <28^0 weeks.

Table 4: Percentage of Patients with Delivery <37^0, 35^0, 32^0, and 28^0 Weeks of Gestation (Intent-to-Treat Population - Meis)

Time of Delivery (Gestational Age)	17P N=310 %	Vehicle N=153 %	Treatment difference[a] [95% CI[b]]
<37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
<35^0 weeks	21.6	30.7	-9.1% [-18%, 0.3%]
<32^0 weeks	12.6	19.6	-7.05 [-14%, 0.8%]
<28^0 weeks	10.0	10.5	-0.5% [-6.9, 5.9]

Source: FDA Background Gestiva (August 2, 2006), Table 7.
[a] Chi-square test.
[b] CI based on a t-test are adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, a p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

1.5.1.2.2. Neonatal Morbidity and Mortality

A prespecified key secondary endpoint was the incidence rate of having a qualifying event in the composite neonatal morbidity index. The neonatal composite index included neonates with death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 IVH, proven sepsis, or NEC) was lower in the 17P group, but the between group difference was not statistically significant (11.9% vs 17.2%; p=0.119)

The study was not powered to detect statistically significant differences between 17P and vehicle treatments in neonatal mortality or morbidities, however, reductions were observed with 17P in the rates of NEC, any grade of IVH, and the need for supplemental oxygen.

Although the overall rate of neonatal deaths was lower in the 17P arm versus vehicle, it was observed that miscarriages (defined as spontaneous loss of fetus from 16^0 to 19^6 weeks gestation) were numerically higher in the 17P arm, as were stillbirths (defined as birth of an infant ≥20 weeks gestation who died prior to delivery) (Table 5). In the vehicle group, the incidence of neonatal death was twice the rate of the 17P group, however the between group difference was not statistically significant due to the small sample size (p=0.116). Two other NICHD MFMU studies were subsequently conducted; when miscarriage and stillbirth are reviewed in the totality of these studies, the rates were similar between 17P and vehicle [Rouse et al 2007, Caritis et al 2009].

Table 5: Miscarriages, Stillbirths, and Neonatal Deaths (Meis)

Pregnancy Outcome	17P (N=306) n (%)	Vehicle (N=153) n (%)	Nominal p-value[a]
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.689**
Miscarriages <20 weeks gestation	5 (1.6)	0	0.175
Stillbirth	6 (2.0)	2 (1.3)	0.725
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.116

Source: FDA Background Gestiva (August 2, 2006), Table 8.
[a] No adjustment for multiple comparisons.

1.5.2. Safety

The most common type of adverse event (AE) reported during the Meis study was injection site reactions, which was expected considering that patients received weekly 1 mL IM injections. Pain, swelling, itching, and nodule formation were among the most common reactions regardless whether the solution being injected was 17P or vehicle. However, there was a significantly higher incidence of swelling at the injection site in the 17P group than vehicle (17.1% vs. 7.8%; p=0.007). Nevertheless, few women (1.7%) discontinued the study due to injection site reactions.

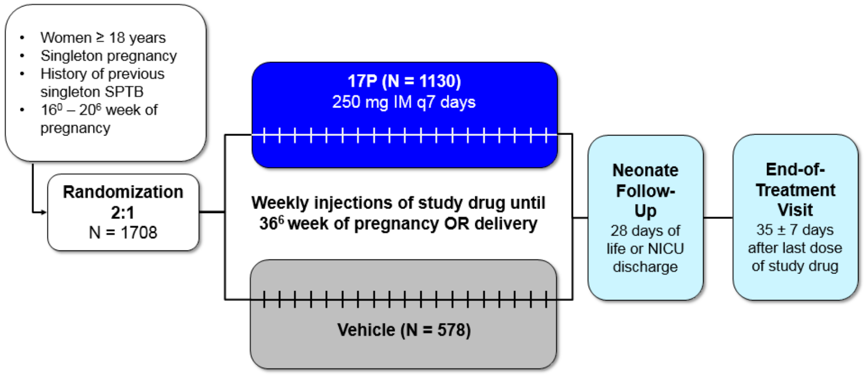
The incidence of pregnancy complications, such as preeclampsia, gestational diabetes, or clinical chorioamnionitis, as well as the incidence of serious adverse events (SAEs), was not different between the 17P and vehicle groups. SAEs reported were predominately miscarriages, stillbirths, and neonatal deaths, which were not unexpected events in the high-risk patient population, and were considered by the Investigator to be unrelated to study drug.

1.6. PROLONG: Trial Results

PROLONG was an international, double-blind, randomized, placebo-controlled trial in pregnant women with a documented history of spontaneous preterm delivery conducted from 2009 through 2018. PROLONG was approximately four times the size of the Meis trial, and was powered to detect a 30% and 35% difference between treatments in the co-primary endpoints, PTB <35 weeks gestation and neonatal composite index, respectively.

The design of PROLONG is provided in Figure 3.

Figure 3: Study Schematic (PROLONG)



PROLONG began in 2009, and once the North America enrollment requirement was met in 2011, Makena received FDA approval. Following approval of Makena, recruitment and enrollment in the US became increasingly difficult. Additional sites were then opened in Ukraine and Russia, as these countries had previously been the top enrollers in Europe.

Women were enrolled at 93 clinical centers in 9 countries. Russia and Ukraine accounted for 61% of study patients, and the US had 23%. The remaining 16% of patients were enrolled in Hungary, Spain, Bulgaria, Canada, Czech Republic, and Italy, each enrolling less than 100 patients. Enrollment in PROLONG was completed in 2018.

1.6.1. Efficacy

A total of 1708 patients were randomized 2:1 (1130 to 17P and 578 to Vehicle) and were included in the Intent-to-Treat (ITT) Population.

Although the study entry criteria were similar between PROLONG and Meis, there were differences in the patient populations that were enrolled. When comparing demographics and baseline characteristics of patients enrolled in the two studies, the differences across race and other potential surrogates of socioeconomic status were noteworthy, with Meis representing a much higher-risk population. In comparison to Meis, PROLONG patients had lower risk for spontaneous PTB based on the following key features:

- The majority of patients were White (approximately 89%), non-Hispanic or Latino (approximately 91%) with a mean age of 30 years.
- Approximately 90% of patients were married at the time of study entry.
- Substance use during pregnancy was low in PROLONG (~8% smoked, ~3% consumed alcohol, and 1.4% used illicit drugs).
- Approximately 15% of patients in PROLONG reported >1 previous spontaneous preterm delivery (compared to ~35% in Meis).

1.6.1.1. Primary Endpoint Analysis

The study did not meet its co-primary efficacy objectives, which were to demonstrate a reduction in PTB prior to 35^0 weeks gestation and in the neonatal composite index.

Rate of PTB

The overall rate of PTBs prior to 35^0 weeks gestation was lower than anticipated based on the event rates observed in Meis. Rates of PTB <35^0 weeks were low in both groups and not statistically different between groups (11.0% for 17P and 11.5% for vehicle; Table 6)

Neonatal Composite Index

No statistically significant differences in the rates of neonatal mortality or morbidity as measured by the neonatal composite index, were noted (5.4% for 17P and 5.2% for vehicle; Table 6).

The incidence of individual components of the neonatal composite were similar between treatment groups (Table 7). RDS accounted for almost all of the infants who met the criteria for this index, and rates across treatment groups were not statistically significantly different, at 4.9% and 4.6% in neonates born to patients in the 17P treatment group and vehicle group, respectively.

Table 6: Primary Efficacy Outcomes (PROLONG)

Primary Efficacy Outcomes	17P (N=1130)	Vehicle (N=578)
PTB <35^0 Weeks Gestation (ITT Population)		
Overall Outcome rate n/N* (%)	**122/1113 (11.0)**	**66/574 (11.5)**
p-value[a]	0.716	
Relative risk (95% CI)	0.95 (0.71, 1.26)	
Neonatal Composite Index (Liveborn Neonatal Population)	**(N=1091)**	**(N=560)**
Neonatal Composite Index – Overall, n (%)[d]	**59 (5.4)**	**29 (5.2)**
p-value[b]	0.840	
Relative risk (95% CI)	1.05 (0.68, 1.61)	

Source: PROLONG CSR Table 14.2.1.1.1 and Table 14.2.1.1.2, PROLONG Ad Hoc Table 14.2.1.1.1.26.
[a] p-value from the Cochran-Mantel-Haenszel test.
[b] p-value from the Cochran-Mantel-Haenszel test.
N*=number of ITT patients with non-missing delivery data or who were known to still be pregnant at 35^0 weeks in the specified category.
The composite index was defined as a liveborn neonate with any of the following occurring at any time during the birth hospitalization up through discharge from the NICU: neonatal death, Grade 3 or 4 IVH, RDS, BPD, NEC, or proven sepsis.

Table 7: Components of Neonatal Composite Index from NICU Outcomes (Liveborn Neonatal Population - PROLONG)

Individual Components of Neonatal Composite Index	17P (N=1091) n (%)	Vehicle (N=560) n (%)
Neonatal Composite Index – Overall	**59 (5.4)**	**29 (5.2)**
Neonatal death prior to discharge	3 (0.3)	2 (0.4)
Grade 3/4 intraventricular hemorrhage	2 (0.2)	1 (0.2)
Respiratory distress syndrome	54 (4.9)	26 (4.6)
Bronchopulmonary dysplasia	6 (0.5)	1 (0.2)
Necrotizing enterocolitis	2 (0.2)	2 (0.4)
Proven sepsis	5 (0.5)	3 (0.5)

Source: PROLONG CSR Table 15.

1.6.1.1.1. Subgroup Analysis

Subgroup analyses of the primary endpoints were conducted by geographic region and obstetric history.

Geographic Region

The event rates for PTB and the neonatal composite index were 1.5 to 2 times higher at 16 to 18% in the US relative to ex-US regions (10%). The rates of PTB among US patients were the highest of the three top enrolling countries in the study (Russia, Ukraine and US), while the rates in Russia and Ukraine were the lowest. The rates of the neonatal composite index in the regions with the highest enrollments (Russia and Ukraine) were among the lowest observed. This is consistent with the known epidemiology, as well as the substantially different health care delivery systems in these countries, where early intervention to improve prenatal care and reduce neonatal complications is emphasized and universally available [Healthy Newborn Network 2015; Russian Federation: Federal State Statistics Service 2012; UNICEF 2017; USAID 2011].

Obstetric History

Rates of PTB <35^0 weeks gestation and neonatal composite index were also examined for differences in obstetrical history including gestational age of qualifying delivery, gestational age of earliest prior PTB, and number of previous preterm deliveries. Results were similar for both treatment groups across subgroups.

1.6.1.2. Key Secondary Endpoint Analyses

1.6.1.2.1. Preterm Birth <37 and <32 Weeks Gestational Age

There were no statistically significant differences in births at <37^0 (p=0.567) or <32^0 weeks gestation (p=0.698) (Table 8).

Table 8: Percentage of Patients with Delivery <37⁰ and <32⁰ Weeks of Gestation (Intent-to-Treat Population, PROLONG)

	17P (N=1130) n/N* (%)	Vehicle (N=578) n/N* (%)
$<32^0$ Weeks Gestation	**54/1116 (4.8)**	**30/574 (5.2)**
p-value[a]	0.698	
Relative risk (95% CI)	0.92 (0.60, 1.42)	
$<37^0$ Weeks Gestation	**257/1112 (23.1)**	**125/572 (21.9)**
p-value[a]	0.567	
Relative risk (95% CI)	1.06 (0.88, 1.28)	

Source: PROLONG Table 14.2.3.2.1 and Table 14.2.3.1.1, PROLONG Ad Hoc Table 14.2.1.1.1.26.
[a] p-value Cochran-Mantel-Haenszel test.
Notes: n=number of patients with delivery $<32^0$ or 37^0 weeks (as indicated) gestation.
N*=number of ITT patients with non-missing delivery data or who were known to still be pregnant at 32^0 or 37^0 weeks (as indicated) in the specified category.

1.6.2. Safety

1.6.2.1. Fetal and Early Infant Death (Primary Safety Outcome)

The primary safety objective of PROLONG was to rule out a doubling in the risk of fetal or early infant death in the 17P group compared to vehicle. This objective was included specifically to address the Agency's concern of a potential "safety signal" relative to the numerically higher rate of both miscarriage and stillbirth from the Meis study.

Fetal/early infant death was defined as a spontaneous abortion or miscarriage occurring at 16 weeks 0 days through 19 weeks 6 days; a stillbirth, either antepartum or intrapartum; or a neonatal death, occurring minutes after birth until 28 days of life.

If the upper bound of the CI is less than or equal to 2.0, a doubling in risk of fetal/early infant death can be ruled out. A doubling of risk was selected and agreed upon with FDA based on sample size calculations.

Rates were low and similar between treatment groups (1.68% and 1.90% in the 17P and vehicle groups, respectively) with a relative risk of 0.79 (95% CI 0.37–1.67) (Table 9). Given that the upper bound of the 95% CI is less than 2.0, a doubling in the risk of fetal/early infant death was adequately and firmly excluded.

Table 9: Fetal and Early Infant Death (Intent-to-Treat Population, PROLONG)

Primary Safety Outcome	17P (N=1130) n (%)	Vehicle (N=578) n (%)
Fetal/Early Infant Death	**19 (1.68)**	**11 (1.90)**
Relative Risk (95% CI) [a]	**0.79 (0.37 - 1.67)**	

Source: 17P-ES-003 CSR, Table 14.3.1.1.1.
[a] Relative risk of fetal/early infant death is from the Cochran-Mantel-Haenszel test.
Notes: N=number of patients in the ITT Population in the specified treatment group.
n=number of patients with Fetal/Early Infant Death in the specific category. Fetal/Early Infant Death is defined as neonatal death occurring in liveborns born at less than 24 weeks of gestation, spontaneous abortion/miscarriage or stillbirth

1.6.2.2. Treatment-emergent Adverse Events

The AE profile between the two treatment groups was comparable. There were 57.3% and 57.8% of patients with at least one treatment-emergent AEs (TEAEs) in the 17P and vehicle group, respectively. The majority of TEAEs were mild in intensity, and most were considered unrelated to study drug. There was a low percentage of TEAEs leading to study drug withdrawal (1.0% and 0.9%) in the 17P and vehicle group, respectively, with both groups experiencing similar and low rates of serious adverse events (SAEs; 3.0% and 3.1% in the 17P and vehicle group, respectively).

The most frequently reported TEAEs in either treatment group were anemia (9.2% in 17P and 9.7% in vehicle) and headache (6.0% in 17P and 4.8% in vehicle). Other commonly reported TEAEs in the 17P group included nausea (4.9%) and back pain (4.4%).

1.6.2.3. Maternal Pregnancy Complications (MPC)

There were 27.7% and 28% of patients who experienced at least one MPC in the 17P and vehicle group respectively. The majority of patients who experienced MPC experienced mild events, and most were unrelated to study drug. The most frequently reported MPCs by PT for the 17P group were cervical incompetence (3.0%), gestational diabetes (2.9%), anemia of pregnancy (2.7%), and placental disorder and pre-eclampsia (2.6% each). The incidence of these MPC were similar in the vehicle group.

The number of patients diagnosed with gestational diabetes during PROLONG was low (~4% in both treatment groups), and consistent with the incidence each year in the US (2 to 10% of pregnancies) per Center for Disease Control estimates [CDC 2019].

1.6.2.4. Miscarriage and Stillbirth

Stillbirths were reported for 12 (1.1%) 17P patients and 3 (0.5%) vehicle patients (Table 37). All of the stillbirths were deemed unrelated to study drug by the Investigator. Among the 12 that occurred in the 17P group, 8 were listed as "definitely not related," 3 as "unlikely related", and 1 "not related." Two women in the 17P group who delivered stillbirths reported smoking during pregnancy, one tested positive for cannabinoids, 1 had a large subserous myoma, and another had uncontrolled Type 1 diabetes mellitus with documented nephropathy and retinopathy.

Ten women had a miscarriage: 4 (0.35%) in the 17P group and 6 (1.04%) in the vehicle group.

1.6.2.5. Serious Adverse Events

Overall, 34 (3.0%) 17P patients and 18 (3.1%) vehicle patients experienced serious TEAEs or MPCs. The most frequently reported serious TEAE or MPC for patients treated with 17P were premature separation of placenta (5 patients, 0.4%), placental insufficiency (4 patients, 0.4%), and pneumonia (3 patients, 0.3%); Escherichia coli sepsis, pyelonephritis, and wound infection were each reported by 2 patients in the 17P group. The most frequently reported serious TEAE or MPC for patients treated with vehicle were cholestasis (3 patients, 0.5%), and premature separation of placenta (2 patients, 0.3%).

Two patients each had one serious TEAE/MPC considered possibly related to study treatment (one patient in the 17P group had the TEAE of mild nephrolithiasis considered possibly related and one patient in the vehicle group had the severe MPC of cholestasis considered probably related).

1.6.2.6. Discontinuation due to Adverse Event

In total, 11 (1.0%) 17P patients and 5 (0.9%) vehicle patients experienced a TEAE and/or MPC that led to discontinuation of study medication (predominantly associated with the injection site). None of these events were deemed serious by the study investigator.

1.7. Exploratory Analyses

Unlike the Meis trial, which showed a treatment benefit, treatment with 17P in PROLONG did not decrease rates of PTB or the overall neonatal composite index in the overall study population.

To better understand these discrepant results, exploratory analyses were conducted. These post hoc analyses examined the potential role that differences between the study populations (demographics and patient characteristics associated with baseline risk levels), and differences in health care delivery systems and geography (access to universal health care, emphasis on preventative care) may have had on the results of the study.

1.7.1. Comparison of Demographics

When comparing demographics and baseline characteristics from PROLONG and Meis, the differences across race and other potential surrogates of socioeconomic status that have been linked to higher rates of PTB were noteworthy, with most of those differences driven by the ex-US PROLONG subset population (Table 10). Compared to the US PROLONG subset and Meis, the ex-US PROLONG population represented a cohort with a lower baseline risk for PTB.

- **Prior spontaneous PTB:** In ex-US PROLONG, 11% had more than 1 prior spontaneous PTB, compared to 27% in US PROLONG and 32% in Meis.
- **Race/ethnicity:** In ex-US PROLONG, only 1 patient was Black or African American, compared to 29% in US PROLONG and nearly 60% in Meis. Hispanic or Latinos accounted for approximately 8% of patients in ex-US PROLONG, 14% in US PROLONG, and 15% in Meis.
- **Marital status:** In ex-US PROLONG, 4% of patients were unmarried with no partner, compared to 31% in US PROLONG and 50% in Meis.

- **Substance use:** In ex-US PROLONG, approximately 4% of patients reported any substance use during pregnancy (smoking, alcohol or illicit drugs), compared to 28% in US PROLONG and 26% in Meis.

Table 10: Differences in Race and Socioeconomic Status (Meis and PROLONG)

Demographics/Baseline Characteristics – n (%)	Ex-US PROLONG (N=1317)	US PROLONG (N=391)	Meis (N=463)
>1 previous SPTB	141 (10.7)	107 (27.4)	149 (32.2)
Race/ethnicity			
Black/African American	1 (0.1)	113 (28.9)	273 (59.0)
Hispanic or Latino	101 (7.7)	54 (13.8)	69 (14.9)
Gestational age at randomization			
16-17 weeks	603 (45.8)	138 (35.3)	151 (32.6)
18-20[6] weeks	714 (54.2)	253 (64.7)	312 (67.4)
Unmarried with no partner	53 (4.0)	120 (30.7)	233 (50.3)
Educational status (≤12 years)	549 (41.7)	197 (50.5)	330 (71.3)
Any substance use during pregnancy	47 (3.6)	111 (28.4)	121 (26.1)
Smoking	44 (3.3)	89 (22.8)	100 (21.6)
Alcohol	6 (0.5)	36 (9.2)	37 (8.0)
Illicit drugs	1 (0.1)	23 (5.9)	15 (3.2)

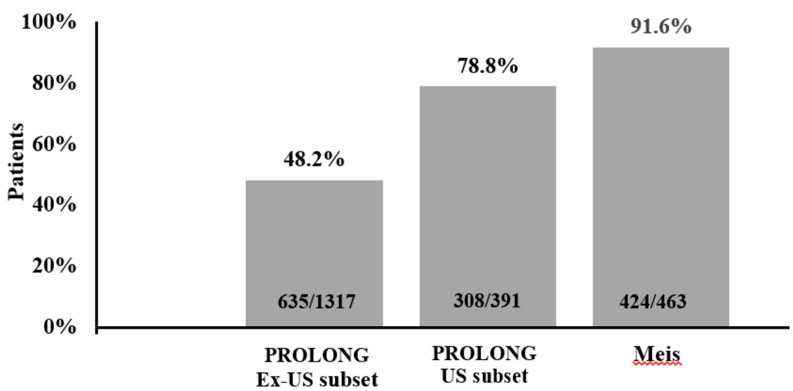
Source: PROLONG Ad Hoc Table 14.1.3.1.9

It is important to note that while US PROLONG patients were more similar to those in Meis, there remain differences related to baseline levels of risk for PTB.

Figure 4 displays a post hoc assessment of select composite risk factors associated with risk of PTB across Meis and PROLONG. The components selected for inclusion (beyond the required entry criteria for at least one prior spontaneous PTB) are >1 prior spontaneous PTB, any substance use, ≤12 years of education, unmarried with no partner, and Black or African American. Importantly, other than a prior history of more than 1 spontaneous PTB, the other components are merely imperfect surrogates of socioeconomic status, an important known predictor of rates of PTB.

The ex-US subset of PROLONG (a low risk population) had a much lower percentage of patients (48.2%) with more than one additional risk factor for PTB compared to the subset of US patients in PROLONG, an intermediate risk population (78.8%) and patients in Meis, a high risk population (91.6%).

Figure 4: Differences in Baseline Risk Factors (Known or Surrogate) Associated with Preterm Birth - Post Hoc (Meis and PROLONG)



Source: PROLONG Ad Hoc Table 14.1.3.1.9
Notes: The composite risk factors (in addition to the required prior spontaneous PTB) included >1 prior spontaneous PTB, substance use, educational status (≤12 years), unmarried with no partner, and Black/African American. Percentages expressed as n/N x 100, where n is the number of patients with at least 1 additional risk factor and N is the number of patients in the cohort.

1.7.2. Comparison of Efficacy Outcomes

Study populations with a greater percentage of high risk patients defined by the previously described composite of risk factors appeared to show improved treatment benefit with 17P compared to those with a lower percentage of those patients as shown in Figure 5.

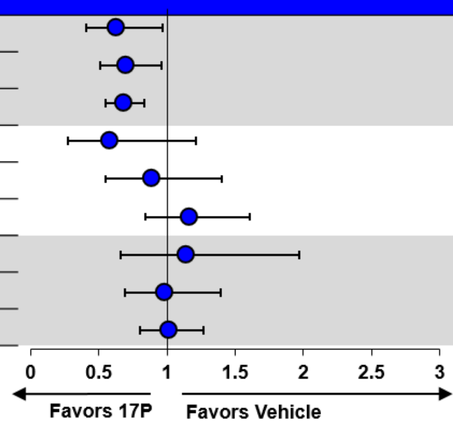
In Meis, which was a higher risk population, a treatment benefit favoring 17P was observed not only with the <37 weeks gestational age, but also at <35 weeks and even at <32 weeks, an important endpoint since it is known that babies born at earlier than 32 weeks have a significant risk of mortality and neonatal complications.

In addition, the intermediate risk population from the US subset of PROLONG also shows trends of a treatment effect favoring 17P beginning to emerge, as this population becomes more similar to Meis. These trends can be seen at <35 weeks and even at <32 weeks, however not at <37 weeks.

In contrast, the lower risk population of patients from the ex-US subset of PROLONG tend to show no trends of 17P treatment benefit compared to vehicle.

Figure 5: Comparison of Maternal Efficacy Endpoints – Post Hoc (Meis and PROLONG)

Study Population	Gestational Age (weeks)	17P (n/N)	Vehicle (n/N)	Relative Risk (95% CI)
Meis	32	39/310	30/153	0.63 (0.41, 0.97)
Meis	35	67/310	47/153	0.70 (0.51, 0.96)
Meis	37	115/310	84/153	0.68 (0.55, 0.83)
Prolong US	32	14/256	12/131	0.58 (0.27, 1.21)
Prolong US	35	40/256	23/131	0.88 (0.55, 1.40)
Prolong US	37	85/256	37/131	1.16 (0.84, 1.61)
Prolong Ex- Us	32	40/860	18/443	1.14 (0.66, 1.97)
Prolong Ex- Us	35	82/857	43/443	0.98 (0.69, 1.39)
Prolong Ex- Us	37	172/856	88/441	1.01 (0.80, 1.27)



Source: PROLONG Ad Hoc Table 14.2.1.1.1.26.

1.8. Discussion

PROLONG did not meet the predefined co-primary objectives. AMAG believes that the results from PROLONG were influenced by differences in the study population from that previously studied in Meis. While the entry criteria of Meis and PROLONG were similar, the study population in PROLONG was different than that of Meis, with the latter comprised of a higher risk population.

Efficacy

When comparing demographics and baseline characteristics from PROLONG and Meis, the differences across race and other potential surrogates of socioeconomic status that have been linked to higher rates of PTB were noteworthy, with most of those differences were driven by the ex-US PROLONG subset population. As a result, key differences in baseline risk associated with PTB even within the PROLONG study population, notably US vs. ex-US subset populations, make the applicability of the efficacy data particularly challenging in the US.

A review of the baseline characteristics of patients who enrolled in PROLONG in the US demonstrates that although they are more similar to Meis than that of the overall PROLONG population, they remain differ from Meis on many of the risk factors thought to be associated with risk of PTB.

A post-hoc investigation into baseline risk factors indicate that, compared to Meis (a high-risk population), the PROLONG US subset was an intermediate risk group for recurrent PTB, with the PROLONG ex-US subset at lower risk. The lower baseline risk for PTB in ex-US PROLONG could be attributed to varying healthcare delivery systems (more preventive than acute care) with universal access in ex-US countries, which represented 75% of the study population (61% from Russia and Ukraine alone). In a number of these countries, there are dedicated programs that target prevention of PTB and adverse fetal outcomes with evidence-based technologies to improve the quality of perinatal care. Often, these programs include comprehensive measures for pregnancy planning, screening, primary prophylaxis, and risk factor reduction, as well as providing healthcare and treatment of co-morbid conditions prior to pregnancy. In addition, compliance with prenatal care is associated with state-provided financial incentives for new mothers [Healthy Newborn Network 2015; Russian Federation: Federal State Statistics Service 2012; UNICEF 2017; USAID 2011].

Of note, exploratory analyses of PTB rates by baseline risk suggest an increasing treatment benefit associated with 17P with increasing levels of baseline risk for recurrent PTB. Treatment effect was observed at <37, <35, and <32 weeks gestation for the highest risk group (Meis), while the lowest risk group (ex-US PROLONG) showed no effect. Trends favoring 17P emerge in the US PROLONG subset as the population becomes more similar to that of Meis, with increased effect at <35 and <32 weeks, but not at <37 weeks gestation.

In totality, it is possible that differences in baseline risk for PTB underpin the lack of correlation between the efficacy results observed in Meis and PROLONG.

Safety

The key safety outcome of PROLONG was to rule out a doubling of risk of fetal or early infant death in the 17P group relative to vehicle. This endpoint was included specifically to address the Agency's concern of a potential safety signal relative to the numerically higher rate of both miscarriage and stillbirth from the Meis study. The relative risk of 0.79 with an upper bound of the 95% CI of 1.67 excludes that risk.

The favorable maternal and fetal safety profile of 17P was reaffirmed as there were no new or unexpected safety findings, and no clinically meaningful differences in the safety profile across treatment groups. Specifically, there were no clinically meaningful differences in TEAEs across the two treatment groups (17P and vehicle).

Proposed Changes to Prescribing Information

Based on the results from PROLONG, AMAG is proposing to maintain the indication with the current limitations of use and to amend the current prescribing information to include the following updates:

- Section 6 Adverse Reactions: to include pooled (Meis and PROLONG) safety information
- Section 14.1 Clinical Trials to Evaluate Reduction of Risk of Preterm Birth: to include findings from PROLONG. In particular AMAG proposes that it is important to include information that helps place the results from PROLONG in context with those observed from Meis.

1.8.1. Conclusions

Differences in study populations between Meis and PROLONG as it relates to baseline levels of risk associated with PTB contributed to the vastly lower rates of PTB and associated prematurity complications seen in PROLONG. It is relevant to acknowledge that in the nearly 20 years since Meis was initiated and PROLONG was completed, there have been substantial improvements in neonatal care that have increased survival. However, rates of PTB in the US have remained relatively constant over that time period and there remains a significant public health concern regarding PTB. Moreover, women with a prior history of spontaneous PTB, particularly if the preterm birth is early (<32 week gestation), or if there is a history of more than one prior spontaneous PTB, are at the highest risk for a recurrent PTB.

The totality of clinical data including more than 16 years of clinical use support 17P's positive benefit-risk profile and support its availability for clinicians to make patient-specific prescribing decisions, based upon their clinical judgment and shared decision-making with their patients.

2. PRETERM BIRTH

Summary

- Preterm birth (PTB), defined as birth before the 37th week of gestation, is a serious health concern and is recognized as the leading cause of neonatal mortality and morbidity in the United States (US) [ACOG 2012].
  - Women who have had a prior PTB have a 2.5-fold greater risk for subsequent PTB than women with no prior history of PTB [Iams et al 1998; Mercer et al 1999].
- Infants born prematurely have increased risks of mortality and morbidity throughout childhood, especially during the first year of life. Infants who do survive premature birth often suffer long-term health problems.
- Despite advances in perinatal care, the incidence of PTB remains high in the US, with rates among the highest among industrialized countries [March of Dimes 2015].
  - Approximately 10% of liveborn births each year, or nearly 400,000, are born prematurely
  - The PTB rate in the US worsened for a third consecutive year.
- Preterm birth rates vary significantly by race and geographic location.
  - Black women are twice as likely as White women to have preterm deliveries and three times as likely to have very preterm deliveries (<32 weeks) [Carmichael et al 2014; McKinnon et al 2016].
  - While the rate of PTB in the US is lower than the estimated global rate, the US ranked among the top ten countries in total number of PTBs and remains among the highest in developed countries [Chawanpaiboon et al 2019].

2.1. Preterm Birth: Definitions and Complications

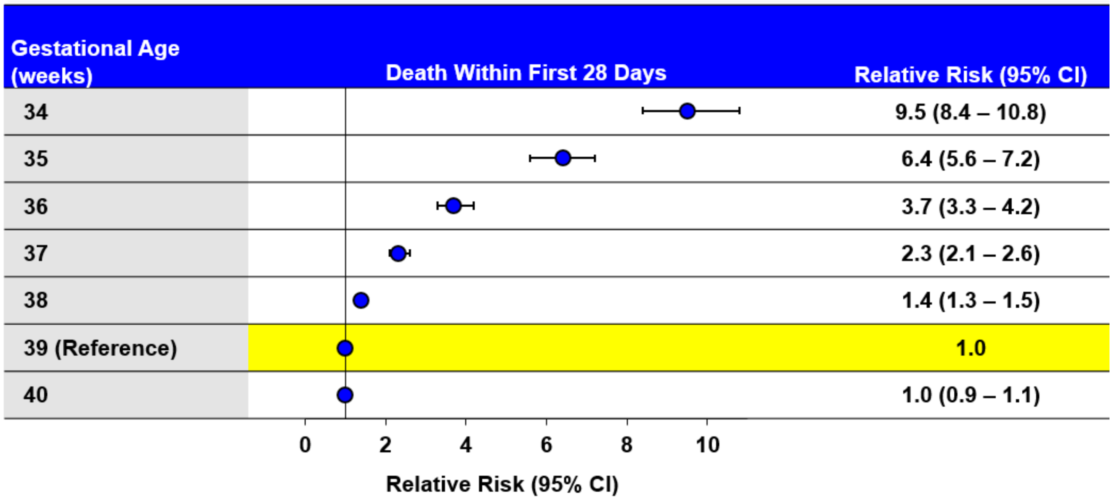
Preterm birth (PTB), defined as birth before the 37th week of gestation, is a serious health concern, and is recognized as the leading cause of neonatal mortality and morbidity in the United States (US) [ACOG 2012]. The World Health Organization (WHO) further subcategorizes PTB on the basis of gestational age:

- extremely preterm (<28 weeks);
- very preterm (28 to <32 weeks);
- moderate or late preterm (32 to <37 completed weeks of gestation)

One of the most significant risk factors for spontaneous singleton PTB is a patient's history of PTB. Women who have had a prior PTB have a 2.5-fold greater risk for subsequent PTB than women with no prior history of PTB [Iams et al 1998; Mercer et al 1999].

Infants born prematurely have increased risks of mortality and morbidity throughout childhood, especially during the first year of life. Premature birth is the number one cause of death of children under 5 years old worldwide. Of the estimated 5.43 million deaths of children under the age of 5 in 2017, complications from preterm births accounted for nearly 1 million deaths [WHO 2018]. When using 39 weeks as the reference point of 1.0 for both neonatal and infant mortality, death within the first 28 days is significantly higher for those babies born at 34, 35 and even 36 weeks of gestation, with the relative risk of neonatal mortality being 9.5 times for a baby born at 34 weeks than that of a baby born at 39 weeks and 3.7 times greater for a baby born at 36 weeks (Figure 6).

Figure 6: Neonatal Mortality Rates by Gestational Age



Source: Reddy et al 2009, Table 2.

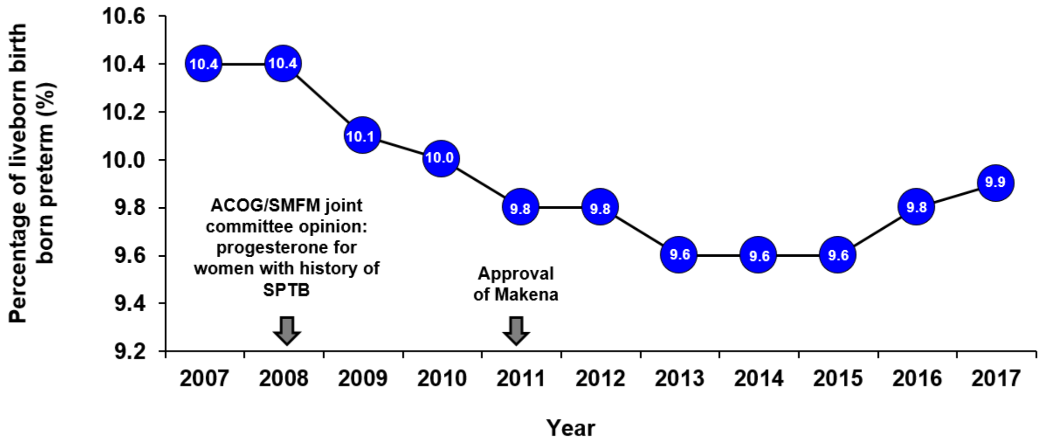
Infants who do survive premature birth often suffer long-term health problems and potential for long-term physical and cognitive disabilities. During the birth hospitalization, late preterm infants are at increased risk for morbidities such as respiratory distress, hypothermia, feeding difficulties, hyperbilirubinemia, and hypoglycemia. After discharge, late preterm infants are at increased risk for rehospitalization, mortality, and other morbidities, including neurologic, respiratory, developmental, and psychiatric/behavioral disorders [Huff et al 2019].

2.2. Prevalence

Despite advances in perinatal care, the incidence of PTB remains high in the US, with rates among the highest among industrialized countries [March of Dimes 2015].

According to the Centers for Disease Control and Prevention, ~10% of liveborn births each year, or nearly 400,000, are born prematurely (Figure 7). Rates of PTB are highest in the areas of the country with the greatest disparities in health care, particularly in minorities and poor communities.

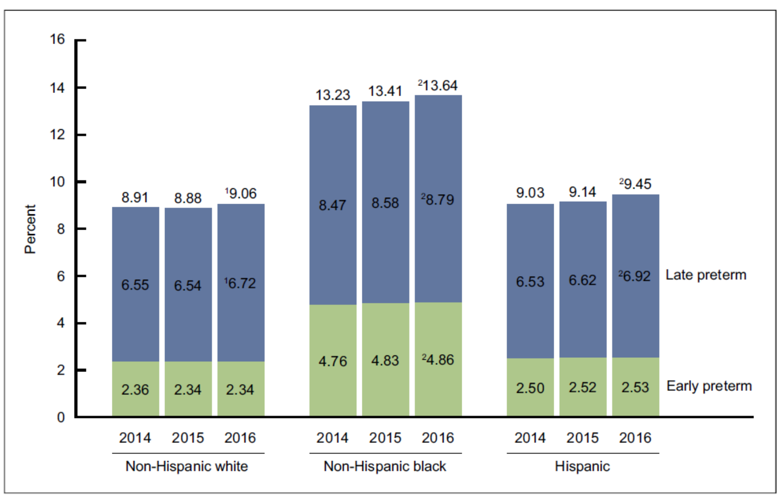
Figure 7: Preterm Birth Rates in United States (2007 through 2017)



Source: Adapted from March of Dimes 2018.
Data from NCHS, National Vital Statistics System, Natality.

Approximately 30% of women who deliver preterm had a history of a prior singleton spontaneous PTB [Gallagher et al 2018]. In addition to prior PTB, there are additional known risk factors. A review of rates of PTB in the US demonstrates a higher PTB rates in non-Hispanic Black women (Figure 8), who are more likely to experience adverse pregnancy outcomes such as PTB, hypertensive disease of pregnancy, and small-for-gestational age birth [Grobman et al 2018]. Other studies have reported that Black women are twice as likely as White women to have preterm deliveries and three times as likely to have very preterm deliveries (<32 weeks), which are the most vulnerable to mortality and long-term morbidities [Carmichael et al 2014; McKinnon et al 2016]. In 2009, reported PTB rates were as high as 17.5% in Black Americans, compared to just 10.9% in White Americans [Martin et al 2011].

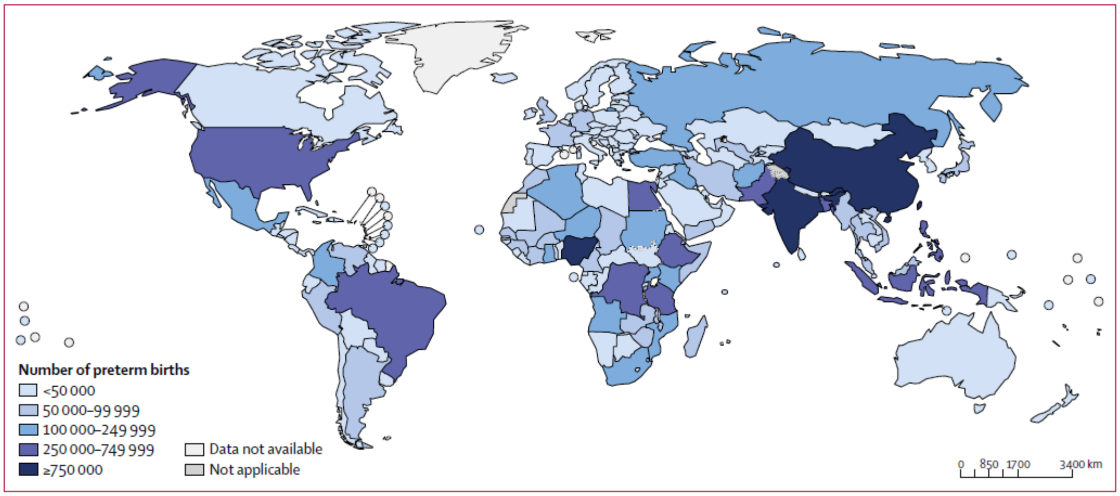
Figure 8: Preterm Birth Rates in the United States by Race and Ethnicity (2014 to 2016)



Source: Martin and Osterman 2018, Figure 3
[1] Significant increase from 2014 and 2015 ($p<0.05$).
[2] Significantly increasing linear trend for 2014-2016 ($p<0.05$).
Notes: Preterm is <37 weeks, late preterm is 34-36 weeks, and early preterm is <34 weeks of gestation. Figures may not add to totals because of rounding. Data source from NCHS, National Vital Statistics System, Natality.

In 2014, the estimated global PTB rate was 10.6%, equating to an estimated 14.84 million (12.65 million to 16.73 million) live preterm births [Chawanpaiboon et al 2019]. While the rate of PTB in the US is lower than the estimated global rate, the US ranked among the top ten countries in total number of PTBs (Figure 9), and remains among the highest in developed countries. In 2010, the World Health Organization ranked the US as 131st out of 184 countries in regard to rates of PTB.

Figure 9: Estimated Numbers of Preterm Births Worldwide (2014)



Source: Chawanpaiboon et al 2019, Figure 2.

3. PREVENTION OF PRETERM BIRTH

Summary

- Hydroxyprogesterone caproate (HPC) or "17P", has a history of being prescribed for use in pregnant women dating back approximately 6 decades, supported by 7 controlled studies on the use of HPC for prevention of PTB [Levine 1964; Papiernik-Berkhauser 1970; Johnson et al 1975; Yemini et al 1985; Suvonnakote 1986, Meis et al 2003, Saghafi et al 2011].
- In a large (N=463), controlled clinical study (Meis et al 2003), 17P was shown to:
  - Reduce the incidence of PTB <37^0 weeks of gestation compared with vehicle (p <0.001);
  - reduce the incidence of PTB when defined as <35^0 (p=0.026) or <32^0 (p=0.027) weeks of gestation;
  - Prolong the duration of pregnancy from time of enrollment (p=0.002);
  - Lower the rates of low birth-weight infants (<2500 g), neonates with necrotizing enterocolitis (NEC), neonates having any grade 3 or 4 intraventricular hemorrhage (IVH), neonates requiring supplemental oxygen, and neonates requiring admission to the neonatal intensive care unit (NICU) (p<0.05).
- Progestogens, including 17P, have been recommended for use in treatment guidelines issued by professional societies.
- Clinicians rely on 17P as the only FDA-approved therapy to prevent recurrent PTB.
- Given the adverse consequences associated with PTB, coupled with the increasing incidence of PTB in the US, there is a clear continued medical need for effective prophylaxis agents such as 17P.

3.1. Prophylactic Methods

Prophylactic methods for prevention of PTB, including tocolytic drugs, bed rest, and other interventions such as cerclage, have been shown in most studies to be ineffective [Creasy 1993; Keirse et al 1989]. One of the preventive measures that has shown effectiveness in randomized trials is the use of progesterone agents [Keirse 1990; Meis and Aleman 2004]. Progesterone has been shown to support gestation and to inhibit uterine activity.

3.1.1. Hydroxyprogesterone Caproate

Hydroxyprogesterone caproate (HPC), or "17P", has a history of use in pregnant women dating back approximately 6 decades when it was marketed as Delalutin® (E.R. Squibb & Sons, Inc.). In addition, a number of controlled studies support the use of 17P for prevention of preterm births [Levine 1964; Papiernik-Berkhauser 1970; Johnson et al 1975; Yemini et al 1985; Suvonnakote 1986, Meis et al 2003, Saghafi et al 2011].

In a large (N=463), controlled clinical study conducted by the National Institutes of Child Health and Human Development (NICHD) through the Maternal Fetal Medicine Units Network (MFMU) (Study 17P-CT-002, hereafter referred to as the "Meis study" [Meis et al 2003]), HPC injection, 250 mg/mL (17P) was shown to:

- significantly reduce the rate of recurrent PTB among women at high-risk for PTB;
- reduce the incidence of PTB <37^0 weeks of gestation compared with vehicle (p<0.001);
- reduce the incidence of PTB when defined as <35^0 (p=0.026) or <32^0 (p=0.027) weeks of gestation;
- prolong the duration of pregnancy from time of enrollment (p=0.002); and
- lower the rates of low birth-weight infants (<2500 g), neonates with necrotizing enterocolitis (NEC), neonates having any grade 3 or 4 intraventricular hemorrhage (IVH), neonates requiring supplemental oxygen, and neonates requiring admission to the neonatal intensive care unit (NICU) (p<0.05).

Additional details regarding the design and results for this study are presented in Section 6.1.

A follow-up study of children born to mothers who participated in the Meis study was conducted. Of 348 eligible surviving children, 278 (80%) were available for evaluation (194 in the 17P group and 84 in the placebo group). The mean age at follow-up was 48 months. The authors reported that they did not detect differences in developmental delays, safety concerns related to overall health or physical development, or genital or reproductive anomalies between children with in-utero exposure to placebo and in-utero exposure to 17P [Northen et al 2007].

Based on data from the Meis study, 17P was approved under the accelerated approval provisions of Subpart H of 21 CFR Part 314 in February 2011 (New Drug Application [NDA] 21945). Under Subpart H, FDA may grant approval based on demonstrating an effect on a surrogate endpoint that is reasonably likely to predict a drug's clinical benefit.

3.1.2. Vaginal Progesterone

Vaginal progesterone has been studied for the reduction of PTB in women with a history of spontaneous PTB. Several large placebo-controlled trials have failed to find a benefit of vaginal progesterone in patients with a history of SPTB [O'Brien et al 2007; Norman et al 2009; Crowther et al 2017). A 2003 Brazilian study [daFonseca et al 2003] using vaginal progesterone in 142 high-risk women (the majority of whom had a history of preterm delivery) reported a reduction in preterm birth; however, questions have been raised regarding the 14 subjects excluded from the statistical analysis [Tita and O'Day 2004]. A small number of studies have been conducted comparing 17P to vaginal progesterone; these studies have varied in their inclusion criteria. A 2017 Society for Maternal-Fetal Medicine (SMFM) statement noted that the largest of the studies, a Saudi Arabian study by Maher et al [Maher et al 2013], was not generalizable to the US and that vaginal progesterone is not an appropriate substitute for 17P in women with a history of SPTB. Vaginal progesterone has also been studied for a different PTB risk factor of short cervical length; while there have been several studies [Fonseca et al 2007; Hassan et al 2011] indicating a benefit (using varying doses, formulation and inclusion criteria), a 2012 FDA Advisory Committee voted to not approve vaginal progesterone for short cervix as the single study cited in support of the application had inconsistent results, with overall efficacy driven by only two ex-US countries (Belarus and South Africa) [Soule 2012].

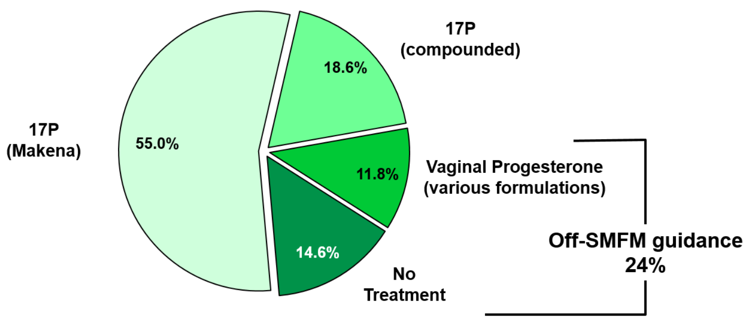
3.1.3. Treatment Guidelines

Progestogens, including 17P, have been recommended for use in treatment guidelines issued by professional societies. In 2008, the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice and SMFM issued a joint opinion that progesterone should be offered to patients to prevent recurrent PTB [ACOG 2008].

In 2012, ACOG and SMFM issued separate guidelines regarding the management of women at risk for PTB. In the SMFM guideline, an algorithm recommends the use of vaginal progesterone for women with an incidental short cervix and the use of 17P for women with histories of spontaneous PTB. The ACOG guideline was more general and stated only that "progesterone supplementation should be offered" to women with histories of spontaneous PTB [Practice Bulletin 2012].

Based on a retrospective chart review conducted in 2017, the majority of treatment for the prevention of PTB in women with a history of spontaneous PTB in the US is via branded 17P (Makena) (Figure 10) [Gallagher et al 2018].

Figure 10: Type of Treatment for Prevention of Preterm Birth



Source: Adapted from Gallagher et al 2018, Figure 2.
Note: Proportion of SMFM guidance-eligible patients managed by study physicians in previous 12 months by type of treatment/no treatment option based on retrospective chart review (April to June 2017).

3.2. Compounding of 17P

Prior to the approval of Makena in 2011, 17P was available to patients only through pharmacy compounding. Unlike pharmaceutical manufacturers, compounding pharmacies do not have to demonstrate the safety and efficacy of compounded products or adhere to FDA Good Manufacturing Practices (GMPs). GMPs are legally enforceable regulations that specify how pharmaceutical manufacturing, packaging, labeling, testing, and distribution must be done for FDA-approved medications manufactured domestically or imported into the US in order to ensure their identity, strength, quality, and purity. Manufacturing processes must be validated to consistently meet quality standards. Further, GMPs require an independent quality control unit to oversee the manufacturing, packaging, and testing processes and to reject substandard batches [Gudeman et al 2013]. Only about 2% of compounding pharmacies participate in the industry's voluntary accreditation program [Kliff 2012].

When Makena was approved, there were initial concerns regarding patient access to the FDA approved therapy. In March 2011, FDA issued a statement, noting:

> *"In order to support access to this important drug, at this time and under this unique situation, FDA does not intend to take enforcement action against pharmacies that compound hydroxyprogesterone caproate based on a valid prescription for an individually identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile products. As always, FDA may at any time revisit a decision to exercise enforcement discretion."* [FDA 2011]

The original sponsor of Makena (KV Pharmaceuticals) subsequently obtained samples of compounded 17P and the active pharmaceutical ingredient (API) used by pharmacists to compound 17P, and identified that compounded versions of 17P did not meet the purity and potency specifications designated for Makena [Chollet and Jozwiakowski 2012].

In June 2012, FDA issued an updated statement pertaining to compounding and Makena; of particular relevance is the following position:

> *"If there is an FDA-approved drug that is medically appropriate for a patient, the FDA-approved product should be prescribed and used. Makena was approved based on an affirmative showing of safety and efficacy. The company also demonstrated the ability to manufacture a quality product. The pre-market review process included a review of the company's manufacturing information, such as the source of the API used in the manufacturing of the drug, proposed manufacturing processes, and the firm's adherence to current good manufacturing practice.*
>
> *Compounded drugs do not undergo the same premarket review and thus lack an FDA finding of safety and efficacy and lack an FDA finding of manufacturing quality. Therefore, when an FDA-approved drug is commercially available, the FDA recommends that practitioners prescribe the FDA-approved drug rather than a compounded drug unless the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant difference for the patient as compared to the FDA-approved commercially available drug product."* [FDA 2012]

In addition to lack of comparability, there are significant potential safety risks associated with pharmacy compounding products. A stark reminder of these potential safety concerns that can arise from the lack of regulation around purity, potency and sterility of drug products, occurred in the Fall of 2012 when a fungal meningitis outbreak was traced to contaminated compounded drugs formulated and distributed by the New England Compounding Center (NECC). There were 76 deaths attributed to these substandard sterile injectable drugs produced by the NECC, with over 700 patients being gravely sickened [FDA 2017; Raymond 2017]. This public health catastrophe resulted in the passage of the Drug Quality and Security Act, which has expanded FDA's oversight of pharmacy compounding (traditionally regulated under the practice of pharmacy by individual State Boards of Pharmacy).

The key issue is the lack of standard quality oversight of compounded products from a GMP perspective. Whenever this process is lacking or deficient, there is the potential for untoward effects and unnecessary harm to patients. Without FDA-approved forms of 17P (Makena, plus the 4 generic products available), pharmacy compounding may be the only available source of this injectable drug for pregnant women.

3.3. Continued Medical Need

Clinicians rely on 17P as the only FDA-approved therapy to prevent recurrent PTB. In 2018, an estimated 59,000 of the 135,000 eligible patients were treated with Makena.

Given the adverse consequences associated with PTB, coupled with the increasing incidence in the US, there is a clear continued medical need for effective prophylaxis agents such as 17P, manufactured in a GMP environment.

4. HYDROXYPROGESTERONE CAPROATE

Summary

- Makena, designated as an orphan drug, was approved by FDA in 2011.
- Makena (HPC injection) is available in single or multi-dose vials for intramuscular (IM) injection; it is can be administered via autoinjector for subcutaneous injection.
- HPC is a synthetic progestin with actions similar to naturally occurring progesterone but unlike progesterone it is not metabolized into estrogen or androgens.
- The exact mechanism by which HPC prevents recurrent PTB is not known but is thought to work by decreasing inflammation and stabilizing the myometrium.
- The FDA-approved indication for 17P (Makena, HPC Injection) is that it is a progestin indicated to reduce the risk of PTB in women with a singleton pregnancy who have a history of singleton spontaneous PTB.
- Following the expiration of the orphan drug exclusivity in February 2018, four generic HPC products have been approved.

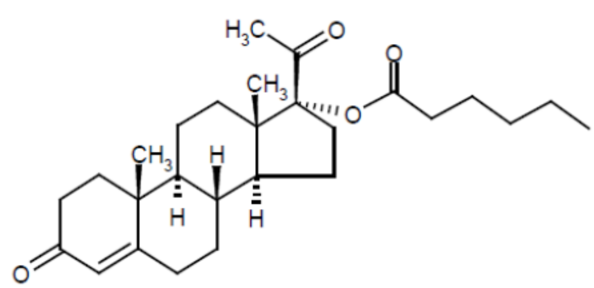
4.1. Makena (HPC Injection)

4.1.1. Product Description

Makena was approved by FDA in 2011 and is a clear, yellow, sterile, non-pyrogenic solution for intramuscular (vials) or subcutaneous (auto-injector) injection. Each 1.1 mL Makena auto-injector for subcutaneous use and each 1 mL single-dose vial for intramuscular use contains HPC USP, 250 mg/mL (25% w/v), in a preservative-free solution containing castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v). Each 5 mL multi-dose vial contains HCP USP, 250 mg/mL (25% w/v), in castor oil USP (28.6%) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

The structural formula of HPC is depicted in Figure 11.

Figure 11: Makena Structural Formula



4.1.2. Mechanism of Action

HPC is a synthetic progestin with actions similar to naturally occurring progesterone but unlike progesterone is not metabolized into estrogen or androgens. The exact mechanism by which HPC prevents recurrent PTB is not known but it is thought to work by decreasing inflammation and stabilizing the myometrium.

4.1.3. Indication

"Makena is a progestin indicated to reduce the risk of PTB in women with a singleton pregnancy who have a history of singleton spontaneous PTB. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation of use: While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth."

4.2. Generic HPC

Following the expiration of the orphan drug exclusivity for Makena in February 2018, four generic 17P products have been approved. The first generic product was approved by FDA in June 2018, with three others subsequently approved.

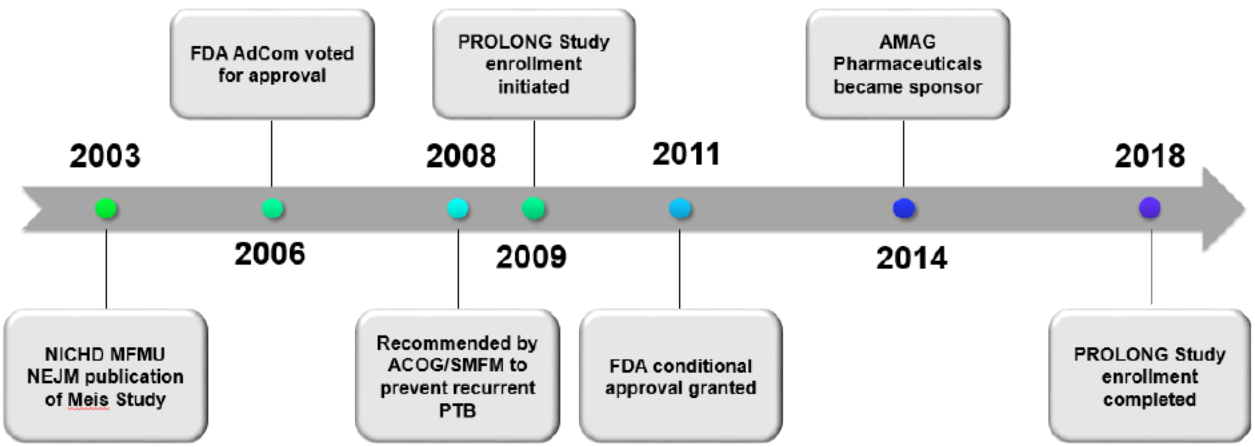
5. REGULATORY HISTORY

Summary

- The Meis trial was conducted by the NICHD and MFMU Network at 19 study centers in the US from 1999 to 2002.
- An FDA Advisory Committee Meeting was held in 2006, with the panel voting unanimously that an additional confirmatory study was required to evaluate safety/efficacy.
- The confirmatory trial (Study 17P-ES-003 or "PROLONG") was initiated in 2009.
- Conditional approval of Makena was granted by FDA in 2011.
- Enrollment in PROLONG was completed in 2018.

A summary of the regulatory history for Makena is depicted in Figure 12.

Figure 12: Makena Regulatory Timeline



Abbreviation: NEJM=New England Journal of Medicine.

The Meis study was a multi-center, double-blind, placebo-controlled trial of pregnant women with a documented history of spontaneous preterm delivery conducted by the NICHD and MFMU Network. The study enrolled 463 patients at 19 clinical centers in the US from 1999 through 2002 [Meis et al 2003]. Treatment with 17P significantly reduced the risk of delivery at <37 weeks of gestation and delivery at <35 weeks of gestation. Patients treated with 17P also had numerically lower rates of delivery at <32 weeks of gestation. Infants of women treated with 17P had lower rates of NEC, IVH, and need for supplemental oxygen.

Recognizing the benefit of having an HPC product manufactured under FDA-regulated GMPs, the NICHD provided Adeza Biomedical access to the clinical data for the purpose of seeking FDA approval of 17P (referred to as "Gestiva" at that time).

5.1. FDA Advisory Committee Meeting (2006)

Following the Gestiva NDA submission in April 2006 which included data from Meis trial as well as follow-up information on infants born to mothers enrolled in that trial, an FDA Advisory Committee Meeting was held in August 2006. Only 5 of 21 panelists felt that a reduction in PTB prior to 37 weeks gestation was an adequate surrogate endpoint. However, the committee felt that reductions in PTB <35 weeks (yes: 13, no: 8) and <32 weeks (yes: 20, no: 1) were adequate surrogates for neonatal outcomes.

Twelve (12) of the 21 members voted that the Applicant's data provided substantial evidence that 17P treatment prevented preterm birth <35 weeks gestation, and 13 of the 21 members voted that the existing safety data were sufficient to support marketing approval of 17P without the need for additional pre-approval safety data.

All panelists agreed that additional data post-approval was needed to further investigate the safety and efficacy profile of 17P.

5.2. FDA Review of NDA Submission

The original NDA submission for 17P underwent 3 review cycles with FDA.

Cycle 1 (April 2006 to October 2006)

FDA issued an Approvable Letter indicating that future approval under Subpart H would be possible but that additional well-controlled trial(s) would be required to 1) confirm the clinical benefit of 17P, and 2) evaluate the association of 17P treatment with a potential increased risk of second trimester miscarriage and stillbirth. A draft protocol(s) and evidence of feasibility of conducting these trial(s) was required. Additional deficiencies regarding chemistry, manufacturing, and controls and reproductive toxicology were also described in the Approvable Letter.

Cycle 2 (April 2008 to January 2009)

In a Complete Response Letter, FDA stated that "adequate assurance of feasibility could only be addressed by actual initiation of the confirmatory trial".

Cycle 3 (July 2010 to February 2011)

FDA acknowledged the more recent concerns regarding the increased morbidity and mortality of late PTB relative to term births, and recommended that reduction in PTB <37 weeks was an adequate surrogate for clinical benefit.

5.3. Orphan Drug Designation

Orphan status is given to drugs and biologics defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug [CFR 21 Part 316]. Orphan drug designation for use of 17P for the prevention of preterm birth in singleton pregnancies was granted on 25 January 2007.

5.4. Confirmatory Study Requirement for Makena

Study 17P-ES-003 (Progestin's Role in Optimizing Neonatal Gestation Trial; hereafter referred to as "PROLONG"), was designed in conjunction with FDA to address the Agency's review of the NDA. In that review and subsequent communication, the FDA requested that efficacy be established based on both an outcome of PTB and neonatal morbidity/mortality and that the safety endpoint of early fetal loss be examined. Enrollment in PROLONG was initiated in 2009.

During the review process, FDA recognized the difficulty of conducting a study once the drug was approved and adopted due to guidelines supporting its use in this patient population. As a result FDA required that at least 5% of the patients be enrolled prior to approval of Makena, and that at least 10% of the patients be enrolled from North America. After the requisite 10% of patients from North America were enrolled, Makena received approval in 2011.

Given the approval under the accelerated approval pathway, the Indications and Usage section of the label also provides "The effectiveness of [Hydroxyprogesterone Caproate Injection] is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity."

At the time of approval, the Division director commented that:

"Since the time of the meeting, there has been reconsideration of this view, with new recognition of the impact of "late" preterm birth on infant morbidity and mortality. For this reason, the Advisory Committee's overall opinion regarding the merits of a reduction in preterm births at <37 week gestation as an adequate surrogate for a reduction in fetal and neonatal morbidity/mortality is not likely to reflect views currently held by most obstetricians and pediatricians."

However, data that supports the surrogacy of this endpoint to improved neonatal outcomes has been reported. Late PTB (currently defined as occurring 34 to 36 weeks gestation) represents approximately 75% of all PTB. Late preterm births have been increasingly recognized as contributing to both short-term complications and long-term consequences [Moster et al 2008; Reddy et al 2009; Kugelman and Colin 2013]. At 34 weeks gestation, the brain weight is 65% of that of term weight and formation is incomplete [Kugelman and Colin 2013]. Cerebral palsy, mental retardation, psychosocial disorders and other disabilities reported at greater frequency at 34 to 36 weeks compared to >37 weeks [Moster et al 2008]. In addition, neonatal and infant mortality significantly decreases as delivery is closer to 39 to 40 weeks of gestation [Reddy et al 2009].

5.4.1. Postmarketing Commitments

5.4.1.1. PROLONG Study

PROLONG was managed by numerous Sponsors over this period of time (Hologic, KV Pharmaceutical, Lumara Health, and AMAG Pharma USA, Inc.). In 2014, AMAG acquired Lumara Health, who continued to function as a wholly owned subsidiary of AMAG, and from 2016 onward, the study was managed directly by AMAG.

As a result of enrollment challenges for this orphan indication, AMAG submitted two requests to extend the post-marketing requirement timeline (in 2017 and 2019). Enrollment into PROLONG was completed in 2018, and topline data were shared with FDA in early 2019.

Results from PROLONG are provided in Section 6.2.

5.4.1.2. Infant Follow-up Study

A second post-marketing commitment required a clinical follow-up safety study of children born to women who participated in PROLONG. Study 17P-FU-004 is ongoing; participating sites and study staff are blinded to treatment assignment of the subject's mother during PROLONG.

The primary objective of the study is to determine whether there is a difference in developmental status between children, aged 23 to 25 months after adjustment for gestational age, whose mothers received 17P or vehicle while participating in PROLONG.

Although AMAG has been unblinded to PROLONG, it is still blinded to the treatment arm associated with the infant. As of April 1, 2019, a total of 402 child subjects have been consented to participate by their parent(s)/legal guardian(s). Of these, 232 patients have reached 22 months of age and, therefore, their parent(s)/legal guardian(s) have been mailed the Ages and Stages Questionnaire version 3 (ASQ). Of the 232 ASQ's mailed, to date, 183 (78.9%) questionnaires have been returned. Of the 183 received, 42 patients (23%) have scored positive for developmental delay in at least one of the five ASQ domains and have been referred for Bayley Scales of Infant and Toddler Development and neurological exam.

The estimated date for study completion is 4Q2020.

6. CLINICAL DEVELOPMENT PROGRAM

Summary

- The Makena clinical development program was comprised of two key studies:
  - Meis, the pivotal study that served as the basis for approval
    - 19 sites in US (17P N=310; Vehicle: N=153)
    - Enrollment from 1999 to 2002
  - PROLONG, the confirmatory study
    - 93 sites in 9 countries (17P: N=1130; Vehicle: N=578)
    - Enrollment from 2009 to 2018
- Key design elements of both studies:
  - Patients at 16 to 20 weeks of gestation with history of prior PTB
  - Randomized 2:1 to receive weekly IM injections of 17P (250 mg) or vehicle through 36 weeks of gestation or delivery
  - Maternal endpoints of PTB <37 weeks, <35 weeks, and <32 weeks
  - Neonatal morbidity endpoints (death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 IVH, proven sepsis, or NEC)

Meis Study

- Risk of PTB $<37^0$ weeks gestation was significantly reduced in the 17P group (37.1% vs 54.9%; p=0.0003).
- 17P also reduced the risk of PTB $<35^0$ weeks gestation (p=0.032) and PTB $<32^0$ weeks gestation (p=0.046).
- The composite neonatal morbidity was numerically lower in the 17P group, but the between group difference was not statistically significant.
- There were no statistical differences in neonatal death rate between the two groups, although the incidence of neonatal death was numerically twice the rate in the vehicle group.

PROLONG

- Study was powered to detect a difference in the co-primary endpoints based on the effect size observed in Meis.
- The study did not meet its co-primary efficacy objectives.
  - Rates of PTBs $<35^0$ weeks gestation were lower than expected (11.0% for 17P and 11.5% for vehicle) and not statistically different (p=0.716).
  - No statistically significant difference in the rates of neonatal mortality or morbidity were noted (5.4% for 17P and 5.2% for vehicle; p=0.840).
- No statistically significant differences between groups were observed in the rates of PTB $<32^0$ weeks (p=0.698) or $<37^0$ weeks gestation (p=0.567).
- Rates of fetal/infant death were low and excluded a doubling of the risk of fetal/early infant death (relative risk 0.79 [95% CI 0.37–1.67].
- Treatment with 17P was generally well tolerated, reaffirming that the safety profile remains acceptable and unchanged.

An overview of the key adequate and well-controlled safety and efficacy studies comprising the Makena clinical development program is provided in Table 11.

Table 11: Overview of Key Clinical Studies

	Meis	PROLONG
Year	1999 to 2002	2009 to 2018
Sites	19 sites, US Only	93 sites, 9 countries
Randomization	2:1	2:1
Study Drug	17P 250 mg/mL or vehicle	17P 250 mg/mL or vehicle
Dose	1 dose/week through 36^6 weeks gestation or delivery	1 dose/week through 36^6 weeks gestation or delivery
Study Population	Women 16 to 20 weeks gestation with history of spontaneous preterm delivery	Women 16 to 20 weeks gestation with history of spontaneous preterm delivery
Sample Size	17P: N=310 Vehicle: N=153	17P: N=1130 Vehicle: N=578
Primary Endpoint(s)	• PTB <37 weeks	• PTB <35 weeks • Neonatal Composite Index
Key Secondary Endpoints	• PTB <35 and <32 weeks • Neonatal morbidity/mortality	• PTB <37 and <32 weeks • Fetal/early infant death

In addition to Meis and PROLONG, an initial formulation study (Study 17P-IF-001) was conducted by the NICHD. The study began in February 1998, but treatment was terminated in March 1999 because the active study drug (17P) was recalled by its manufacturer, under the direction of the FDA, due to violations of manufacturing practices potentially affecting the potency of the drug. At the time of termination, only 150 of the proposed 500 patients had been randomized, and no data analysis had been done. Eighty six (86) patients completed the treatment regimen before the study was stopped: 57 on 17P and 29 on Vehicle. Information from this study was considered to be of limited value in supporting either the safety or efficacy of 17P and is not discussed further as it was not part of the initial approval.

6.1. Meis: Pivotal Trial Design and Results

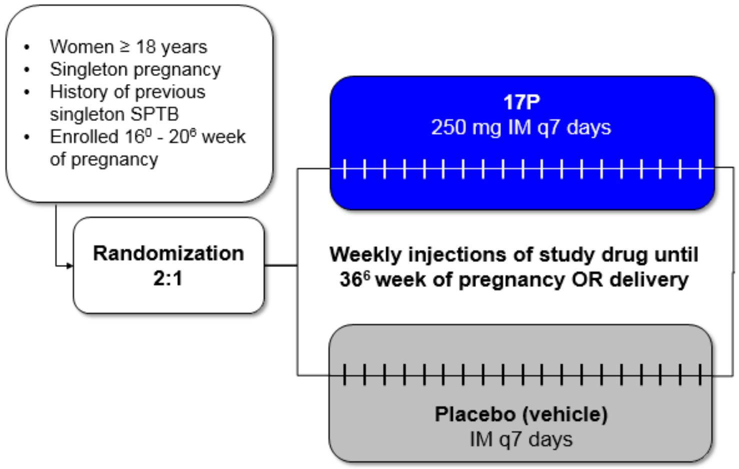
6.1.1. Study Design

The Meis study was conducted by the NICHD through the MFMU from 1999 to 2002. The study was a US-only, double-blind, placebo-controlled trial in pregnant women with a documented history of spontaneous preterm delivery.

The design of the study is depicted in Figure 13. Patients were randomly assigned in a 2:1 ratio, to receive either 17P (250 mg) or vehicle. The vehicle contained all the excipients used in the manufacturing of 17P and contained no active drug. Study drug was administered weekly by IM injection. Weekly study injections continued until delivery or to 36^6 weeks of gestation.

A dose of 250 mg IM was selected based on earlier clinical trials designed to determine if 17P could prevent premature delivery [LeVine 1964; Johnson et al 1975; Yemini et al 1985].

Figure 13: Meis Study Schematic



6.1.1.1. Study Objectives

The primary efficacy outcome was delivery <37^0 weeks. All deliveries occurring from randomization through 36^6 weeks gestation, including miscarriages occurring from 16^0 to 19^6 weeks gestation and elective abortions, were included in the primary outcome.

Secondary objectives of the study were to determine if treatment with 17P:

- reduced the use of tocolytic therapy and/or cervical cerclage.
- reduced neonatal morbidity/mortality.
- reduced the risk of PTB at <35^0 weeks gestation.
- reduced the risk of PTB at <32^0 weeks gestation.
- reduced overall neonatal morbidity based on a composite measure of neonatal morbidity.

6.1.1.2. Statistical Analysis

The primary analysis population was the Intention-To-Treat (ITT), consisting of all randomized patients. Patients with missing outcome data were considered to have delivered at the date last known pregnant.

All statistical comparisons were between 17P and vehicle. Except where explicitly indicated, data were pooled across study centers for all statistical analyses. Patients were analyzed based on the group to which they were randomized.

Summary statistics consisted of numbers and percentages of patients for categorical measures and were compared for statistical significance between treatment groups using the chi-square test, Fisher's Exact test, or the Wilcoxon Rank Sum test for ordered categorical data. For categorical variables, percentages were calculated based on available data.

All statistical tests were reported as 2-sided p-values. The final primary efficacy analysis utilized the Type 1 α=0.034 level of statistical significance as required by the O'Brien Fleming boundary. For all other analyses, no adjustments were made for multiple comparisons and a nominal α=0.05 level of statistical significance was used.

6.1.1.3. Calculation of Gestational Age

Gestational age calculated from the last menstrual period (LMP), date of the first ultrasound (required prior to randomization), and the patient's gestational age at the first ultrasound, derived from the ultrasound measurements. If the LMP date was sure and the ultrasound confirmed the gestational age within a specified number of days, the LMP derived gestational age was used. Otherwise, the ultrasound was used to determine project gestational age.

6.1.2. Study Enrollment

Women were enrolled at 19 clinical centers in the US. In 2002, the prespecified stopping criterion (p=0.015) for efficacy was met at the second interim analysis and the Data Monitoring Committee recommended stopping the trial prior to enrolling the proposed 500 patients. Stopping criteria were in place to assure that once efficacy was established the drug could be made available to all appropriate patients.

6.1.3. Demographics and Baseline Characteristics

In Meis, patients randomized to the two treatment groups were comparable in mean age, race, body mass index (BMI) prior to pregnancy, marital status, years of education, and substance use during pregnancy (Table 12). The majority of patients were Black (approximately 59%), with a mean age of 26.2 years. The mean pre-pregnancy BMI was approximately 26.6 kg/m^2. Approximately 50% of patients in the study were married, and approximately 22% smoked, approximately 8% consumed alcohol, and 3% used illicit drugs during the study pregnancy.

Table 12: Demographic and Baseline Characteristics (Intent-to-Treat Population, Meis)

Characteristic	17P (N=310) n (%)	Vehicle (N=153) n (%)
Age, years		
Mean (SD)	26.0 (5.6)	26.5 (5.4)
Race/ethnic group		
African American	183 (59.0)	90 (58.8)
Caucasian	79 (25.5)	34 (22.2)
Hispanic	43 (13.9)	26 (17.0)
Asian	2 (0.6)	1 (0.7)
Other	3 (1.0)	2 (1.3)
Marital status		
Married or living with partner	159 (51.3)	71 (46.4)
Divorced, widowed, or separated	32 (10.3)	18 (11.8)

Characteristic	17P (N=310) n (%)	Vehicle (N=153) n (%)
Never married	119 (38.4)	64 (41.8)
Pre-pregnancy BMI (kg/m^2)		
Mean (SD)	26.9 (7.9)	26.0 (7.0)
Years of education		
Mean (SD)	11.7 (2.3)	11.9 (2.3)
Substance use during current pregnancy		
Smoking	70 (22.6)	30 (19.6)
Alcohol	27 (8.7)	10 (6.5)
Illicit drugs	11 (3.5)	4 (2.6)

Source: Study 17P-CT-002 Table 11-1.

Obstetrical histories were comparable in the 17P and vehicle groups for gestational age at randomization, gestational age of qualifying delivery, number of previous term deliveries, percentage with previous miscarriages and stillbirths (Table 13). Compared to the vehicle group, the 17P patients had significantly fewer previous preterm deliveries, fewer previous spontaneous preterm deliveries, and a lower percentage of patients with >1 previous preterm delivery.

Table 13: Obstetrical Risk Factors for Preterm Delivery (Intent-to-Treat Population, Meis)

Obstetrical History	17P (N=310) n (%)	Vehicle (N=153) n (%)	p-value
No. of previous preterm deliveries			0.007[a]
Mean (SD)	1.4 (0.7)	1.6 (0.9)	
>1 Previous preterm birth	86 (27.7)	63 (41.2)	0.004[b]
No. of previous SPTB			0.002[a]
Mean (SD)	1.3 (0.7)	1.5 (0.9)	
No. of previous term deliveries			0.665[a]
Mean (SD)	0.8 (1.1)	0.7 (1.0)	
Duration of gestation at randomization, week			0.593[a]
Mean (SD)	18.9 (1.4)	18.8 (1.5)	
Gestational age of qualifying delivery, week			0.208[a]
Mean (SD)	30.6 (4.6)	31.3 (4.2)	
Previous miscarriage	93 (30.0)	57 (37.3)	0.117[b]
Previous stillbirth	31 (10.0)	13 (8.5)	0.604[b]
Infection during pregnancy (before randomization)	98 (31.6)	55 (35.9)	0.351[b]
Corticosteroids during pregnancy (before randomization)	5 (1.6)	8 (5.2)	0.036[c]

Source: Study 17P-CT-002 Table 11-2.
[a] p-value from the Wilcoxon rank sum test.
[b] p-value from the chi-square test.
[c] p-value from the Fisher exact test.

6.1.4. Efficacy

6.1.4.1. Primary Efficacy Endpoint Analysis: Preterm Birth

The risk of delivering prior to 37^0 weeks gestation in the Meis study was significantly reduced in the 17P group (37.1% vs 54.9%; p=0.0003) (Table 14).

Table 14: Percentage of Patients with Delivery <37^0 Weeks of Gestation (Meis)

Data Source	17P n (%)	Vehicle n (%)	Nominal p-value[a]	Treatment difference [95% CI[b]]
ITT Population	115 (37.1)	84 (54.9)	0.0003	-17.8% [-28%, -7%]
Only available data	111 (36.3)	84 (54.9)	0.0000	-18.6% [-29%, -8%]

Source: FDA Background Gestiva (August 2, 2006), Table 4.
Note: ITT population was all randomized patients (17P N=310; Vehicle N=153). The 4 patients with missing outcome data were classified as having a preterm birth of <37^0 weeks (i.e., treatment failure). "Only available data" does not include the 4 patients in the 17P group with missing outcome data.
[a] Chi-square test. Adjusting for interim analyses, p-values should be compared to 0.035 rather than the usual 0.05.
[b] CI adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, a p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

Because there was an imbalance between the 17P and vehicle groups with regard to the number of previous preterm deliveries, an analysis with adjustment for this variable was performed. The adjusted relative risk of delivery before 37 weeks of gestation in the 17P group as compared with the vehicle group was 0.70 (95% CI, 0.57 to 0.85).

6.1.4.2. Secondary Endpoint Analyses

6.1.4.2.1. Preterm Birth <35 and <32 Weeks Gestational Age

Despite the fact that the study was not powered to determine statistically significant differences in births at <35^0 and <32^0 weeks gestation, 17P demonstrated clinically important reductions in the number of births before 35^0 weeks (p=0.0324) and before 32^0 weeks gestation (p=0.0458) (Table 15).

Table 15: Percentage of Patients with Delivery <35^0 and <32^0 Weeks of Gestation (Meis)

Pregnancy Outcome	17P (N=310) n (%)	Vehicle (N=153) n (%)	Nominal p-value[a]
Delivery <35^0	67 (21.6)	47 (30.7)	0.032
Delivery <32^0	39 (12.6)	30 (19.6)	0.046

Source: FDA Background Gestiva (August 2, 2006), Table 6.
Data presented are from the ITT population (i.e., all randomized patients). The 4 patients with missing outcome data were classified as having a preterm birth <37^0 weeks (i.e., treatment failure).
[a] Adjusting for interim analyses, p-values should be compared to 0.035 rather than the usual 0.05.

At the <37^0, <35^0, and <32^0 weeks gestation, the percentage of deliveries was numerically lower in the 17P treatment arm (Table 16). There was no difference between treatment groups for the percentages of deliveries <28^0 weeks.

Table 16: Percentage of Patients with Delivery <37^0, 35^0, 32^0, and 28^0 Weeks of Gestation (Intent-to-Treat Population - Meis)

Time of Delivery (Gestational Age)	17P N=310 %	Vehicle N=153 %	Treatment difference[a] [95% CI[b]]
<37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
<35^0 weeks	21.6	30.7	-9.1% [-18%, 0.3%]
<32^0 weeks	12.6	19.6	-7.05 [-14%, 0.8%]
<28^0 weeks	10.0	10.5	-0.5% [-6.9, 5.9]

Source: FDA Background Gestiva (August 2, 2006), Table 7.
[a] Chi-square test.
[b] CI based on a t-test are adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, a p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

6.1.4.2.2. Neonatal Morbidity and Mortality

A prespecified key secondary endpoint was the incidence rate of having a qualifying event in the composite neonatal morbidity index. The neonatal composite index included neonates with death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 IVH, proven sepsis, or NEC) was lower in the 17P group, but the between group difference was not statistically significant (11.9% vs 17.2%; p=0.119) (Table 17).

The study was not powered to detect statistically significant differences between 17P and vehicle treatments in neonatal mortality or morbidities, however, reductions were observed with 17P in the rates of NEC, any grade of IVH, and the need for supplemental oxygen.

Although the overall rate of neonatal deaths was lower in the 17P arm versus vehicle, it was observed that miscarriages (defined as spontaneous loss of fetus from 16^0 to 19^6 weeks gestation) were numerically higher in the 17P arm, as were stillbirths (defined as birth of an infant ≥20 weeks gestation who died prior to delivery) (Table 18). The incidence of neonatal death was twice the rate in the vehicle group, but the between group difference was not statistically significant (p=0.116). Two other NICHD MFMU studies were subsequently conducted; when miscarriage and stillbirth are reviewed in the totality of these studies, the rates were similar between 17P and vehicle [Rouse et al 2007, Caritis et al 2009].

Table 17: Neonatal Morbidity for Live Births (Meis)

Morbidity	17P (N=295) n (%)	Vehicle (N=151) n (%)
Transient tachypnea	11 (3.7)	11 (7.3)
Respiratory distress syndrome	29 (9.9)	23 (15.3)
Bronchopulmonary dysplasia	4 (1.4)	5 (3.3)
Persistent pulmonary hypertension	2 (0.7)	1 (0.7)
Ventilator support	26 (8.9)	22 (14.8)
Supplemental oxygen	45 (15.4)	36 (24.2)
Patent ductus arteriosus	7 (2.4)	8 (5.4)
Seizures	3 (1.0)	0
Any intraventricular hemorrhage	4 (1.4)	8 (5.3)
Grade 3 or 4 IVH	2 (0.7)	0
Other intracranial hemorrhage	1 (0.3)	2 (1.3)
Retinopathy of prematurity	5 (1.7)	5 (3.3)
Proven newborn sepsis	9 (3.1)	4 (2.6)
Confirmed pneumonia	3 (1.0)	4 (2.7)
Necrotizing enterocolitis	0	4 (2.7)
Composite Neonatal Morbidity Score[a]	35 (11.9)	26 (17.2)

Source: FDA Background Gestiva (August 2, 2006), Table 10.
[a] The composite neonatal morbidity measure counted any liveborn infant who experienced death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC.

Table 18: Miscarriages, Stillbirths, and Neonatal Deaths (Meis)

Pregnancy Outcome	17P (N=306) n (%)	Vehicle (N=153) n (%)	Nominal p-value[a]
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.689**
Miscarriages <20 weeks gestation	5 (1.6)	0	0.175
Stillbirth	6 (2.0)	2 (1.3)	0.725
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.116

Source: FDA Background Gestiva (August 2, 2006), Table 8.
[a] No adjustment for multiple comparisons.

6.1.4.3. Subgroup Analysis

A post-hoc subgroup analysis of results for PTB <32 weeks, and <35 weeks stratified by race was conducted (Table 19). This analysis demonstrated significant reductions in PTB across all gestational ages in Black patients. Additionally, significant reductions in PTB <37 weeks were observed in non-Black patients. Of note, the study was stopped early based on <37 weeks data, and Blacks made up 59% of the study population relative to 41% non-Black patients.

Table 19: Preterm Birth Stratified by Race (Intent-to-Treat Population, Meis)

	17P (N=310) n/N (%)	Vehicle (N=153) n/N (%)	Difference in % (95% CI)
<32^0 Weeks Gestation			
Black	23/183 (12.6)	22/90 (24.4)	-11.9 (-22.0, -1.8)
Non-Black	16/127 (12.6)	8/63 (12.7)	-0.1 (-10.1, 9.9)
<35^0 Weeks Gestation			
Black	39/183 (21.3)	32/90 (35.6)	-14.2 (-25.8, -2.7)
Non-Black	28/127 (22.0)	15/63 (23.8)	-1.8 (-14.5, 11.0)
<37^0 Weeks Gestation			
Black	66/183 (36.1)	47/90 (52.2)	-16.2 (-28.6, -3.7)
Non-Black	49/127 (38.6)	37/63 (58.7)	-20.1 (-35.0, -5.3)

Source: FDA Table 1, FDA Table 2, and FDA Table 3

6.1.5. Safety

The most common type of adverse event (AE) reported during the study was injection site reactions, which was expected considering that patients received weekly 1 mL IM injections. Pain, swelling, itching, and nodule formation were among the most common reactions regardless whether the solution being injected was 17P or vehicle. However, there was a significantly higher incidence of swelling at the injection site in the 17P group than vehicle (17.1% vs. 7.8%; p=0.007). Nevertheless, few women (1.7%) discontinued the study due to injection site reactions.

The incidence of pregnancy complications, such as preeclampsia, gestational diabetes, or clinical chorioamnionitis, as well as the incidence of serious adverse events (SAEs), was not different between the 17P and vehicle groups. SAEs reported were predominately miscarriages, stillbirths, and neonatal deaths, which were not unexpected events in the high-risk patient population, and were considered by the Investigator to be unrelated to study drug.

6.2. PROLONG: Trial Design and Results

As noted above, Meis was a US-only study that demonstrated that treatment with 17P resulted in a statistically significant reduction in PTB (<37 weeks gestation). The endpoint of PTB defined as <37 weeks gestation was considered an adequate surrogate for clinical benefit to support approval of 17P under subpart H regulations with a single trial. A confirmatory trial

(PROLONG) was required, and FDA requested that PTB defined as <35 weeks and an effect on the neonatal composite index be analyzed as co-primary endpoints.

PROLONG was an international, double-blind, randomized, placebo-controlled trial in pregnant women with a documented history of spontaneous preterm delivery conducted from 2009 through 2018.

6.2.1. Study Design

The design of PROLONG is depicted in Figure 14.

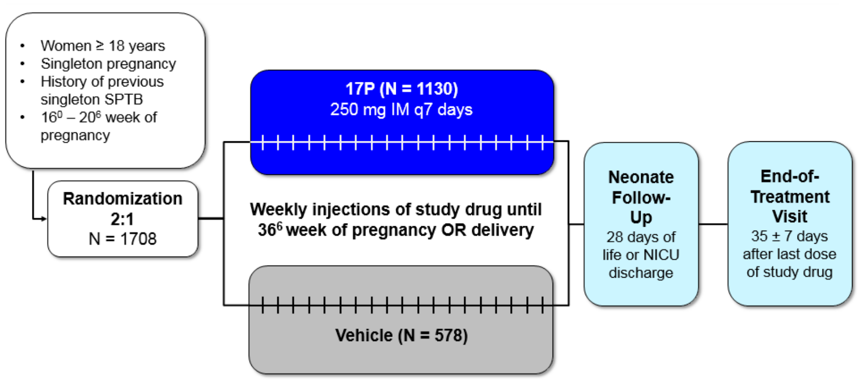
Each patient was randomized in a 2:1 ratio to receive either 17P (250 mg/mL) or vehicle, respectively. Patients received weekly injections of study drug from randomization (16^0 through 20^6 weeks of gestation) through 36^6 weeks of gestation or delivery, whichever occurred first. All injections were administered at the study site.

Randomized patients were to be followed for efficacy outcomes through the date of delivery and for AEs up to the End-of-Treatment Period Visit, defined as 35 ± 7 days after the last dose of study drug. Neonates of randomized patients were followed until Day 28 or the date of discharge from the NICU or equivalent, whichever occurred later. Following delivery, follow-up visits were conducted for both mother and baby.

A prospective, non-interventional infant follow-up study, similar to what was done for Meis, is also being conducted for PROLONG, and is described in Section 5.4.1.2.

Pharmacokinetic (PK) assessments were made based on a sparse sampling of approximately 450 patients (300 active and 150 vehicle), stratified according to BMI to analyze the dose-plasma concentration-time relationship of 17P.

Figure 14: Study Schematic (PROLONG)



6.2.1.1. Study Objectives

There were two co-primary objectives of the study:

- Determine if treatment with 17P injection, 250 mg/mL reduced the rate of PTB <35^0 weeks of gestation in women with a singleton pregnancy, aged 18 years or older, with a previous singleton spontaneous preterm delivery.

- Determine if 17P reduced the rate of neonatal mortality or morbidity. Neonatal mortality or morbidity was measured by a composite index comprised of:
  - Neonatal death
  - Grade 3 or 4 IVH
  - RDS
  - BPD
  - NEC
  - Proven sepsis

A key secondary objective of the study was to exclude a doubling of the risk of fetal/early infant death, which was included to address concerns from the original review. Fetal/early infant death was defined as spontaneous abortion/miscarriage (delivery from 16^0 through 19^6 weeks of gestation) or neonatal death (from minutes after birth until 28 days of life) occurring in liveborns born at <24 weeks gestation or stillbirth (antepartum or intrapartum death from 20 weeks gestation through term), in the 17P group compared to the vehicle group.

Additional secondary objectives were to:

- Determine if 17P reduced the rate of PTB <32^0 weeks of gestation.
- Determine if 17P reduced the rate of PTB <37^0 weeks of gestation.
- Determine if 17P reduced the rate of stillbirth, defined as all stillbirths/fetal deaths/in-utero fetal losses occurring from 20 weeks gestation until term.
- Determine if 17P reduced the rate of neonatal death (from minutes after birth until 28 days of life) occurring in liveborns born at 24 weeks gestation or greater.
- Evaluate the PK/pharmacodynamics of 17P in a subset of pregnant women.

6.2.1.2. Study Population

Study eligibility criteria for PROLONG were based on those used for women in Meis.

Key inclusion criteria included:

- Age ≥18 years
- Singleton gestation
- Project gestational age between 16^0 weeks and 20^6 weeks of gestation at the time of randomization, based on clinical information and evaluation of the first ultrasound
- Documented history of a previous singleton spontaneous preterm delivery, defined as delivery from 20^0 to 36^6 weeks of gestation following spontaneous preterm labor or preterm premature rupture of membranes (pPROM)

Key exclusion criteria included:

- Multifetal gestation
- Known major fetal anomaly or fetal demise (as determined by ultrasound examination between 14^0 through 20^3 weeks of gestation)
- Receipt of a progestin during the current pregnancy AND met one of the following criteria were excluded.
  - Progestin was administered in the 4 weeks preceding the first dose of study medication
  - Patients received HPC
  - Progestin was administered by a route other than oral or intra-vaginal.
- Heparin therapy during current pregnancy or history of thromboembolic disease.
- Maternal medical/obstetrical complications including cerclage, hypertension requiring medication, or seizure disorder
- Presence of a uterine anomaly (except uterine fibroids)
- Prior participation in the trial in a previous pregnancy
- Known hypersensitivity to HPC injection or its components.

6.2.1.3. Statistical Methodology

Analyses were conducted as per the Statistical Analysis Plan, which was approved prior to database lock. All statistical analyses in PROLONG were performed using SAS Version 9.4

6.2.1.3.1. Analysis Populations

Efficacy analyses were conducted using the ITT Population, the Per Protocol (PP) Population, and the Liveborn Neonatal Population. The ITT Population consisted of all randomized patients regardless of whether they received study medication. The efficacy analysis utilized the ITT population which included all randomized patients. No patients were excluded from the efficacy analysis.

The PP Population consisted of all patients who complied with the study protocol. Compliance was based on the following criteria: patient did not have a major protocol deviation potentially affecting efficacy or the evaluation of efficacy as determined by the Sponsor in a blinded review, received the correct blinded study medication for the majority of the duration of study drug receipt, was at least 90% compliant with study medication (based on receipt of study medication through 36^6 weeks of gestation or delivery, whichever occurred first), and had outcome data available.

The Liveborn Neonatal Population consisted of all babies of randomized women who were liveborn and have morbidity data available.

The Safety Population consisted of patients who received any amount of blinded medication.

6.2.1.3.2. Determination of Sample Size

PROLONG was approximately four times the size of the Meis trial and was powered to detect a 30% and 35% treatment difference in the co-primary endpoints (PTB <35 weeks gestation and neonatal composite index).

With 2:1 randomization of 17P and vehicle, a total of 1707 patients were needed to detect a 30% reduction in PTB <35 weeks (from 30% to 21%), giving the study 98% power assuming two-sided type 1 error at 5%. A total of 1665 liveborn infants were needed to detect a 35% reduction in the neonatal composite index (from 17% to 11%), giving 90% power assuming two-sided type 1 error at 5%. Assuming 2.5% of pregnancies result in miscarriage or stillbirth, another 42 women were required (N=1707; 1138 active and 569 vehicle).

Since the outcome measures were co-primary endpoints, the power to detect statistically significant differences between treatments was reduced:

- If outcome measures were independent, power was 88.2%
- If outcome measures were highly correlated (as with Meis), power was 90%.

Assuming 4% fetal/early infant death rate in both treatment arms, a sample size of 1707 provided 82.8% power to rule out a doubling of risk of early fetal/infant death (i.e. the upper bound of the confidence interval for relative risk of 17P compared to vehicle was ≤2.0).

6.2.1.3.3. Interim Analysis

No interim analysis of efficacy was conducted for PROLONG.

6.2.1.3.4. Efficacy Analyses

Primary Efficacy Analyses

Statistically significant differences between the 17P and vehicle treatments in the percentage of patients who delivered <35^0 weeks gestation were determined using a Cochran-Mantel-Haenszel (CMH) test stratified by project gestational age at randomization (16^0 weeks – 17^6 weeks gestation and 18^0 weeks – 20^6 weeks gestation).

The number and percentage of neonates in the Liveborn Neonatal Population with the neonatal composite index are presented by project gestational age at randomization stratum and overall for each treatment group. Statistically significant differences between the 17P and vehicle treatment groups were determined using the CMH test stratified by project gestational age at randomization.

Patients with missing delivery data who were known to be pregnant at ≥35 weeks were included in the analysis as not having a PTB<35 weeks. Multiple imputation was used to address other missing data.

Secondary Efficacy Analyses

Statistically significant differences between the 17P and vehicle treatments were determined using the CMH test stratified by project gestational age at randomization. Multiple imputation was used to address missing data for the secondary outcomes as well as was the date last known pregnant as described above for PTB <35 weeks.

6.2.1.3.5. Safety Analyses

Primary Safety Analysis

Analysis of the safety outcome of fetal/early infant death was conducted in the ITT Population. For each gestational age at randomization stratum and overall, the percentage of patients with a fetal/early infant death is provided. The relative risk of fetal/early infant death for the 17P treatment relative to the vehicle treatment was determined using the CMH procedure stratified by project gestational age at randomization stratum. A two-sided 95% CI for the relative risk was constructed using the CMH method adjusted for project gestational age at randomization stratum. If the upper bound of the 95% CI was ≤2.0, a doubling in the risk of fetal/early infant death was ruled out.

6.2.1.3.6. Other Analyses

Study Drug Administration

Dosing information was summarized as the number of injections received and compliance with the expected dosing regimen. Differences between treatment groups in the number of injections and compliance were determined using the Wilcoxon Rank Sum test and for the percentage of patients fully compliant, with the chi-square test.

Gestational Age at Delivery and Neonatal Outcome

A logistic regression model of the neonatal composite index with covariate terms for treatment and gestational age at randomization as a continuous variable was conducted. The odds ratio and 95% CI for the odds ratio for each covariate were calculated.

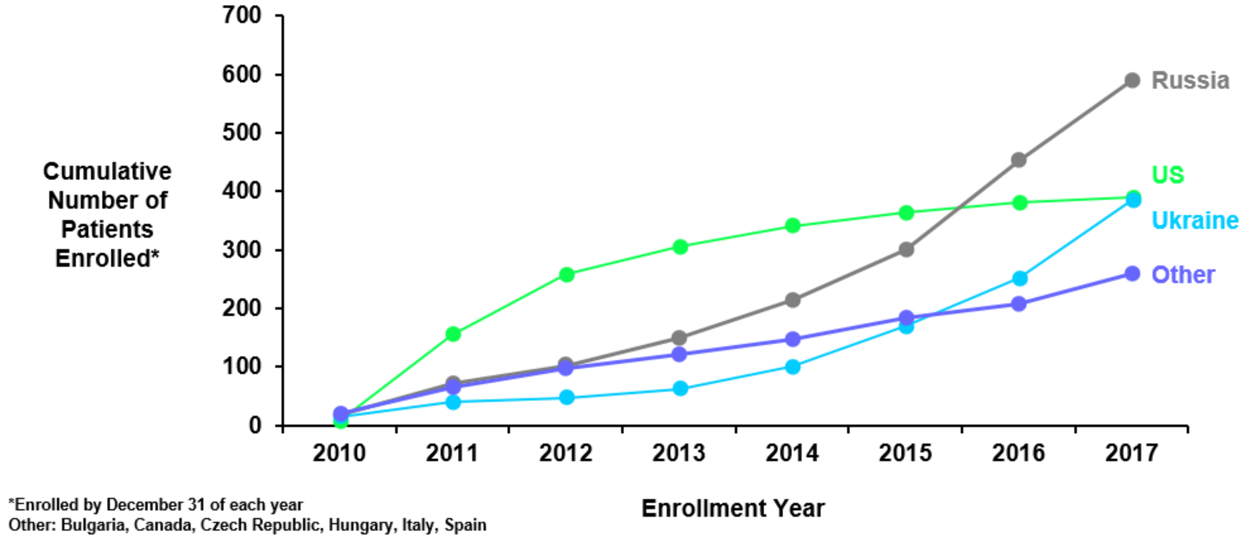
6.2.1.4. Calculation of Gestational Age

Similar to Meis, gestational age in PROLONG was calculated from the patient's menstrual history and measurements obtained at the patient's first ultrasound.

6.2.2. Study Enrollment

Enrollment into PROLONG began in 2009. Following approval of Makena in the US, recruitment in the US became increasingly difficult. Cumulative enrollment rates by year and geographical region showed that, although the overall study enrollment occurred from 2009 to 2018, there was a gradual decline in enrollment rates in the US each year, with nearly 80% of all US patients enrolled by 2013 and nearly 90% by 2014 (Figure 15). By contrast, enrollment rates in Russia and the Ukraine continued to increase with time. It is important to note that both US and ex-US sites were held to the same ICH/GCP standards and ethic committee approvals. Sites in Russia and Ukraine were audited and there were no Major or Critical Findings.

Figure 15: PROLONG Cumulative Enrollment at Year-end (All Countries)



Source: PROLONG CSR, Listing 16.1.1.1.

There were 43 sites in the US that enrolled at least 1 patient in PROLONG. Most of these sites, in contrast to Meis, were in non-urban areas, with 25% of patients residing on military bases.

Table 20 provides an overview of patient enrollment by country. Russia and Ukraine accounted for 61% of study patients, and the US had 23%. The remaining 16% of patients were enrolled in Hungary, Spain, Bulgaria, Canada, Czech Republic, and Italy, each enrolling less than 100 patients.

Table 20: Patient Enrollment by Country (PROLONG)

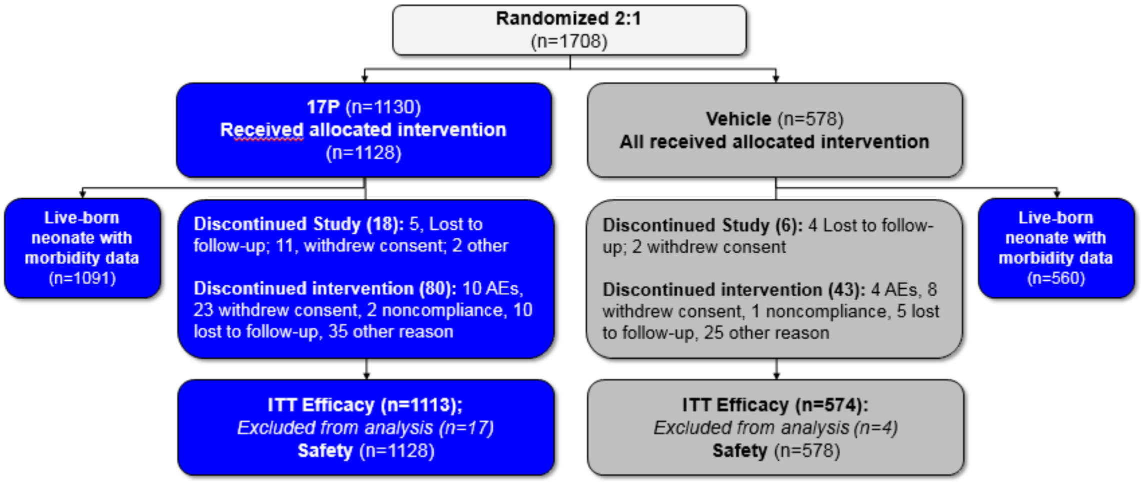
Country	Sites (n)	Patients Receiving Trial Injection (n)	Patients Randomized (n)	Randomized to 17P (n)	Randomized to Vehicle (n)
Overall	**93**	**1740**	**1708**	**1130**	**578**
Russia	12	628	621	414	207
Ukraine	10	424	420	277	143
United States	41	407	391	258	133
Hungary	5	91	91	59	32
Spain	8	85	85	57	28
Bulgaria	6	50	50	33	17
Canada	5	34	31	19	12
Czech	5	15	14	9	5
Italy	1	6	5	4	1

Source: PROLONG CSR Table 14.1.1.1.2.

6.2.3. Disposition

The disposition of patients in PROLONG is presented in Figure 16. A total of 1708 patients were randomized (1130 to 17P and 578 to Vehicle) and included in the ITT Population.

Figure 16: Disposition of Patients (PROLONG)



Source: PROLONG CSR, Figure 1.

A summary of analysis populations is provided in Table 21.

Table 21: Analysis Populations (PROLONG)

	17P n (%)	Vehicle n (%)
Patients randomized (ITT Population)	1130	578
Patients who are protocol compliant (PP Population)	1057 (93.5)	530 (91.7)
Patients excluded from the PP Population:	73 (6.5)	48 (8.3)
Major protocol deviation [a]	29 (2.6)	30 (5.2)
<90% blinded study medication compliance [b]	46 (4.1)	21 (3.6)
No delivery data	18 (1.6)	6 (1.0)
Safety Population	1128 (99.8)	578 (100)
Number of liveborn infants with morbidity data available	1091 (96.5)	560 (96.9)

Source: PROLONG CSR Table 14.1.1.4.
[a] Includes not meeting inclusion/exclusion criteria.
[b] 90% study medication compliance was based on a 10-day cycle.
[c] The Liveborn Neonatal Population consists of all babies of randomized women who were liveborn and have morbidity data available. Excluded are stillbirths (n=16), miscarriages (n=10), elective abortions (n=2), babies for which insufficient data were available to determine liveborn status (n=5) and babies with no morbidity data (n=1).

6.2.4. Demographics and Baseline Characteristics

The treatment groups were comparable across demographic (Table 22), social history (Table 23), and obstetrical characteristics, as well as for social history characteristics (Table 24).

Although the study entry criteria were similar between PROLONG and Meis, the enrolled patient populations differed. When comparing demographics and baseline characteristics of patients enrolled in the two studies, the differences across race and other potential surrogates of socioeconomic status were noteworthy, with Meis representing a much higher-risk population. In comparison to Meis, PROLONG patients had lower risk for spontaneous PTB based on the following key features:

- The majority of patients were White (approximately 89%), non-Hispanic or Latino (approximately 91%) with a mean age of 30 years.
- Approximately 90% of patients were married at the time of study entry.
- Substance use during pregnancy was low in PROLONG (~8% smoked, ~3% consumed alcohol, and 1.4% used illicit drugs).
- Approximately 15% of patients in PROLONG reported >1 previous spontaneous preterm delivery (compared to ~35% in Meis).

Table 22: Demographic and Baseline Characteristics (Intent-to-Treat Population, PROLONG)

	17P (N=1130) n (%)	Vehicle (N=578) n (%)
Age (years), n	1130	578
Mean (SD)	30.0 (5.17)	29.9 (5.22)
Ethnicity		
Hispanic or Latino	101 (8.9)	54 (9.3)
Non-Hispanic or Latino	1029 (91.1)	524 (90.7)
Race		
White	1004 (88.8)	504 (87.2)
Black, African American/African heritage	73 (6.5)	41 (7.1)
Native Hawaiian/Pacific Islander	1 (0.1)	0 (0)
Asian	23 (2.0)	22 (3.8)
American Indian or Alaska native	3 (0.3)	0 (0)
Mixed race	8 (0.7)	7 (1.2)
Other	18 (1.6)	4 (0.7)
Pre-pregnancy BMI (kg/m^2), n	1130	577
Mean (SD)	24.3 (7.05)	24.7 (8.65)

Source: PROLONG CSR Table 14.1.3.1.

Table 23: Social History at Baseline (Intent-to-Treat Population, PROLONG)

	17P (N=1130) n (%)	Vehicle (N=578) n (%)
Marital Status		
Married/living with partner	1013 (89.6)	522 (90.3)
Divorced/widowed/separated	31 (2.7)	16 (2.8)
Never married	86 (7.6)	40 (6.9)
Years of Education, n	1129	578
Mean (SD)	13.0 (2.37)	13.0 (2.36)
Substance Use During Current Pregnancy		
Smoking	92 (8.1)	41 (7.1)
Alcohol	24 (2.1)	18 (3.1)
Illicit drugs	16 (1.4)	8 (1.4)

Source: PROLONG CSR Table 14.1.3.2.

Table 24: Obstetrical Risk Factors for Preterm Delivery (Intent-to-Treat Population, PROLONG)

	17P (N=1130) n (%)	Vehicle (N=578) n (%)	p-value[a]
Gestational age at randomization (weeks)[b]			
$<16^0$	6 (0.5)	4 (0.7)	0.051
16^0-17^6	495 (43.8)	236 (40.8)	
18^0-20^6	28 (55.6)	333 (57.6)	
$>20^6$	1 (0.1)	5 (0.9)	
Number of previous preterm deliveries			
Only 1 previous spontaneous preterm delivery	964 (85.3)	494 (85.5)	0.828
>1 previous spontaneous preterm delivery	166 (14.7)	82 (14.2)	
Number of previous miscarriages			
None	644 (57.0)	337 (58.3)	0.873
1	278 (24.6)	139 (24.0)	
>1	208 (18.4)	102 (17.6)	
Number of previous stillbirths			
None	1071 (94.8)	543 (93.9)	0.762
1	55 (4.9)	33 (5.7)	
>1	4 (0.4)	2 (0.3)	
Gestational age of qualifying delivery (weeks)			
20^0-$<28^0$	238 (21.1)	102 (17.6)	0.425
28^0-$<32^0$	202 (17.9)	105 (18.2)	
32^0-$<35^0$	347 (30.7)	187 (32.4)	
35^0-$<37^0$	340 (30.1)	181 (31.3)	

Source: PROLONG CSR Table 14.1.3.3 and PROLONG CSR Erratum Table 14.1.3.4.
[a] p-value is for 17P vs. Vehicle and is from chi-square test or Fisher's exact text for dichotomous variables and the Wilcoxon Rank Sum test for ordinal and continuous variables.
[b] Refers to project gestational age which is the correct gestational age calculated from the patient's menstrual history and measurements obtained at the patient's first ultrasound
[c] Cervical length measurement was not captured for some patients.

6.2.5. Exposure to Study Treatment

Treatment groups were comparable in the mean number of injections received (17.6 and 17.5 injections for patients in the 17P and vehicle groups, respectively; Table 25). More than 96% of patients were considered in full compliance with the injection schedule.

Table 25: Study Medication Administration (Intent-to-Treat Population, PROLONG)

	17P (N=1130)	Vehicle (N=578)	p-value[a]
Number of Injections Received			
N	1128	578	0.991
Mean (SD)	17.6 (3.65)	17.5 (3.81)	
Injection Schedule Compliance (%)[b]			
N	1128	578	0.957
Mean (SD)	96.0 (13.93)	96.4 (13.12)	
Number of patients with Full Compliance[c]	1087 (96.2)	561 (97.1)	0.484
Injection Schedule Compliance (%)			
<80 %	33 (2.9)	17 (2.9)	0.845
80-120 %	44 (3.9)	19 (3.3)	
>120 %	1051 (93.0)	542 (93.8)	

Source: PROLONG CSR Table 14.3.4.
[a] p-value for the Number of Injections Received and Compliance (a) is from the Wilcoxon Rank Sum Test. p-value for Full Compliance (b) and Compliance (c) is from the chi-square test.
[b] Compliance is defined as the number of injections received divided by the number of expected injections (x 100) based on a 7-day injection schedule.
[c] Full compliance is defined as ≥90% compliance based on a 10-day injection schedule.

6.2.6. Efficacy

The study did not meet its co-primary efficacy objectives, which were to demonstrate a reduction in PTB prior to 35^0 weeks gestation and in the neonatal composite index. When comparing demographics and baseline characteristics of patients enrolled in the two studies, the differences across race and other potential surrogates of socioeconomic status were noteworthy, with Meis representing a much higher-risk population.

6.2.6.1. Primary Endpoint Analysis

Rate of PTB

Rates of PTB $<35^0$ weeks were low in both groups and not statistically different between groups (11.0% for 17P and 11.5% for vehicle; Table 26).

Neonatal Composite Index

No statistically significant difference in the rates of neonatal mortality or morbidity as measured by the neonatal composite index, were noted (5.4% for 17P and 5.2% for vehicle; Table 26).

The incidence of individual components of the neonatal composite were similar between treatment groups (Table 27). RDS accounted for almost all of the infants who met the criteria for this index, and rates across treatment groups were not statistically significantly different, at 4.9% and 4.6% in neonates born to patients in the 17P treatment group and vehicle group, respectively

Table 26: Primary Efficacy Outcomes (PROLONG)

Primary Efficacy Outcomes	17P (N=1130)	Vehicle (N=578)
PTB <35[0] Weeks Gestation (ITT Population)		
Overall Outcome rate n/N* (%)	**122/1113 (11.0)**	**66/574 (11.5)**
p-value[a]	0.716	
Relative risk (95% CI)	0.95 (0.71, 1.26)	
Neonatal Composite Index (Liveborn Neonatal Population)	**(N=1091)**	**(N=560)**
Neonatal Composite Index – Overall, n (%)[d]	**59 (5.4)**	**29 (5.2)**
p-value[b]	0.840	
Relative risk (95% CI)	1.05 (0.68, 1.61)	

Source: PROLONG CSR Table 14.2.1.1.1 and Table 14.2.1.1.2, PROLONG Ad Hoc Table 14.2.1.1.1.26.
[a] p-value from the Cochran-Mantel-Haenszel test.
[b] p-value from the Cochran-Mantel-Haenszel test.
N*=number of ITT patients with non-missing delivery data or who were known to still be pregnant at 35[0] weeks in the specified category.
The composite index was defined as a liveborn neonate with any of the following occurring at any time during the birth hospitalization up through discharge from the NICU: neonatal death, Grade 3 or 4 IVH, RDS, BPD, NEC, or proven sepsis.

Table 27: Components of Neonatal Composite Index from NICU Outcomes: Liveborn Neonatal Population (PROLONG)

	17P (N=1091) n (%)	Vehicle (N=560) n (%)
Neonatal Composite Index – Overall	**59 (5.4)**	**29 (5.2)**
Neonatal death prior to discharge	3 (0.3)	2 (0.4)
Grade 3/4 intraventricular hemorrhage	2 (0.2)	1 (0.2)
Respiratory distress syndrome	54 (4.9)	26 (4.6)
Bronchopulmonary dysplasia	6 (0.5)	1 (0.2)
Necrotizing enterocolitis	2 (0.2)	2 (0.4)
Proven sepsis	5 (0.5)	3 (0.5)

Source: PROLONG CSR Table 14.2.4.1
N=number of babies in the Liveborn Neonatal population in the specified treatment group.

6.2.6.1.1. Assessment for Interaction

Logistic regression analyses of PTB <35^0 weeks gestation and neonatal composite index were conducted to assess whether there was an interaction between treatment and gestational age at the time of randomization. The logistic regression analyses showed no significant interaction between treatment and gestational age at randomization for either primary outcome, indicating a consistent treatment effect regardless of gestational age at randomization.

6.2.6.2. Key Secondary Endpoint Analyses

6.2.6.2.1. Preterm Birth <37 and <32 Weeks of Gestation

There were no statistically significant differences in births at <37^0 (p=0.567) or <32^0 weeks gestation (p=0.698) (Table 28). Rates of PTB were comparable between treatment groups regardless of gestational age at randomization.

Table 28: Percentage of Patients with Delivery <37^0 and <32^0 Weeks of Gestation (Intent-to-Treat Population, PROLONG)

	17P (N=1130) n/N* (%)	Vehicle (N=578) n/N* (%)
<32^0 Weeks Gestation	**54/1116 (4.8)**	**30/574 (5.2)**
p-value[a]	0.698	
Relative risk (95% CI)	0.92 (0.60, 1.42)	
<37^0 Weeks Gestation	**257/1112 (23.1)**	**125/572 (21.9)**
p-value[a]	0.567	
Relative risk (95% CI)	1.06 (0.88, 1.28)	

Source: PROLONG Table 14.2.3.2.1 and Table 14.2.3.1.1, PROLONG Ad Hoc Table 14.2.1.1.1.26.
[a] p-value Cochran-Mantel-Haenszel test.
Notes: n=number of patients with delivery <32^0 or 37^0 weeks (as indicated) gestation.
N*=number of ITT patients with non-missing delivery data or who were known to still be pregnant at 32^0 or 37^0 weeks (as indicated) in the specified category.

Similar rates of spontaneous PTB were observed in each treatment group (Table 29). In addition, the mean gestational age at delivery was comparable for both treatment groups

Table 29: Gestational Age at Delivery (Intent-to-Treat Population, PROLONG)

Gestational Age at Randomization (weeks)[a]	17P (N=1130)	Vehicle (N=578)
16^0-17^6, n	493	238
Mean (SD)	37.6 (3.6)	37.5 (4.0)
18^0-20^6, n	619	334
Mean (SD)	37.8 (2.7)	37.7 (2.9)
Overall, n	**1112**	**572**
Mean (SD)	**37.7 (3.1)**	**37.6 (3.4)**
p-value[b]	0.952	
p-value[c]	0.981	

Source: PROLONG CSR Table 14.2.4.6.1.
[a] Refers to project gestational age which is the correct gestational age calculated from the patient's menstrual history and measurements obtained at the patient's first ultrasound.
[b] p-value is from the Van Elteren test for continuous variables stratified by gestational age at randomization.
[c] p-value is from the Wilcoxon test for differences in Kaplan-Meier curves.

The treatment groups also had similar maternal delivery characteristics. Most patients had spontaneous labor (71.9% 17P patients and 72.3% vehicle patients). At least one episode of preterm labor was reported for 16.5% 17P patients and 14.5% vehicle patients. Approximately 25% of patients in both treatment groups underwent cesarean section. The median duration of hospitalization was 5.0 days for patients in both treatment groups.

6.2.6.2.2. NICU Outcomes

Table 30 summarizes the NICU outcomes for liveborn neonates. Among the liveborn population of neonates born at ≥24 weeks gestational age, deaths were reported for 3 neonates born to mothers treated with 17P and 2 neonates born to mothers treated with vehicle. In total, 12.4% of neonates born to patients in the 17P treatment group and 10.4% of neonates born to patients in the vehicle group were admitted to the NICU.

Table 30: Infant NICU Outcome (Liveborn Neonatal Population, PROLONG)

	17P (N=1091) n (%)	Vehicle (N=560) n (%)
Components of Neonatal Composite Index		
Neonatal death[a]	3 (0.3)	2 (0.4)
Grade 3/4 intraventricular hemorrhage	2 (0.2)	1 (0.2)
Respiratory distress syndrome	54 (4.9)	26 (4.6)
Bronchopulmonary dysplasia	6 (0.5)	1 (0.2)
Necrotizing enterocolitis	2 (0.2)	2 (0.4)
Proven sepsis	5 (0.5)	3 (0.5)
Other NICU Outcomes[c]		
Any intraventricular hemorrhage	46 (4.2)	19 (3.4)
Transient tachypnea	37 (3.4)	11 (2.0)
Neonatal hypoglycemia	10 (0.9)	5 (0.9)
Confirmed pneumonia	10 (0.9)	2 (0.4)
Retinopathy of prematurity	5 (0.5)	7 (1.3)
Patent ductus arteriosis	4 (0.4)	4 (0.7)
Seizures	5 (0.5)	0 (0)
Persistent pulmonary hypertension	2 (0.2)	2 (0.4)
Other intracranial hemorrhage	3 (0.3)	0 (0)
Grade 3/4/5 retinopathy of prematurity	2 (0.2)	0 (0)
Periventricular leukomalacia	1 (0.1)	0 (0)
Infant NICU Outcome		
All infants admitted (N*)	135 (12.4)	58 (10.4)
Died before final discharge from NICU	3 (2.2)	2 (3.4)
Discharged to home	107 (79.3)	46 (79.3)
Discharged to chronic care facility	6 (4.4)	1 (1.7)
Discharged to non-medical facility (other than home)	2 (1.5)	1 (1.7)
Discharged to step-down unit	15 (11.1)	8 (13.8)
Unknown	2 (1.5)	0 (0.0)
Respiratory Needs		
Number of neonates on ventilator support/ receiving supplemental oxygen	130 (11.9)	54 (9.6)
Number of days of respiratory therapy, n	130	54
Mean (SD)	8.3 (23.8)	10.4 (23.4)
Median	2.0	2.0

Source: PROLONG CSR Table 14.2.2 and Table 14.2.4.1.
[a] Number and percent of neonatal deaths was based on the Liveborn Neonatal Population Born at ≥24 Weeks Gestational Age (N for 17P=1089 and for vehicle=558).
[c] NICU outcomes that were part of the Neonatal Composite Index as well as an NICU outcome are presented here only once as part of the Neonatal Composite Index.
Notes: N=number of babies in the Liveborn Neonatal population in the specified treatment group.
n=number of babies within a specific category. Percentages are calculated as 100 x (n/N) except for the Infant NICU Outcome section in which percentages are calculated as 100 x (n/N*) where N* is the value in the All Infants Admitted row.

6.2.6.3. Subgroup Analysis

6.2.6.3.1. Efficacy by Geographic Region

The event rates for PTB and the neonatal composite index were 1.5 to 2 times higher at 16 to 18% in the US relative to ex-US regions (10%) (Table 31). The rates of PTB among US patients were the highest of the three top enrolling countries in the study (Russia, Ukraine and US), while the rates in Russia and Ukraine were the lowest (Table 32). The rates of the neonatal composite index in the regions with the highest enrollments (Russia and Ukraine) were among the lowest observed. This is consistent with the known epidemiology, as well as the substantially different health care delivery system in these countries, where early intervention to improve prenatal care and reduce neonatal complications is universally available [Healthy Newborn Network 2015; Russian Federation: Federal State Statistics Service 2012; UNICEF 2017; USAID 2011].

Table 31: Primary Efficacy Outcomes by Geographic Region (PROLONG)

Primary Efficacy Outcomes	**17P (N=1130)**	**Vehicle (N=578)**
PTB <35^0 Weeks Gestation (ITT Population) (Note 1)		
US Outcome rate n/N* (%)	**40/256 (15.6)**	**23/131 (17.6)**
Relative Risk (95% CI)	**0.88 (0.55, 1.40)**	
Ex-US Outcome rate n/N* (%)	**82/857 (9.6)**	**43/443 (9.7)**
Relative Risk (95% CI)	**0.98 (0.69, 1.39)**	
Russia	27/406 (6.7)	18/206 (8.7)
Ukraine	27/270 (10.0)	14/142 (9.9)
Hungary	11/59 (18.6)	4/32 (12.5)
Spain	8/57 (14.0)	3/28 (10.7)
Canada	5/19 (26.3)	3/12 (25.0)
Bulgaria	4/33 (12.1)	0/17 (0)
Czech Republic	0/9 (0)	1/5 (20.0)
Italy	0/4 (0)	0/1 (0)
Neonatal Composite Index (Liveborn Neonatal Population) (Note 2)	**(N=1091)**	**(N=560)**
US Outcome rate n/N* (%)	**18/252 (7.1)**	**12/126 (9.5)**
Relative Risk (95% CI)	**0.77 (0.39, 1.54)**	
Ex-US Outcome rate n/N* (%)	**41/839 (4.9)**	**17/434 (3.9)**
Relative Risk (95% CI)	**1.27 (0.73, 2.21)**	
Russia	17/401 (4.2)	8/200 (4.0)
Ukraine	13/265 (4.9)	5/140 (3.6)
Canada	4/19 (21.1)	2/12 (16.7)
Spain	3/54 (5.6)	1/27 (3.7)
Hungary	2/57 (3.5)	1/32 (3.1)
Bulgaria	1/30 (3.3)	0/17 (0)
Czech Republic	1/9 (11.1)	0/5 (0)
Italy	0/4 (0)	0/1 (0)

Source: PROLONG CSR Table 14.2.1.5, Table 14.2.1.6, Table 14.2.1.10, and Table 14.2.1.11, PROLONG Ad Hoc Table 14.2.1.1.1.26.

Note 1: N=number of patients in the ITT Population in the specified treatment group.
n=number of patients with delivery <35^0 weeks of gestation in the specified category.
N*=number of ITT patients with non-missing delivery data or who were known to still be pregnant at 35^0 weeks in the specified category.

Note 2: N=number of babies in the Liveborn Neonatal population in the specified treatment group.
N*=number of babies of patients in the indicated region.
n=number of babies in the specific category. Percentages are calculated as 100 x (n/N*).

Table 32: Preterm Birth by Weeks Gestation for the Three Countries with Largest Enrollments (Intent-to-Treat Population, PROLONG)

Gestation Age at Randomization [a] Outcome Rate	17P (N=1130) n/N* (%)	Vehicle (N=578) n/N* (%)
<32^0 Weeks Gestation		
Russia	13/407 (3.2)	7/206 (3.4)
Ukraine	14/272 (5.1)	6/142 (4.2)
United States	14/256 (5.5)	12/131 (9.2)
<35^0 Weeks Gestation		
Russia	27/406 (6.7)	18/206 (8.7)
Ukraine	27/270 (10.0)	14/142 (9.9)
United States	40/256 (15.6)	23/131 (17.6)
<37^0 Weeks Gestation		
Russia	60/406 (14.8)	35/204 (17.2)
Ukraine	61/269 (22.7)	30/142 (21.1)
United States	85/256 (33.2)	37/131 (28.2)

Source: PROLONG CSR Table 14.2.1.5, Table 14.2.3.1.3, and Table 14.2.3.2.3.
[a] Refers to project gestational age which is the correct gestational age calculated from the patient's menstrual history and measurements obtained at the patient's first ultrasound.
Notes: N=number of patients in ITT Population in the specified treatment group.
n=number of patients with delivery <32^0, 35^0, or 37^0 weeks (as indicated) gestation in the specified category.
N*=number of ITT patients with non-missing delivery data or who were known to still be pregnant at 32^0, 35^0, or 37^0 weeks (as indicated) in the specified category.

6.2.6.3.2. Efficacy by Obstetric History

Rates of PTB <35^0 weeks gestation and neonatal composite index were also examined for differences in obstetrical history including gestational age of qualifying delivery, gestational age of earliest prior PTB, and number of previous preterm deliveries. Results were similar for both treatment groups across subgroups (Table 33).

Table 33: Primary Efficacy Outcomes by Gestational Age of Qualifying Delivery, Earliest Prior Preterm Birth, and Number of Previous Preterm Deliveries (PROLONG)

Primary Efficacy Outcomes	17P n/N* (%)	Vehicle n/N* (%)
PTB <35^0 Weeks Gestation (ITT Population)	**(N=1130)**	**(N=578)**
Gestational Age of Qualifying Delivery		
20^0-<28^0	29/229 (12.7)	9/101 (8.9)
28^0-<32^0	24/201 (11.9)	20/104 (19.2)
32^0-<35^0	36/344 (10.5)	24/186 (12.9)
35^0-<37^0	32/336 (9.5)	13/180 (7.2)
Gestational Age of Earliest Prior PTB		
20^0-<28^0	40/275 (14.5)	14/125 (11.2)
28^0-<32^0	26/207 (12.6)	20/105 (19.0)
32^0-<35^0	30/336 (8.9)	20/177 (11.3)
35^0-<37^0	26/295 (8.8)	12/165 (7.3)
Number of Previous Preterm Deliveries, n (%)		
1	80/949 (8.4)	51/491 (10.4)
>1	42/164 (25.6)	15/81 (18.5)
Neonatal Composite Index (Liveborn Neonatal Population)[a]	**(N=1091)**	**(N=560)**
Gestational Age of the Qualifying Delivery		
20^0-<28^0	17/221 (7.7)	3/97 (3.1)
28^0-<32^0	14/198 (7.1)	13/102 (12.7)
32^0-<35^0	15/339 (4.4)	9/182 (4.9)
35^0-<37^0	13/330 (3.9)	4/176 (2.3)
Gestational Age of Earliest Prior PTB		
20^0-<28^0	20/265 (7.5)	5/121 (4.1)
28^0-<32^0	13/202 (6.4)	13/103 (12.6)
32^0-<35^0	15/333 (4.5)	8/173 (4.6)
35^0-<37^0	11/291 (3.8)	3/161 (1.9)
Number of Previous Preterm Deliveries, n (%)		
1	43/933 (4.6)	22/478 (4.6)
>1	16/158 (10.1)	7/80 (8.8)

Source: PROLONG CSR Table 14.2.1.2, Table 14.2.1.3, Table 14.2.1.4, Table 14.2.1.7, Table 14.2.1.8, and Table 14.2.1.9.
For PTB <35^0 weeks gestation, n=number of patients with delivery <35^0 weeks of gestation in the specified category and N*=number of ITT patients with non-missing delivery data or who were known to still be pregnant at 35^0 weeks in the specified category.
[a] For neonatal composite index, n=number of babies of patients in the specified category and N*=number of babies of patients in the Liveborn Neonatal Population in the specified category.

6.2.7. Safety

6.2.7.1. Primary Safety Outcome: Fetal and Early Infant Death

The primary safety objective of PROLONG was to rule out a doubling in the risk of fetal or early infant death in the 17P group compared to vehicle. This objective was included specifically to address the Agency's concern of a potential "safety signal" relative to the numerically higher rate of both miscarriage and stillbirth from the Meis study.

Fetal/early infant death was defined as a spontaneous abortion or miscarriage occurring at 16 weeks 0 days through 19 weeks 6 days; a stillbirth, either antepartum or intrapartum; or a neonatal death, occurring minutes after birth until 28 days of life.

If the upper bound of the CI is less than or equal to 2.0, a doubling in risk of fetal/early infant death can be ruled out. A doubling of risk was selected and agreed upon with FDA based on sample size calculations.

Rates were low and similar between treatment groups (1.68% and 1.90% in the 17P and vehicle groups, respectively) with a relative risk of 0.79 (95% CI 0.37–1.67) (Table 34).Given that the upper bound of the 95% CI is less than 2.0, a doubling in the risk of fetal/early infant death was adequately excluded.

Table 34: Fetal and Early Infant Death (Safety Population, PROLONG)

Primary Safety Outcome	17P (N=1130) n (%)	Vehicle (N=578) n (%)
Fetal/Early Infant Death	**19 (1.68)**	**11 (1.90)**
Relative Risk (95% CI) [a]	**0.79 (0.37 - 1.67)**	

Source: PROLONG CSR, Table 14.3.1.1.1.
[a] Relative risk of fetal/early infant death is from the Cochran-Mantel-Haenszel test.
Notes: N=number of patients in the ITT Population in the specified treatment group.
n=number of patients with Fetal/Early Infant Death in the specific category. Fetal/Early Infant Death is defined as neonatal death occurring in liveborns born at less than 24 weeks of gestation, spontaneous abortion/miscarriage or stillbirth

6.2.7.2. Adverse Events and Maternal Pregnancy Complications (MPC)

Treatment-emergent Adverse Events

The AE profile between the two treatment groups was comparable. There were 57.3% and 57.8% of patients with at least one treatment-emergent AEs (TEAEs) in the 17P and vehicle group, respectively (Table 35). The majority of TEAEs were mild in intensity, and most were considered unrelated to study drug. There was a low percentage of TEAEs leading to study drug withdrawal (1.0% and 0.9%) in the 17P and vehicle group, respectively, with both groups experiencing similar and low rates of serious adverse events (SAEs; 3.0% and 3.1% in the 17P and vehicle group, respectively).

The most frequently reported TEAEs in either treatment group were anemia (9.2% in 17P and 9.7% in vehicle) and headache (6.0% in 17P and 4.8% in vehicle). Other commonly reported TEAEs in the 17P group included nausea (4.9%) and back pain (4.4%).

Table 35: Most Common (≥2% for Either Treatment Group by PT) Treatment Emergent Adverse Events (Safety Population, PROLONG)

System Organ Class Preferred Term	17P (N=1128) n (%)	Vehicle (N=578) n (%)
Patients with at least one TEAE	**653 (57.9)**	**336 (58.1)**
Blood and lymphatic system disorders		
Anaemia	104 (9.2)	56 (9.7)
Anaemia of pregnancy	30 (2.7)	18 (3.1)
Gastrointestinal disorders		
Abdominal pain	40 (3.5)	27 (4.7)
Abdominal pain lower	23 (2.0)	7 (1.2)
Constipation	38 (3.4)	17 (2.9)
Diarrhea	23 (2.0)	13 (2.2)
Dyspepsia	37 (3.3)	25 (4.3)
Nausea	55 (4.9)	26 (4.5)
Vomiting	42 (3.7)	19 (3.3)
General disorders and administration site conditions		
Injection site pain	36 (3.2)	24 (4.2)
Injection site pruritus	42 (3.7)	23 (4.0)
Oedema peripheral	25 (2.2)	11 (1.9)
Infections and infestations		
Nasopharyngitis	39 (3.5)	27 (4.7)
Urinary tract infection	44 (3.9)	23 (4.0)
Vaginal infection	41 (3.6)	21 (3.6)
Vaginitis bacterial	35 (3.1)	22 (3.8)
Vulvovaginal candidiasis	21 (1.9)	12 (2.1)
Metabolism and nutrition disorders		
Gestational diabetes	33 (2.9)	21 (3.6)
Musculoskeletal and connective tissue disorders		
Back pain	50 (4.4)	20 (3.5)
Nervous system disorders		
Dizziness	22 (2.0)	13 (2.2)
Headache	68 (6.0)	28 (4.8)

Table 35 Most Common (≥2% for Either Treatment Group by PT) Treatment Emergent Adverse Events and Maternal Pregnancy Complications (Safety Population, PROLONG) (Continued)

System Organ Class Preferred Term	17P (N=1128) n (%)	Vehicle (N=578) n (%)
Pregnancy, puerperium and perinatal conditions		
Afterbirth pain	48 (4.3)	24 (4.2)
Cervical incompetence	34 (3.0)	16 (2.8)
Placental disorder	28 (2.5)	11 (1.9)
Pre-eclampsia	29 (2.6)	23 (4.0)
Psychiatric disorders		
Insomnia	36 (3.2)	13 (2.2)
Reproductive system and breast disorders		
Shortened cervix	18 (1.6)	15 (2.6)
Skin and subcutaneous tissue disorders		
Pruritus	17 (1.5)	13 (2.2)

Source: NDA 021945 Module 2.7.4 Table 7A-003.
Notes: Version 21.1 of MedDRA was used to code maternal pregnancy complications.
Patients reporting a particular AE (preferred term) or MPC more than once are counted only once by preferred term and System Organ Class.
TEAE were AE occurring on/after randomization through the End of Treatment Period Visit.

Maternal Pregnancy Complications (MPC)

There were 10% and 11.1% of patients who experienced at least one MPC in the 17P and vehicle group respectively (Table 36). The majority of patients who experienced MPC experienced mild events, and most were unrelated to study drug. The most frequently reported MPCs for the 17P group was pre-eclampsia (4.2%) and gestational diabetes (2.9%). The incidence of MPC were similar to that in the vehicle group.

The number of patients diagnosed with gestational diabetes during PROLONG was low, and consistent with the incidence each year in the US (2 to 10% of pregnancies) per Center for Disease Control estimates [CDC 2019].

Table 36: Maternal Pregnancy Complications (Safety Population, PROLONG)

	17P (N=1128) n (%)	Vehicle (N=578) n (%)
Patients with at least one maternal pregnancy complication	**113 (10.0)**	**64 (11.1)**
Gestational diabetes	33 (2.9)	21 (3.6)
Antepartum hemorrhage	5 (0.4)	1 (0.2)
Oligohydramnios	8 (0.7)	11 (1.9)
Preclampsia or gestational hypertension	47 (4.2)	30 (5.2)
Chorioamnionitis	9 (0.8)	2 (0.3)
Premature separation of placenta	16 (1.4)	4 (0.7)
HELLP syndrome	2 (0.2)	0 (0.0)
Eclampsia	1 (0.1)	0 (0.0)

Source: NDA 021945 Module 2.7.4 Table 5A-003.

6.2.7.3. Serious Adverse Events

Overall, 34 (3.0%) 17P patients and 18 (3.1%) vehicle patients experienced serious TEAEs or MPCs. The most frequently reported serious TEAE or MPC for patients treated with 17P were premature separation of placenta (5 patients, 0.4%), placental insufficiency (4 patients, 0.4%), and pneumonia (3 patients, 0.3%); Escherichia coli sepsis, pyelonephritis, and wound infection were each reported by 2 patients in the 17P group. The most frequently reported serious TEAE or MPC for patients treated with vehicle were cholestasis (3 patients, 0.5%), and premature separation of placenta (2 patients, 0.3%).

Two patients each had one serious TEAE/MPC considered possibly related to study treatment (one patient in the 17P group had the TEAE of mild nephrolithiasis considered possibly related and one patient in the vehicle group had the severe MPC of cholestasis considered probably related).

6.2.7.4. Stillbirth and Miscarriage

Stillbirths were reported for 12 (1.1%) 17P patients and 3 (0.5%) vehicle patients (Table 37). All of the stillbirths were deemed unrelated to study drug by the Investigator. Among the 12 that occurred in the 17P group, 8 were listed as "definitely not related," 3 as "unlikely related", and 1 "not related." Two women in the 17P group who delivered stillbirths reported smoking during pregnancy, one tested positive for cannabinoids, 1 had a large subserous myoma, and another had uncontrolled Type 1 diabetes mellitus with documented nephropathy and retinopathy. Ten women had a miscarriage: 4 (0.5%) in the 17P group and 6 (1.3%) in the vehicle group.

Table 37: Stillbirths, Miscarriages, and Early Infant Deaths (Safety Population, PROLONG)

	17P (N=1128) n/N (%)	Vehicle (N=578) n/N (%)	Relative Risk (95% CI)[a]
Fetal/Early Infant Death	**19/1128 (1.7)**	**11/578 (1.9)**	**0.87 (0.42, 1.81)**
Miscarriage	4/866 (0.5)	6/448 (1.3)	0.32 (0.09, 1.14)
Stillbirth	12/1124 (1.1)	3/571 (0.5)	2.07 (0.59, 7.29)
Antepartum stillbirth	4/1124 (0.4)	0/571 (0.0)	-
Intrapartum stillbirth	8/1124 (0.7)	3/571 (0.5)	1.38 (0.37, 5.17)
Early Infant Death	3/1112 (0.3)	2/569 (0.4)	0.73 (0.12, 4.48)

Source: PROLONG Ad Hoc Table 9A-003.
Notes: Fetal/Early Infant Death is defined as spontaneous abortion/miscarriage, stillbirth, or death (from minutes after birth until 28 days of life) occurring in liveborns born at less than 24 weeks gestation.
Miscarriage is defined as delivery from 16 weeks up until 20 weeks of gestation. Includes subjects enrolled prior to 20 weeks 0 days.
Stillbirth is defined as all stillbirths/fetal deaths/in-utero fetal losses occurring from 20 weeks gestation until term (excludes deliveries <20 weeks gestation).
[a] Relative risk for 17P relative to Vehicle (Placebo) and is from the Cochran-Mantel-Haenszel test adjusted for gestational age at randomization.

There was a low percentage of TEAEs (predominantly associated with the injection site) leading to study drug withdrawal (1.0% and 0.9%) in the 17P and vehicle group, respectively (Table 38). None of these events were deemed serious by the study investigator.

Table 38: Treatment Emergent Adverse Events and Maternal Pregnancy Complications Leading to Premature Discontinuation of Study Medication (Safety Population, PROLONG)

Preferred Term	17P (N=1128)	Vehicle (N=578)
Patients with at least one TEAE/MPC leading to discontinuation of study medication	**11 (1.0)**	**5 (0.9)**
Injection site erythema	2 (0.2)	0
Injection site nodule	0	1 (0.2)
Injection site pruritus	0	1 (0.2)
Injection site rash	0	1 (0.2)
Injection site reaction	2 (0.2)	0
Hypothyroidism	1 (0.1)	0
Nausea	1 (0.1)	0
Vomiting	1 (0.1)	0
Cholestasis	0	2 (0.3)
Headache	0	1 (0.2)
Fetal growth restriction	1 (0.1)	0
Pre-eclampsia	0	1 (0.2)
Mood altered	1 (0.1)	0
Shortened cervix	1 (0.1)	0
Vaginal hemorrhage	1 (0.1)	0
Dermatitis allergic	1 (0.1)	0
Dry skin	1 (0.1)	0

Source: NDA 021945 Module 2.7.4 Table 8A-003.
Notes: Version 21.1 of MedDRA was used to code adverse events.
Patients reporting a particular adverse event (preferred term) or MPC more than once are counted only once by preferred term.

6.2.7.5. Safety Conclusions

Results from PROLONG reaffirmed the safety of 17P demonstrated in the Meis study. Importantly, PROLONG excluded any doubling of risk of fetal/early infant death.

There were no new or unexpected safety findings from PROLONG, as 17P demonstrated a safety profile that was comparable to vehicle. 17P was well-tolerated and the majority of patients in PROLONG who experienced TEAEs or MPCs experienced mild events that were unrelated to study drug.

To date the safety information received from the post-marketing setting is consistent with the known safety profile, and no new safety signals have been identified.

6.2.8. Pharmacokinetics

Patients were offered the opportunity to participate in a PK substudy until approximately 450 patients (300 active and 150 vehicle) had been enrolled. PK assessments were made based on sparse sampling, stratified according to pre-pregnancy BMI, to analyze the dose-plasma concentration-time relationship of 17P.

Three blood samples were obtained:

- Before study drug dosing at either Visit 6 or 7 (i.e., Dose 5 or 6).
- Before study drug dosing at either Visit 8 or 9 (i.e., Dose 7 or 8).
- At a separate, non-dosing visit 1 to 6 days after Visit 9, 10, or 11 (i.e., 1 to 6 days after Doses 8, 9, or 10).

The PK analysis, based on a limited number of samples per patient, demonstrated that apparent clearance increased with each of increasing weight and increasing BMI. In turn, systemic exposure to 17P decreased with increasing weight and BMI. However, the magnitude of difference in exposure between the lowest and highest quartiles of BMI was small.

There was no evidence that the PK characteristics of 17P were altered by administration of concomitant medications known to induce or inhibit pathways believed to be involved in the metabolism of 17P. However, the number of patients using relevant concomitant medications was small.

There was also no evidence that the incidence of PTB varied as a function of exposure to 17P. Similarly, there was no evidence that any of seven neonatal outcomes varied as a function of exposure to 17P; however, the incidence of these outcomes was low in both vehicle and 17P treated patients, minimizing the opportunity to assess an exposure-response relationship.

7. EXPLORATORY POST HOC ANALYSES

Summary

- Differences across race and other potential surrogates of socioeconomic status linked to higher rates of PTB were noteworthy between Meis and PROLONG, with most of those differences driven by the ex-US PROLONG subset.
- Compared to the US PROLONG subset and Meis, the ex-US PROLONG population represented a cohort with a lower baseline risk for PTB:
  - Lower percentage with prior spontaneous PTB (11% ex-US PROLONG, 27% US PROLONG, 32% in Meis).
  - Fewer Black patients (1 Black patient ex-US PROLONG, 29% US PROLONG, 60% in Meis).
  - Lower percentage of unmarried patients (4% ex-US PROLONG, 31% US PROLONG, 50% in Meis).
  - Lower percentage of patients with any substance use during pregnancy (4% ex-US PROLONG, 28% US PROLONG, and 26% in Meis).
- The ex-US and US PROLONG subsets had patient populations with lower risk for future PTBs than that of Meis.
  - Nearly 92% of patients in Meis had at least one additional risk factor for PTB (beyond 1 previous spontaneous PTB), compared to 79% in US PROLONG and 48% in ex-US PROLONG.
- A treatment benefit associated with 17P was correlated with increasing levels of baseline risk for recurrent PTB.
  - Meis, the highest risk population, had a treatment benefit favoring 17P at <37, <35, and <32 weeks gestation.
  - No treatment effect favoring 17P was observed in the ex-US PROLONG subset, a decidedly lower risk study population.
  - In the US PROLONG subset, a more intermediate and higher risk population, trends of a treatment effect favoring 17P begin to emerge at <35 weeks and <32 weeks.

PROLONG was the largest trial to date to study the effects of 17P in women with prior spontaneous PTB. Unlike the Meis trial, which showed a treatment benefit, treatment with 17P in PROLONG did not decrease rates of PTB or the overall neonatal composite index.

To better understand these discrepant results, exploratory analyses were conducted. These post hoc analyses examined the potential role that differences between the study populations (demographics and patient characteristics associated with baseline risk levels), and differences in health care delivery systems and geography (access to universal health care, emphasis on preventative care) may have had on the results of the study.

7.1. Comparison of Study Demographics

When comparing demographics and baseline characteristics from PROLONG and Meis, the differences across race and other potential surrogates of socioeconomic status that have been linked to higher rates of PTB were noteworthy, with most of those differences driven by the ex-US PROLONG subset population (Table 39). Compared to the US PROLONG subset and Meis, the ex-US PROLONG population represented a cohort with a lower baseline risk for PTB.

- **Prior spontaneous PTB:** In ex-US PROLONG, 11% had more than 1 prior spontaneous PTB, compared to 27% in US PROLONG and 32% in Meis.
- **Race/ethnicity:** In ex-US PROLONG, only 1 patient was Black or African American, compared to 29% in US PROLONG and nearly 60% in Meis. Hispanic or Latinos accounted for approximately 8% of patients in ex-US PROLONG, 14% in US PROLONG, and 15% in Meis.
- **Marital status:** In ex-US PROLONG, 4% of patients were unmarried with no partner, compared to 31% in US PROLONG and 50% in Meis.
- **Substance use:** In ex-US PROLONG, approximately 4% of patients reported any substance use during pregnancy (smoking, alcohol or illicit drugs), compared to 28% in US PROLONG and 26% in Meis.

Table 39: Demographics and Baseline Characteristics – Post Hoc (Meis and PROLONG)

Variable	PROLONG (Overall)		PROLONG (Ex-US)		PROLONG (US Only)		Meis	
	17P (N=1130)	Vehicle (N=578)	17P (N=872)	Vehicle (N=445)	17P (N=258)	Vehicle (N=133)	17P (N=310)	Vehicle (N=153)
Age, years (mean ±SD)	30.0 ± 5.2	29.9 ± 5.2	30.5 ± 5.1	30.9 ± 4.9	28.1 ± 5.1	26.7 ± 5.1	26.0 ± 5.6	26.5 ± 5.4
Race, n (%)								
Black or African	73 (6.5)	41 (7.1)	1 (0.1)	0	72 (27.9)	41 (30.8)	183 (59.0)	90 (58.8)
White	1004 (88.8)	504 (87.2)	834 (95.6)	420 (94.4)	170 (65.9)	84 (63.2)	79 (29.6)	34 (26.8)
Hispanic or Latino	101 (8.9)	54 (9.3)	70 (8.0)	31 (7.0)	31 (12.0)	23 (17.3)	43 (13.9)[a]	26 (17.0)[a]
>1 previous SPTB	166 (14.7)	82 (14.2)	95 (10.9)	46 (10.3)	71 (27.5)	36 (27.1)	86 (27.7)[b]	63 (41.2)[b]
Gestational age of qualifying delivery, weeks	31.3 ± 4.35	31.6 ± 4.16	30.9 ± 4.40	31.3 ± 4.21	32.5 ± 3.92	32.5 ± 3.86	30.6 ± 4.6	31.3 ± 4.2
Married or living with partner	1013 (89.6)	522 (90.3)	833 (95.5)	431 (96.9)	180 (69.8)	91 (68.4)	159 (51.3)	71 (46.4)
BMI before pregnancy	24.3 ± 7.1	24.7 ± 8.7	23.4 ± 4.47	23.3 ± 4.39	27.4 ± 11.76	29.3 ± 15.29	26.9 ± 7.9	26.0 ± 7.0
Years of education	13 ± 2.4	13 ± 2.4	13.1 ± 2.40	13.1 ± 2.39	13.0 ± 2.25	12.5 ± 2.22	11.7 ± 2.3	11.9 ± 2.3
Any substance use during pregnancy - n (%)	105 (9.3)	51 (8.8)	36 (4.1)	11 (2.5)	69 (26.7)	40 (30.1)	85 (27.4)	36 (23.5)
Smoking	92 (8.1)	40 (6.9)	34 (3.9)	10 (2.2)	58 (22.5)	31 (23.3)	70 (22.6)	30 (19.6)
Alcohol	23 (2.0)	18 (3.1)	4 (0.5)	2 (0.4)	20 (7.8)	16 (12.0)	27 (8.7)	10 (6.5)
Illicit drugs	15 (1.3)	8 (1.4)	1 (0.1)	0	15 (5.8)	8 (6.0)	11 (3.5)	4 (2.6)

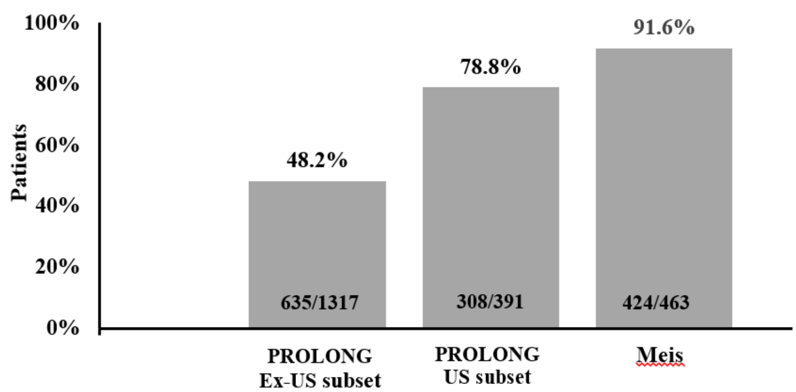
Source: PROLONG Ad Hoc Table 14.1.3.1.10 and Ad Hoc Table 14.1.3.1.11.
[a] Hispanic or Latino included in both race and ethnicity category.
[b] Study 002/PROLONG preterm delivery tables differ. PROLONG % PTB deliveries calculated manually.
NC=not collected.

It is important to note that while US PROLONG patients were more similar to those in Meis, there remain differences related to baseline levels of risk for PTB.

Figure 17 displays a post hoc assessment of select composite risk factors associated with risk of PTB across Meis and PROLONG. The components selected for inclusion (beyond the required entry criteria for at least one prior spontaneous PTB) are >1 prior spontaneous PTB, any substance use, ≤12 years of education, unmarried with no partner, and Black or African American. Importantly, other than a prior history of more than 1 spontaneous PTB, the other components are merely imperfect surrogates of socioeconomic status, an important known predictor of rates of PTB.

The ex-US subset of PROLONG (a low risk population) had a much lower percentage of patients (48.2%) with more than one additional risk factor for PTB compared to the subset of US patients in PROLONG, an intermediate risk population (78.8%) and patients in Meis, a high risk population (91.6%).

Figure 17: Differences in Baseline Risk Factors (Known or Surrogate) Associated with Preterm Birth - Post Hoc (Meis and PROLONG)



Source: PROLONG Ad Hoc Table 14.1.3.1.9.
Notes: The composite risk factors (in addition to the required prior spontaneous PTB) included >1 prior spontaneous PTB, substance use, educational status (≤12 years), unmarried with no partner, and Black/African American. Percentages expressed as n/N x 100, where n is the number of patients with at least 1 additional risk factor and N is the number of patients in the cohort.

7.2. Comparison of Efficacy Outcomes

Study populations with a greater percentage of high risk patients defined by the previously described composite of risk factors appeared to show improved treatment benefit with 17P compared to those with a lower percentage of those patients as shown in Figure 18.

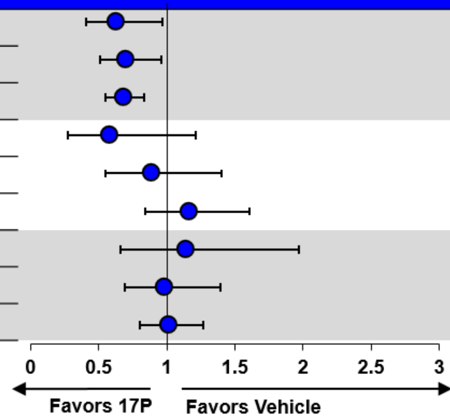
In Meis, which was a higher risk population, a treatment benefit favoring 17P was observed not only with the <37 weeks gestational age, but also at <35 weeks and even at <32 weeks, an important endpoint since it is known that babies born at earlier than 32 weeks have a significant risk of mortality and neonatal complications.

In addition, the intermediate risk population from the US subset of PROLONG also shows trends of a treatment effect favoring 17P beginning to emerge, as this population becomes more similar to Meis. These trends can be seen at <35 weeks and even at <32 weeks, however not at <37 weeks.

In contrast, the lower risk population of patients from the ex-US subset of PROLONG tend to show no trends of 17P treatment benefit compared to vehicle.

Figure 18: Comparison of Maternal Efficacy Endpoints – Post Hoc (Meis and PROLONG)

Study Population	Gestational Age (weeks)	17P (n/N)	Vehicle (n/N)	Relative Risk (95% CI)
Meis	32	39/310	30/153	0.63 (0.41, 0.97)
Meis	35	67/310	47/153	0.70 (0.51, 0.96)
Meis	37	115/310	84/153	0.68 (0.55, 0.83)
Prolong US	32	14/256	12/131	0.58 (0.27, 1.21)
Prolong US	35	40/256	23/131	0.88 (0.55, 1.40)
Prolong US	37	85/256	37/131	1.16 (0.84, 1.61)
Prolong Ex- Us	32	40/860	18/443	1.14 (0.66, 1.97)
Prolong Ex- Us	35	82/857	43/443	0.98 (0.69, 1.39)
Prolong Ex- Us	37	172/856	88/441	1.01 (0.80, 1.27)



Source: PROLONG Ad Hoc Table 14.2.1.1.1.26.

7.3. Integrated Safety (PROLONG and Meis)

In an effort to continue to fully characterize the safety profile of Makena, an integrated safety analysis was conducted, using two data cohorts from PROLONG and Meis:

1. All patients treated across both studies (17P: N=1438; Vehicle: N=731)
2. US patients only (17P: N=567; Vehicle; N=286)
    - The safety profile of the US only group was consistent with that of the overall integrated dataset and is not discussed further in this document.

MedDRA version 8.0 was used to code AEs in Meis, and Version 21.1 was used for PROLONG.

7.3.1. Common Adverse Events

Similar proportions of patients experienced at least 1 TEAE during the study (56.8% of patients in each treatment group). The most commonly reported TEAE was injection site pain, which occurred in ~10% of patients in each treatment group (Table 40).

Table 40: Incidence of Treatment-Emergent Adverse Events Occurring in at least 2% of Patients in Either Treatment Group by System Organ Class and Preferred Term (Safety Population- PROLONG and Meis Combined)

System Organ Class Preferred Term	17P (N=1438)	Vehicle (N=731)
Patients with at least one TEAE	**817 (56.8)**	**415 (56.8)**
Blood and lymphatic system disorders		
Anaemia	104 (7.2)	56 (7.7)
Anaemia of pregnancy	30 (2.1)	18 (2.5)
Gastrointestinal disorders		
Abdominal pain	43 (3.0)	31 (4.2)
Constipation	40 (2.8)	18 (2.5)
Diarrhoea	30 (2.1)	14 (1.9)
Dyspepsia	37 (2.6)	25 (3.4)
Nausea	73 (5.1)	33 (4.5)
Vomiting	52 (3.6)	24 (3.3)
General disorders and administration site conditions		
Injection site nodule	32 (2.2)	12 (1.6)
Injection site pain	144 (10.0)	74 (10.1)
Injection site pruritus	60 (4.2)	28 (3.8)
Injection site swelling	58 (4.0)	14 (1.9)
Infections and infestations		
Nasopharyngitis	39 (2.7)	27 (3.7)
Urinary tract infection	44 (3.1)	23 (3.1)
Vaginal infection	41 (2.9)	21 (2.9)
Vaginitis bacterial	35 (2.4)	22 (3.0)
Metabolism and nutrition disorders		
Gestational diabetes	33 (2.3)	22 (3.0)
Musculoskeletal and connective tissue disorders		
Back pain	54 (3.8)	21 (2.9)
Nervous system disorders		
Headache	72 (5.0)	28 (3.8)
Pregnancy, puerperium and perinatal conditions		
Afterbirth pain	48 (3.3)	24 (3.3)
Cervical incompetence	34 (2.4)	16 (2.2)

System Organ Class Preferred Term	17P (N=1438)	Vehicle (N=731)
Pre-eclampsia	29 (2.0)	23 (3.1)
Psychiatric disorders		
Insomnia	38 (2.6)	14 (1.9)
Reproductive system and breast disorders		
Shortened cervix	18 (1.3)	15 (2.1)
Skin and subcutaneous tissue disorders		
Pruritus	41 (2.9)	22 (3.0)
Urticaria	43 (3.0)	17 (2.3)

Source: NDA 021945 Module 2.7.4 Table 7A.
N=number of patients in the Safety Population in the specified treatment group.
n=number of patients in the specific category. Percentages are calculated as 100 x (n/N).
Patients reporting a particular AE (PT) more than once are counted only once by PT and System Organ Class.

7.3.2. Serious Adverse Events

In the overall pooled population, less than 4% of patients experienced a serious TEAE (17P 3.5%, vehicle 2.9%) (Table 41). Stillbirth, spontaneous abortion, and premature separation of placenta were the most frequently reported SAE in the 17P group. Fetal/early infant deaths, stillbirths, and miscarriages are described further in the sections that follow.

There were no maternal deaths reported in either study.

Table 41: Incidence of Serious Treatment-Emergent Adverse Events Occurring in at least 2 Patients in Either Treatment Group by Preferred Term (Safety Population- PROLONG and Meis Combined)

Preferred Term	17P (N=1438)	Vehicle (N= 731)
Patients with at least one Serious TEAE	**50 (3.5)**	**21 (2.9)**
Stillbirth	6 (0.4)	2 (0.3)
Abortion spontaneous	5 (0.3)	0 (0.0)
Premature separation of placenta	5 (0.3)	2 (0.3)
Placental insufficiency	4 (0.3)	1 (0.1)
Pneumonia	3 (0.2)	0 (0.0)
Endometritis	2 (0.1)	1 (0.1)
Escherichia sepsis	2 (0.1)	0 (0.0)
Pyelonephritis	2 (0.1)	1 (0.1)
Wound infection	2 (0.1)	0 (0.0)
Cholestasis	0 (0.0)	3 (0.4)

Source: NDA 021945 Module 2.7.4 Table 6A.
N=number of patients in the Safety Population in the specified treatment group.
n=number of patients in the specific category. Percentages are calculated as 100 x (n/N).
Patients reporting a particular AE (PT) more than once are counted only once by PT.
Maternal pregnancy complications are included as TEAEs where applicable.

7.3.2.1. Fetal and Early Infant Deaths

In the overall pooled population, the incidence of fetal death was low and similar in both treatment arms (relative risk 1.01 [95% CI 0.57, 1.79]) (Table 42).

Table 42: Fetal and Early Infant Death (Safety Population- PROLONG and Meis Combined)

Fetal/Early Infant Death[a] by Gestational Age at Randomization		17P (N=1438)	Vehicle (N=731)
16 - <18 Weeks	n[b]/N[c] (%)	17/605 (2.8)	9/287 (3.1)
18 - <21 Weeks	n/N (%)	17/833 (2.0)	8/444 (1.8)
Fetal/Early Infant Death	n/N (%)	34/1438 (2.4)	17/731 (2.3)
Relative Risk[d]	RR (95% CI)	1.01 (0.57, 1.79)	

Source: NDA 021945 Module 2.7.4 Table 1A.

[a] Fetal/Early Infant Death is defined as spontaneous abortion/miscarriage, stillbirth, or death (from minutes after birth until 28 days of life) occurring in liveborns born at less than 24 weeks gestation.

[b] n=number of patients within a specific category. Percentages are calculated as 100 x (n/N).

[c] N=number of patients in the Safety Population in the specified treatment group. The safety population consists of all patients who received any amount of study medication.

[d] Relative risk of fetal/early infant death for 17P relative to vehicle (placebo) and is for the Cochran-Mantel-Haenszel test adjusted for gestational age at randomization.

7.3.2.2. Stillbirths and Miscarriages

In the overall pooled population, miscarriage and stillbirth were infrequent and similar between the treatment groups (Table 43). Stillbirths were reported in 1.3% of 17P patients and 0.7% vehicle-treated patients. Fifteen women had a miscarriage: 9 in the 17P group and 5 in the vehicle group.

Table 43: Stillbirths, Miscarriages, and Early Infant Deaths (Safety Population – PROLONG and Meis Combined)

	17P (N=1438) n/N (%)	Vehicle (N=731) n/N (%)	Relative Risk (95% CI)[a]
Fetal/Early Infant Death	34/1438 (2.4)	17/731 (2.3)	1.01 (0.57, 1.79)
Miscarriage	9/1075 (0.8)	6/555 (1.1)	0.73 (0.26, 2.04)
Stillbirth	18/1429 (1.3)	5/724 (0.7)	1.86 (0.69, 4.99)
Antepartum stillbirth	9/1429 (0.6)	1/724 (0.1)	4.67 (0.58, 37.31)
Intrapartum stillbirth	9/1429 (0.6)	4/724 (0.6)	1.16 (0.36, 3.76)
Early Infant Death	7/1411 (0.5)	6/720 (0.8)	0.58 (0.20, 1.73)

Source: Ad Hoc Table 9A.

Notes: Fetal/Early Infant Death is defined as spontaneous abortion/miscarriage, stillbirth, or death (from minutes after birth until 28 days of life) occurring in liveborns born at less than 24 weeks gestation.

Miscarriage is defined as delivery from 16 weeks up until 20 weeks of gestation. Includes subjects enrolled prior to 20 weeks 0 days.

Stillbirth is defined as all stillbirths/fetal deaths/in-utero fetal losses occurring from 20 weeks gestation until term (excludes deliveries <20 weeks gestation).

[a] Relative risk for 17P relative to Vehicle (Placebo) and is from the Cochran-Mantel-Haenszel test adjusted for gestational age at randomization.

8. DISCUSSION

PROLONG did not meet the predefined co-primary objectives. AMAG believes that the results from PROLONG were influenced by differences in the study population from that previously studied in Meis. While the entry criteria of Meis and PROLONG were similar, the study population in PROLONG was different than that of Meis, with the latter comprised of a higher risk population.

Efficacy

When comparing demographics and baseline characteristics from PROLONG and Meis, the differences across race and other potential surrogates of socioeconomic status that have been linked to higher rates of PTB were noteworthy, with most of those differences were driven by the ex-US PROLONG subset population. As a result, key differences in baseline risk associated with PTB even within the PROLONG study population, notably US vs. ex-US subset populations, make the applicability of the efficacy data particularly challenging in the US.

A review of the baseline characteristics of patients who enrolled in PROLONG in the US demonstrates that although they are more similar to Meis than that of the overall PROLONG population, they remain differ from Meis on many of the risk factors thought to be associated with risk of PTB.

A post-hoc investigation into baseline risk factors indicate that, compared to Meis (a high-risk population), the PROLONG US subset was an intermediate risk group for recurrent PTB, with the PROLONG ex-US subset at lower risk. The lower baseline risk for PTB in ex-US PROLONG could be attributed to varying healthcare delivery systems (more preventive than acute care) with universal access in ex-US countries, which represented 75% of the study population (61% from Russia and Ukraine alone). In a number of these countries, there are dedicated programs that target prevention of PTB and adverse fetal outcomes with evidence-based technologies to improve the quality of perinatal care. Often, these programs include comprehensive measures for pregnancy planning, screening, primary prophylaxis, and risk factor reduction, as well as providing healthcare and treatment of co-morbid conditions prior to pregnancy. In addition, compliance with prenatal care is associated with state-provided financial incentives for new mothers [Healthy Newborn Network 2015; Russian Federation: Federal State Statistics Service 2012; UNICEF 2017; USAID 2011].

Of note, exploratory analyses of PTB rates by baseline risk suggest an increasing treatment benefit associated with 17P with increasing levels of baseline risk for recurrent PTB. Treatment effect was observed at <37, <35, and <32 weeks gestation for the highest risk group (Meis), while the lowest risk group (ex-US PROLONG) showed no effect. Trends favoring 17P emerge in the US PROLONG subset as the population becomes more similar to that of Meis, with increased effect at <35 and <32 weeks, but not at <37 weeks gestation.

In totality, it is possible that differences in baseline risk for PTB underpin the lack of correlation between the efficacy results observed in Meis and PROLONG.

Safety

The key safety outcome of PROLONG was to rule out a doubling of risk of fetal or early infant death in the 17P group relative to vehicle. This endpoint was included specifically to address the

Agency's concern of a potential safety signal relative to the numerically higher rate of both miscarriage and stillbirth from the Meis study. The relative risk of 0.79 with an upper bound of the 95% CI of 1.67 excludes that risk.

The favorable maternal and fetal safety profile of 17P was reaffirmed as there were no new or unexpected safety findings, and no clinically meaningful differences in the safety profile across treatment groups. Specifically, there were no clinically meaningful differences in TEAEs across the two treatment groups (17P and vehicle).

Proposed Changes to Prescribing Information

Based on the results from PROLONG, AMAG is proposing to maintain the indication with the current limitations of use and to amend the current prescribing information to include the following updates:

- Section 6 Adverse Reactions: to include pooled (Meis and PROLONG) safety information
- Section 14.1 Clinical Trials to Evaluate Reduction of Risk of Preterm Birth: to include findings from PROLONG. In particular AMAG proposes that it is important to include information that helps place the results from PROLONG in context with those observed from Meis.

8.1. Conclusions

Differences in study populations between Meis and PROLONG as it relates to baseline levels of risk associated with PTB contributed to the vastly lower rates of PTB and associated prematurity complications seen in PROLONG. It is relevant to acknowledge that in the nearly 20 years since Meis was initiated and PROLONG was completed, there have been substantial improvements in neonatal care that have increased survival. However, rates of PTB in the US have remained relatively constant over that time period and there remains a significant public health concern regarding PTB. Moreover, women with a prior history of spontaneous PTB, particularly if the preterm birth is early (<32 week gestation), or if there is a history of more than one prior spontaneous PTB, are at the highest risk for a recurrent PTB.

The totality of clinical data including more than 16 years of clinical use support 17P's positive benefit-risk profile and support its availability for clinicians to make patient-specific prescribing decisions, based upon their clinical judgment and shared decision-making with their patients.

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FDA Briefing Document
NDA 021945
Hydroxyprogesterone Caproate Injection
(trade name Makena)

Bone, Reproductive, and Urologic Drugs Advisory Committee
(BRUDAC) Meeting
October 29, 2019
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Office of New Drugs

Division of Biometrics III
Division of Biometrics VII
Office of Biostatistics
Office of Translational Sciences

Division of Epidemiology II
Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought new information from the new drug application for Makena (17-hydroxyprogesterone caproate) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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INTRODUCTORY MEMORANDUM

To: Bone, Reproductive and Urologic Drugs Advisory Committee

From: Christine P. Nguyen, MD
Deputy Director for Safety

Hylton V. Joffe, MD, MMSc
Director

Division of Bone, Reproductive, and Urologic Products (DBRUP)

Subject: Makena (hydroxyprogesterone caproate injection)
New Drug Application 021945/Supplement 023
Overview of topics to be discussed at the October 29, 2019, advisory committee meeting

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The FDA is convening this Advisory Committee (AC) meeting to discuss the evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth and improving neonatal outcomes to inform FDA's regulatory decision-making for this product. In 2011, Makena received accelerated approval (a type of approval discussed in greater detail below) based on a reduced risk of recurrent preterm birth (PTB) prior to 37 weeks, a surrogate endpoint that FDA considered reasonably likely to predict clinical benefit to the neonate. Consistent with FDA's accelerated approval framework [21 CFR part 314, subpart H and section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)], FDA required the Applicant to conduct a post-approval confirmatory trial to verify and describe the clinical benefit. Completed at the end of 2018, this confirmatory trial did not verify Makena's efficacy on obstetrical or neonatal outcomes. In a supplemental new drug application (sNDA), the Applicant proposes to add findings from this trial to the drug label.

BACKGROUND:

Current clinical practice

Preterm birth, defined as birth prior to 37 weeks of gestation, currently affects approximately 10% of all births and 8% of singleton pregnancies.[1] Premature birth is a significant public health problem because these infants are at an increased risk of neonatal mortality and significant morbidity, as well as long-term physical and developmental impairment. To date, there are no drugs approved for reducing neonatal morbidity or mortality or long-term sequelae of preterm birth.

Progesterone, administered by intramuscular injection or intravaginally, has been used for certain conditions that may increase a pregnant woman's risk of PTB. Current professional practice

[1] https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm (accessed September 19, 2019)

guidelines recommend progesterone treatment starting in the second trimester of pregnancy to reduce the risk of recurrent preterm birth in women with a singleton pregnancy and a prior spontaneous preterm birth (sPTB). The guidelines also recommend vaginal progesterone to reduce the risk of PTB in women without a prior preterm birth and with a shortened cervix in the current pregnancy, although such use is not FDA-approved.[2] Makena is the only pharmacotherapy approved to reduce the risk of recurrent preterm birth. Based on its accelerated approval, Makena's indication states that it is approved to "reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity."

Regulatory History of Hydroxyprogesterone Caproate:
The drug substance of Makena, hydroxyprogesterone caproate (HPC), also referred to as 17-HPC, 17-OHPC, or 17P, was approved by FDA in 1956 for conditions generally responding to progestogens, under the tradename Delalutin (HPC) injection 125 mg/mL and 250 mg/ml (NDAs 010347, 016911). This approval was based on safety considerations because it occurred prior to the Kefauver-Harris Amendment of 1962 to the FD&C Act requiring that approved drugs be supported by substantial evidence of effectiveness, in addition to demonstrated safety. Delalutin remained approved for certain gynecologic indications after undergoing the Drug Efficacy Study Implementation review, which determined the efficacy of marketed drugs approved before 1962. At the Applicant's request, FDA withdrew approval of the NDAs for Delalutin in 2000 (not for efficacy or safety reasons) (65 Fed. Reg. 55264, Sept. 13, 2000). FDA has approved generic products of Delalutin that are currently marketed. Note that Delalutin and its generics are not approved for reducing the risk of preterm birth.

Published literature from the 1960s through the 1980s included several clinical studies evaluating the efficacy of HPC for obstetrical uses. Conflicting findings regarding the effectiveness of HPC for the prevention of PTB prompted the National Institute for Child Health and Human Development (NICHD), via the Maternal-Fetal Medicine Units (MFMU) Network, to conduct a multicenter, double-blind, placebo-controlled clinical trial in women with a history of spontaneous preterm singleton birth to assess the efficacy of HPC for preventing recurrent PTB (Study 17P-CT-002, or Trial 002 hereinafter). In June 2003, the trial's findings were published,[3] reporting that HPC 250 mg injection reduced the proportion of women who delivered at less than 37 weeks gestation.

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[2] American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin: Prediction and Prevention of Preterm Birth (2012, reaffirmed 2018); Society for Maternal-Fetal Medicine Statement: "The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth" (March 2017). While the ACOG Practice Bulletin did not specify the formulation of progesterone for women with a prior sPTB, SMFM recommended treatment with hydroxyprogesterone caproate injection and not vaginal progesterone in this population.

[3] Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;348(24):2379-85.

Makena's accelerated approval

In 2006, an applicant submitted NDA 021945 seeking marketing approval of HPC injection for the prevention of recurrent PTB. The NDA relied on data from the MFMU Network Trial 002 for primary support of efficacy and safety. At that time, no drug was approved in the U.S. to reduce the risk of PTB. However, HPC was compounded and used widely for the prevention of PTB in women at high risk.

After three review cycles and one Advisory Committee meeting, in February 2011, the FDA granted Makena accelerated approval based on reduction in preterm birth prior to 37 weeks, a surrogate endpoint considered to be reasonably likely to predict the clinical benefit of reducing neonatal morbidity or mortality.

Initiated in 1999 and completed in 2002, Trial 002 enrolled 463 women with a singleton pregnancy and at least one prior sPTB from 19 university-based clinical centers in the United States in the MFMU Network. The primary efficacy endpoint was the proportion of pregnant women delivering prior to 37 weeks gestation, with those delivering prior to 35 or 32 weeks as secondary endpoints. The trial showed that Makena (HPC 250 mg) injection administered intramuscularly once weekly starting at 16 weeks 0 days (16^0) to 20 weeks 6 days (20^6) gestation and used through 36^6 weeks gestation or birth reduced the proportion of women who delivered <37 weeks gestation from 55% (placebo) to 37% (Makena). The treatment difference was -17.8% [95% confidence interval (CI): -28%, -7.4%]. This treatment benefit appeared independent of race, number of prior preterm deliveries, and gestational age of the prior preterm birth. The treatment effect was sufficiently persuasive to support drug approval based on the findings of a single adequate and well-controlled trial. The proportions of women delivering at <35 and <32 weeks gestation were also statistically lower among women treated with Makena compared to placebo. The treatment difference was -9.4% (95% CI: -19.0%, -0.4%) for delivery <35 weeks gestation and -7.7% (95% CI: -16.1%, -0.3%) for delivery <32 weeks gestation.

Issues regarding generalizability of Trial 002's findings to the broader U.S. population included (a) approximately 60% of the trial participants being self-identified Blacks, (b) subject recruitment from only academic centers, with 25% of subjects from a single academic center, and (c) the notably high rate of recurrent preterm birth in the placebo arm (55%).[4] As a condition of accelerated approval, the Applicant was required to submit data from a confirmatory efficacy and safety trial to verify the clinical benefits of Makena, and the trial was to be completed with due diligence.

CONFIRMATORY TRIAL (Trial 003)

Prior to approving Makena in 2011, the FDA recognized the challenges of the feasibility of conducting a confirmatory efficacy and safety trial in the United States, given the endorsement of professional practice guidelines and accepted clinical practice of using progesterone for preterm birth. Prior to approval, the FDA required that the Applicant provide evidence that it could successfully complete the confirmatory trial, which must be ongoing at the time of approval, and that at least 10% of subjects be enrolled from the U.S. and Canada. Initiated in 2009 and completed in 2018, this confirmatory trial (Trial 003) was a multicenter, international,

[4] Background recurrent preterm birth rate used to power Trial 002 was 36%, as this was the background rate from the MFMUN uterine monitoring trial in the 1990s.

randomized, double-blind, placebo-controlled study that enrolled women with eligibility criteria like those of Trial 002. The trial's coprimary efficacy endpoints were delivery prior to 35 weeks gestation and a neonatal morbidity/mortality composite index (neonatal composite index).[5] The inclusion of a clinical endpoint (the neonatal composite index) addressed the accelerated approval's regulations of verifying that initial findings based on a surrogate endpoint (gestational age at delivery) lead to direct clinical benefit. Trial 003 randomized a total of 1,708 women from nine countries, with Russia, Ukraine, and the United States enrolling 36%, 25%, and 23% of women, respectively. Data were available for 1651 liveborn neonates. The trial did not demonstrate a statistically significant treatment effect for the coprimary endpoints of proportion of women delivering prior to 35 weeks (11% Makena compared to 12% placebo, p=0.72) or neonatal composite index (5.4% Makena compared to 5.2% placebo, p=0.84). Also, no differences between Makena and placebo were seen in the secondary outcomes related to other gestational ages at delivery (<37 weeks [23% Makena vs. 22% placebo, p=0.57), <32 weeks gestation [4.8% Makena vs. 5.2% placebo, p=0.70]) or for the individual components of the neonatal index.

The Applicant raised concerns that the study populations of Trial 002 (U.S only) and Trial 003 (international, including U.S.) differed substantially and that this may have contributed to the discordant outcomes between the two trials. Therefore, exploratory subgroup analyses and comparisons of Trial 003's U.S. population (003-U.S. subgroup) and non-U.S. patients were undertaken. There were no relevant differences in the treatment effect when analyzed by region (U.S. vs. non-U.S.), even though the non-U.S. subgroup appeared to have a lower risk profile based on demographics, social, and behavioral factors compared to the U.S. subgroup. There was no evidence of interaction between treatment and U.S. vs. non-U.S. region for the coprimary endpoints. In the 003-U.S. subgroup:

- Makena did not improve the neonatal composite index. The treatment effect was -2.2% (95% CI: -8.3, 3.9) when analyzed using the stratified Cochran-Mantel-Haenszel (CMH) method and -0.2% (95% CI: -4.9, 2.8) using another approach known as shrinkage analysis.
- Makena did not reduce the risk of delivery <35 weeks (16% Makena vs. 18% placebo). The treatment difference was -2.2% (95% CI: -10.1, 5.7) using the stratified CMH analytical method; this difference was -0.8% (95% CI: -6.0, 3.5) with shrinkage estimation.
- Point estimates of the proportions of women with delivery occurring <37 weeks (33% Makena vs. 28% placebo, a treatment effect of 4.7% [95% CI: -5%, 14%] by the CMH method) or <32 weeks (5.5% Makena vs. 9.2% placebo, a treatment effect of -3.9% [95% CI: -9.6, 1.7] by the CMH method) showed contradictory trends in the treatment effect.

A comparison among Trial 003 overall, the 003-U.S. subgroup, and Trial 002 populations indicated that a greater proportion of subjects in Trial 002 had certain risk factors for PTB, such as being self-identified Blacks or having > 1 prior sPTB, than the 003-U.S. subgroup or Trial 003 overall. However, exploratory subgroup analyses did not show statistically significant

[5] The neonatal morbidity/mortality composite index includes neonatal death, Grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and proven sepsis.

interactions between these risk factors and treatment effect of Makena in Trial 002 or Trial 003. Although these risk factors may have an impact on the PTB rate, there was no evidence in Trial 003 that they impact the treatment effect nor was there consistent convincing evidence of treatment benefit within a specific subpopulation across the two trials.

Published literature on progesterone's effect on preterm birth in women with a prior sPTB

Because findings from Trial 003 were discordant with those of Trial 002, we evaluated published evidence from six randomized, placebo-controlled trials that assessed the effect of progesterone in preterm birth and that included pregnant women with a prior sPTB. These trials studied vaginal progesterone at different doses (90 – 200 mg) in women with various risks for PTB, including a history of sPTB, with different gestational ages at delivery as the primary outcome. The overall evidence based on subgroup analyses in pregnant women with a prior sPTB did not suggest a treatment benefit with progesterone over placebo in reducing the risk of recurrent PTB in these women. These trials and their findings, however, are not directly applicable to Makena; none evaluated injectable HPC in the same target population measuring the same efficacy endpoints as Makena. We also reviewed two recent large meta-analyses. These meta-analyses evaluated progesterone formulations, doses, patient populations, and endpoints dissimilar to those of the trials for Makena and did not reliably inform the treatment effect of Makena for its intended use.

Accelerated approval and evidentiary standards for drug approval

When appropriate, the accelerated approval pathway allows for earlier approval of a drug to treat a serious condition and fill an unmet medical need based on a surrogate endpoint that is reasonably likely to predict clinical benefit but is not itself a direct measure of clinical benefit. The Applicant is required to conduct trial(s) after receiving accelerated approval to confirm the expected clinical benefit. If the confirmatory trial(s) shows that the drug provides clinical benefit, then the conditions initially attached to accelerated approval are generally terminated. (See 21 CFR 314.560.) If the confirmatory trial(s) fail to demonstrate such benefit, FDA may withdraw approval of the drug in accordance with section 506(c)(3) of the FD&C Act and 21 CFR 314.530. With accelerated approval, there is less certainty at the time of approval that the drug will ultimately be shown to improve how patients feel, function or survive; however, this pathway provides earlier patient access than would otherwise be possible to an approved drug that is reasonably likely to confer clinical benefit for a serious condition with an unmet need. In the case of Makena, FDA granted accelerated approval based on the reduction in preterm birth seen in Trial 002; however, confirmatory Trial 003 did not verify clinical benefit on adverse neonatal outcomes to infants born prematurely.

For FDA approval, including accelerated approval, the drug must meet the regulatory standard of "substantial evidence" of effectiveness and the benefits must outweigh the risks. Generally, FDA interprets substantial evidence of effectiveness as evidence of effectiveness from two or more adequate and well-controlled trials. A single positive trial, even if well-designed and well-conducted, may have undetected systemic biases or may reflect a chance finding, increasing the risk of concluding that a drug is effective when in fact it is not. The requirement for at least two adequate and well-controlled trials ensures independent substantiation of experimental findings and strengthens a conclusion of effectiveness. Nonetheless, when appropriate, FDA has the authority and flexibility to conclude that there is substantial evidence of effectiveness based on a single adequate and well-controlled trial. In the case of Makena, FDA determined that Trial 002 was adequate, well-controlled and very persuasive and concluded that this single trial provided substantial evidence of an effect on a surrogate endpoint (effectiveness for reduction in the risk of recurrent preterm birth). It is important to note, however, that at the time this determination was made in 2011, there were no other adequate and well-controlled trials with Makena, and that had there been such additional trial(s), FDA would have considered those data when deciding whether there was substantial evidence of effectiveness.

There are two important scientific and regulatory implications for Makena:

- Accelerated approval: A drug approved under the accelerated approval pathway based on a surrogate endpoint reasonably likely to predict clinical benefit must undergo a confirmatory trial postapproval to verify clinical benefit (i.e., an improvement in how patients feel, function or survive). In the case of Makena, confirmatory Trial 003 did not demonstrate a reduction in adverse neonatal outcomes from preterm birth; therefore, the clinical benefit of Makena remains unverified.

- Substantial evidence of effectiveness: Trial 003 also did not confirm an effect of Makena on gestational age of delivery, the surrogate endpoint used in Trial 002 to support accelerated approval. This raises the question as to whether Makena's accelerated approval is still supported by substantial evidence of effectiveness for the reduction in recurrent preterm birth.

AREAS OF FOCUS FOR ADVISORY COMMITTEE

Based on the above considerations, the key issues are whether there remains substantial evidence of effectiveness of Makena on preterm birth, the unconfirmed clinical benefit of Makena on neonatal outcomes, and implications for Makena's marketing status. Makena received accelerated approval based on findings from Trial 002, which showed a reduction in the proportion of women with preterm delivery <37 weeks compared to placebo, a surrogate endpoint considered reasonably likely to predict clinical benefit. However, Trial 003, an adequate and well-controlled, well-conducted and appropriately powered confirmatory trial, did not show a reduction in preterm birth with Makena compared to placebo, nor did it demonstrate a reduction in neonatal morbidity/mortality. Under accelerated approval regulations, FDA may withdraw the approval of Makena if the Applicant fails to provide confirmatory evidence of efficacy and safety. To place this discussion in the appropriate context, we ask that the Advisory Committee members consider:

- The applicability of the findings of Trial 003 to the U.S. population
- Factors, if any, that may account for the differences in outcomes between Trial 002 and Trial 003
- Whether there continues to be substantial evidence that Makena reduces the risk of recurrent preterm birth in the context of two adequate and well-controlled trials with discrepant efficacy findings on this surrogate endpoint
- If a new confirmatory trial is required, the design of such a trial, including the comparator arm, dose(s) of study medication, location (U.S./North America or international), efficacy endpoints and importantly, the feasibility and likelihood of successfully completing such a trial in a timely manner

- If Makena were to be withdrawn from the market because of lack of efficacy, the likely consequences and their potential impact on public health.

We look forward to a thorough and reasoned discussion of these complex, important matters. Thank you in advance for the vital public health contribution you are making through your participation in this meeting.

Draft Points to Consider:

1. Discuss the effectiveness of Makena, including:
    a. The effects of Makena on recurrent preterm birth in Trial 003, and your interpretation of the discrepant preterm birth results between Trial 002 and Trial 003;
    b. The effects of Makena on neonatal morbidity and mortality;
    c. Relevance of the findings in Trial 003 to the U.S. population and current clinical practice.

2. If a new efficacy trial were to be conducted, discuss the study design, including control, dose(s) of study medication, efficacy endpoints and the feasibility of completing such a trial.

3. Discuss the potential consequences of withdrawing Makena on patients and clinical practice.

4. Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal outcomes?

    Provide rationale for your vote.

5. Based on the findings from Trial 002 and Trial 003, is there substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth?

    Provide rationale for your vote.

6. FDA approval, including accelerated approval, of a drug requires substantial evidence of effectiveness, which is generally interpreted as clinically and statistically significant findings from two adequate and well-controlled trials, and sometimes from a single adequate and well-controlled trial. For drugs approved under the accelerated approval pathway based on a surrogate endpoint, the Applicant is required to conduct adequate and well-controlled postapproval trial(s) to verify clinical benefit. If the Applicant fails to conduct such postapproval trial(s) or if such trial(s) do not verify clinical benefit, FDA may, following an opportunity for a hearing, withdraw approval.

    Should FDA:

    A. Pursue withdrawal of approval for Makena
    B. Leave Makena on the market under accelerated approval and require a new confirmatory trial
    C. Leave Makena on the market without requiring a new confirmatory trial

    Provide rationale for your vote and discuss the following:

    - Vote (A) (withdraw approval) may be appropriate if you believe the totality of evidence does not support Makena's effectiveness for its intended use.

    - Discuss the consequences of Makena removal (if not previously discussed in Discussion point 3)

- Vote (B) (require a new confirmatory trial) may be appropriate if you believe the totality of evidence supports Makena's effectiveness in reducing the risk of recurrent preterm birth, but that there is no substantial evidence of effectiveness on neonatal outcomes. Vote (B) would also reflect a belief that a new confirmatory trial is necessary and feasible.

    - Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth, based on the surrogate endpoint of gestational age at delivery.

    - Also discuss key study elements, including study population, control, dose(s), and efficacy endpoints of the new confirmatory trial (if not previously discussed in Discussion point 2) and approaches to ensure successful completion of such a trial.

- Vote (C) (leave Makena on the market without a new confirmatory trial) may be appropriate if you believe Makena is effective for reducing the risk of recurrent preterm birth and that it is not necessary to verify Makena's clinical benefit in neonates.

    - Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth and why it is not necessary to verify Makena's clinical benefits in neonates.

1. Background

1.1. The Condition and Treatment Options

1.1.1. Preterm Birth

Preterm birth (PTB), defined as delivery between 20 and 37 completed weeks of gestation, is a significant public health concern. Preterm birth may be spontaneous (birth following a spontaneous process, such as preterm labor or preterm premature rupture of membranes) or indicated (delivery initiated by the healthcare provider for maternal or fetal health). According to the Centers for Disease Control and Prevention, in 2017, the U.S. PTB rate was 9.9% overall and 8.1% in singleton pregnancies; the incidence was highest in black women (13.9%) compared to white or Hispanic women (9.1% and 9.6%, respectively).[6] The CDC reported that the rate of preterm birth in the U.S. declined from 2007 (10.4%) to 2014 (9.6%), mostly because of a decline in teenage pregnancy, but has increased from 2014 until 2017 (9.9%). The latter trend is mostly due to an increase in the rate of late preterm birth (delivery 34-36 weeks gestation), while rates for early preterm birth (less 34 weeks) have remained unchanged from 2015. The World Health Organization estimates the global PTB rate to be 10.6%, which is similar to the rate of 11.2% in North America, but there are differences across geographic regions, ranging from 8.7% in Europe to 13.4% in North Africa.[7] In 2015, PTB accounted for 17% of infant deaths [8] and surviving children often suffer developmental delay or long-term neurologic impairment. In 2016, complications of PTB were the leading cause of death globally in children younger than 5 years of age, accounting for approximately 16% of all deaths in this age group, and 35% of deaths among neonates.[9] In general, the risk of adverse outcomes in the preterm neonate decreases with increasing gestational age at delivery.

While the burden of PTB is clear, the causes of PTB are less so, and identifying women who will give birth preterm is challenging. Spontaneous PTB represents a syndrome and its causes are multifactorial. Risk factors for PTB include uterine distension (seen in multifetal pregnancies and polyhydramnios), dysfunction of the cervix (reduced mechanical competence, either resulting from genetic mutations in components of collagen that is required for integrity of the cervix or from repeated surgeries on the cervix), infection of the lower genital tract, and other factors (such as cigarette smoking, inadequate maternal weight, and illicit drug use). The contribution of these factors to PTB, however, is not well-characterized. However, an accepted major risk factor is short cervical length (typically defined as <25 mm observed prior to 24 weeks gestation). Regarding the risk of recurrent PTB, one of the strongest risk factors is a history of a preterm birth, which increases the risk of PTB by about 1.5 to 2-fold. Additionally, the number of prior PTBs and the gestational age of the prior PTBs impact the recurrence risk.

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[6] National Vital Statistics Reports, Vol 67, No. 8, November 7, 2018. https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_08-508.pdf

[7] Chawanpaiboon S, Vogel JP, Moller A-B, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systemic review and modelling analysis. Lancet Glob Health 2019;7(1): e37-46.

[8] CDC – Division of Reproductive Health, National center for Chronic Disease Prevention and Health Promotion. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm

[9] UN Inter-Agency Group for Child Mortality Estimation. Levels and trends in child mortality: Report 2017. New York: United Nations Children's Fund, 2017.

Nonetheless, two-thirds of PTBs occur among women with no identifiable risk factors, causality of PTB has been difficult to determine, and the pathogenesis remains poorly understood.[10]

1.1.2. Treatment to Reduce the Risk of Recurrent Preterm Birth

In January 2003, Trial 002 was presented by the NICHD as the first abstract at the Society for Maternal-Fetal Medicine Meeting. The positive findings from this trial immediately gained extensive media attention, leading to the wide use of compounded HPC to reduce the risk of recurrent PTB. Following the June 2003 publication of Trial 002 in the New England Journal of Medicine, the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice endorsed the use of progesterone only in women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation. In its most recent Practice Bulletin (published 2012, reaffirmed 2018), ACOG recommends progesterone (without specifying the formulation of progesterone) starting in the second trimester in women with a singleton pregnancy and a prior sPTB. ACOG also recommends vaginal progesterone in women with a singleton pregnancy with a shortened cervix and without a prior sPTB. In 2003, the Society for Maternal-Fetal Medicine (SMFM) recommended treatment with either HPC injection or vaginal progesterone for women with a prior spontaneous PTB to prevent the recurrence of PTB; this recommendation was reaffirmed in 2008.[11] Based on published findings of several clinical trials, the SMFM in 2012 revised the guideline to recommend that HPC 250 mg IM weekly be given, starting at 16 to 20 weeks of gestation until 36 weeks or birth, to women with a singleton gestation whose prior sPTB occurred between 20-36$^{6/7}$ weeks gestation.[12] In 2017, SMFM reaffirmed its 2012 recommendation and added that vaginal progesterone should not be considered a substitute for HPC in these patients.[13] As noted previously, Makena is the only FDA-approved treatment for PTB.

1.2. Regulatory Background

1.2.1. Regulatory Standards of Drug Approval

1.2.1.1. Accelerated Approval

Under the accelerated approval pathway [21 CFR part 314, subpart H, and 506(c) of the FD&C Act], FDA may grant marketing approval for a new drug based on adequate and well-controlled clinical trials establishing that the drug has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict

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[10] PRETERM BIRTH CAUSES, CONSEQUENCES, AND PREVENTION. Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Board on Health Sciences Policy. Richard E. Behrman and Adrienne Stith Butler, Editors. INSTITUTE OF MEDICINE OF THE ACADEMIES. THE NATIONAL ACADEMIES PRESS. Washington, D.C. Copyright 2007 by the National Academy of Sciences.

[11] Society for Maternal-Fetal Medicine Publications Committee: Use of progesterone to reduce preterm birth. ACOG Committee opinion number 419, October 2008 (replaces no. 291, November 2003) Obstet Gynecol, 112 (2008), pp. 963-965.

[12] Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. Am J Obstet Gynecol, 206 (2012), pp. 376-386.

[13] The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth Society for Maternal-Fetal Medicine (SMFM) Publications Committee, 2017

clinical benefit. A measurement of clinical benefit directly assesses how a patient feels, functions, or survives. Because gestational age at delivery does not directly measure how a neonate feels, functions, or survives, it is considered a surrogate endpoint, but one that we determined to be a reasonably reliable predictor of the clinical benefit for the neonate. In general, two major concerns with surrogate endpoints are (1) it may not be a true predictor of the clinical benefit and (2) it may not provide a quantitative measure of benefit. Thus, approval under this regulation requires that the Applicant study the drug further to verify and describe its clinical benefit. The confirmatory trials must be adequate and well-controlled and be conducted with due diligence. These trials are usually already ongoing at the time of accelerated approval to ensure their timely completion.

For drugs approved under the accelerated approval pathway, the regulations also outline the conditions that may prompt FDA to withdraw approval:

(1) A postmarketing clinical study fails to verify clinical benefit;
(2) The Applicant fails to perform the required postmarketing study with due diligence;
(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;
(4) The Applicant fails to adhere to the postmarketing restrictions agreed upon;
(5) The promotional materials are false or misleading; or
(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.
(See 21 CFR 314.530)

1.2.1.2. Substantial Evidence of Effectiveness

For FDA approval, including accelerated approval, a drug must meet the regulatory standard of "substantial evidence" of effectiveness for the intended use and the benefits must outweigh the risks.[14] Traditionally, FDA has interpreted substantial evidence of effectiveness as clinically and statistically significant findings from at least two adequate and well-controlled trials. A single positive trial, even if well-conducted, may have biases or may reflect a chance finding, increasing the risk of concluding that a drug is effective when in fact it is not. The requirement for at least two adequate and well-controlled trials ensures independent substantiation of experimental findings and strengthens a conclusion of effectiveness. Nonetheless, when appropriate, FDA has the authority and flexibility to conclude that there is substantial evidence of effectiveness based on a single adequate and well-controlled trial. Conclusions based on two high-quality trials will generally be more secure than those based on a single comparably persuasive study. Therefore, reliance on a single trial is generally limited to situations where a second trial is not feasible (e.g., rare diseases) or ethical (e.g., when one trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a serious disease). Characteristics of a single trial that could support a conclusion of substantial evidence of effectiveness include a large multicenter trial with consistency across study subsets, multiple studies within a single study, multiple endpoints involving different events, and statistically very persuasive findings.

[14] FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998.

1.3. Trial 002 and Approval of Makena

1.3.1. Trial 002

In 1999, the National Institute of Child Health and Human Development initiated a multicenter, double-blind, randomized, placebo-controlled clinical trial through its Maternal-Fetal Medicine Units Network to evaluate the efficacy and safety of HPC injection. The study randomized pregnant women with at least one documented prior sPTB of a singleton fetus to either HPC or placebo in a 2:1 ratio. Eligible subjects were at a gestational age between 16^0 weeks and 20^6 weeks at randomization. Pregnancies with multifetal gestation and known major fetal anomaly (as documented by an ultrasound examination after 14 weeks gestation) were excluded. Women who had progesterone treatment prior to randomization were also excluded, as were women experiencing maternal medical complications (e.g., hypertension requiring medication, seizure disorder) or obstetrical complications. The subjects received HPC 250 mg weekly injections or placebo vehicle beginning on the day of randomization through 36^6 weeks gestation or delivery, whichever occurred first. The primary efficacy endpoint was the proportion of delivery prior to 37^0 weeks gestation in the intent-to-treat (ITT) population.

A total of 463 women were randomized to receive either HPC (N=310) or placebo (N= 153). The two study groups were similar with respect to age, race or ethnicity, body mass index prior to pregnancy, marital status, education, and substance use during pregnancy; 59% of the subjects were African American. Of the 463 women randomized, 418 (90.3%) completed dosing through 36^6 weeks or birth, including 279 (90.0%) in the HPC group and 139 (90.8%) in the placebo group. The efficacy results for gestational age at delivery are shown in Table 1.

Table 1: Proportion of Subjects in Each Treatment Arm Who Delivered at <37 Weeks, <35 Weeks, and <32 Weeks Gestational Age (Trial 002)

Delivery outcome	HPC* %	Placebo %	Treatment Difference and 95% Confidence Interval**
<37 weeks	37.1	54.9	-17.8% [-28.0%. -7.4%]
<35 weeks	21.3	30.7	-9.4% [-19.0%, -0.4%]
<32 weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]

*Four HPC-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact (184, 220, 343, and 364 weeks).
**Adjusted for interim analysis.
Source: FDA-approved Makena prescribing information

Pregnancy after the time of randomization was maintained for an average of six days longer in the HPC group (131 vs. 125 days), with the mean gestational age at delivery being one week greater (36.2 vs. 35.2 weeks for HPC and placebo subjects, respectively).

Makena's effect on reducing recurrent preterm birth appeared independent of race, number of previous preterm deliveries, and gestational age of previous preterm birth. The proportion of women who delivered at <37 weeks in the placebo group appeared notably high (55%). See Table 2.

Table 2: Percentages of Subjects With Delivery <37 Weeks by Gestational Age of Previous Birth, Race, and Number of Previous Preterm Deliveries (Trial 002)

Characteristics	HPC n/N (%)	Placebo n/N (%)
Previous sPTB by gestational age		
20^0 - $<28^0$ weeks	32/82 (40.2%)	19/29 (65.5%)
28^0 - $<32^0$ weeks	21/66 (31.8%)	17/30 (56.7%)
32^0 - $<35^0$ weeks	30/84 (35.7%)	27/55 (49.1%)
35^0 - $<37^0$ weeks	31/78 (39.7%)	21/39 (53.8%)
Race		
Black	66/183 (36.1%)	47/90 (52.2%)
Non-black	49/127 (38.6%)	37/63 (58.7%)
Number of previous PTB		
1 prior PTB	74/224 (33.0%)	40/90 (44.4%)
2 prior PTB	27/56 (48.2%)	31/46 (67.4%)
≥3 prior PTB	14/30 (46.7%)	13/17 (76.5%)

Data based on ITT Population (all randomized subjects). The 4 subjects with missing outcome data were classified as having a preterm birth $<37^0$ weeks (i.e., treatment failure).
Abbreviations: n = number of subjects in a specific category who delivered study pregnancy at $<37^0$ weeks gestation; N = total number of subjects overall in a specific category
Source: Table 11-4, Final Report for Study 17-CT-002

This trial was terminated by the Data and Safety Monitoring Board prior to enrolling the planned 500 subjects because the pre-specified stopping criteria for the primary efficacy endpoint of delivery < 37 weeks gestation were attained at an interim analysis.

Data on the individual components that subsequently constituted the neonatal composite index were prospectively collected. The analysis of a composite index, developed by the Applicant at the request of the FDA, was conducted post-hoc, after the initial submission of the NDA in 2006, to evaluate adverse outcomes in live births and as supportive evidence of Makena's benefit on reducing the risk of recurrent preterm delivery. The neonatal composite index was based on the number of neonates who died or experienced respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis, or necrotizing enterocolitis (NEC). Although the proportion of neonates who experienced one or more events was numerically lower in the Makena arm than placebo (12% vs. 17%, P=0.7), the number of adverse outcomes was limited and the difference between arms was not statistically significant. The same neonatal composite index was prospectively evaluated as a coprimary endpoint for Trial 003.

1.3.2. Approval of Makena

Following the publication of results from Trial 002 in 2003, Adeza Biomedical[15] obtained access to the NICHD data and began discussion with the FDA regarding submission of a new drug application (NDA) based on Trial 002.

[15] The NDA ownership was subsequently transferred to several entities, including Hologics, KV Pharmaceutical, Lumara Health, Inc., and AMAG. Hereafter, all are referred to as "the Applicant."

During the first review cycle of the NDA, FDA brought Makena to the Advisory Committee on Reproductive Health Drugs (the Committee) for discussion in August 2006. As noted previously, the primary endpoint of Trial 002 was the rate of PTB prior to 37 weeks gestation; however, 16 of 21 Committee members found that PTB <37 weeks was not an adequate surrogate for reduction in fetal/neonatal mortality and neonatal morbidity. Thirteen of the 21 Committee members voted that PTB <35 weeks was an adequate surrogate, and 12 members voted that the data submitted provided substantial evidence that Makena prevents PTB at <35 weeks. However, the Committee overwhelmingly voted (19 no, 2 yes) that the submitted data did not provide substantial evidence of benefit on neonatal mortality or morbidity, based on the results of the neonatal morbidity/mortality composite index.[16]

FDA did not approve the application in 2006.[17] The primary deficiency was that efficacy based on a single trial that relied on a surrogate endpoint (deemed by most Committee members to be an inadequate surrogate of neonatal morbidity and mortality) was not sufficiently robust to support approval. FDA determined that further study was needed to provide confirmatory evidence of the drug's efficacy in terms of direct clinical benefit on neonatal outcomes or through an established surrogate such as the rate of preterm birth prior to 35 and 32 weeks gestation. To address this deficiency, the FDA recommended that the Applicant submit a draft protocol and evidence of the feasibility of conducting an additional adequate and well-controlled trial to verify and describe further the clinical benefit of preventing recurrent PTB, as stated under the accelerated approval regulations.

In the second review cycle that began in 2008, the Applicant provided a protocol for a postapproval confirmatory trial for an accelerated approval, and another protocol for an infant follow-up study. During the review, the American College of Obstetricians and Gynecologists (ACOG) issued a revised Committee Opinion on Use of Progesterone to Reduce Preterm Birth.[18] In contrast to the 2003 Committee Opinion,[19] which stated:

> *"When progesterone is used, it is important to restrict its use to only women with a documented history of previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug."*

The 2008 Committee Opinion stated:

> *"Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes."*

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[16] Cross-Discipline Team Leader Review dated February 3, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000CrossR.pdf

[17] Approvable Letter, dated October 20, 2006.

[18] ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 419, October 2008.

[19] ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 291, November 2003.

FDA interpreted this new Opinion as establishing a *de facto* standard of care for women with a previous spontaneous PTB. FDA was concerned that this opinion could adversely impact recruitment of subjects into a placebo-controlled trial. Although the trial protocol (including study design, planned sample size, primary and secondary objectives, and proposed analysis plan) was deemed satisfactory, FDA declined to approve the application again in 2009, requesting that the Applicant provide adequate documentation that it would be feasible to conduct and successfully complete the confirmatory trial. FDA stated that "adequate assurance of feasibility of [the confirmatory trial] can only be addressed by actual initiation of the trial." Further, noting that one clinical site (University of Alabama at Birmingham) contributed 27% of the total number of subjects in Trial 002, FDA requested that the confirmatory trial include at least 15 investigational sites (US and non-US), with no single site enrolling more than 15% of the total number of subjects. Also, at least 10% of the total randomized subjects would need to be from US and Canadian sites.[20]

By the time of the third review cycle for Makena, multiple clinical studies evaluating the consequences of "late preterm birth" (births between 34^0 to 36^6 weeks gestation) had emerged to show that late-preterm infants are less physiologically and metabolically mature than term infants and are thus at higher risk of morbidity and mortality than term infants.[21,22,23,24] This new evidence led the FDA to determine that PTB < 37 weeks was an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit. This determination also led the FDA to reconsider data from Trial 002. For the endpoint of delivery at < 37 weeks, the results were deemed compelling (with a sizeable treatment difference between groups and a p value of 0.0004) and not driven by data obtained from the University of Alabama at Birmingham alone. FDA concluded that evidence in Trial 002 was sufficient to support Makena improving the proportion of PTB occurring at < 37 weeks under accelerated approval.[16] Furthermore, the Applicant initiated the confirmatory trial in 2009 and provided documentation supporting that this trial could be conducted and completed.

1.4. Hydroxyprogesterone and Progesterone Usage

1.4.1. Use During Pregnancy

FDA conducted a Sentinel query to assess the use of HPC or progesterone during the second or third trimester among pregnancies with live-birth deliveries and their potential reasons for use to characterize the context of real-world use of HPC, the drug substance in Makena. The query captured all pregnancies ending in live birth in the Sentinel Distributed Database, including

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[20] Cross-Discipline Team Leader Review dated January 23, 2009 and Complete Response letter dated January 23, 2009.

[21] Engle WA, et al. Committee on Fetus and Newborn, American Academy of Pediatrics. Pediatrics 2007;120(6):1390-401.

[22] McIntire DD, et al. Neonatal mortality and morbidity rates in late preterm births compared with births at term. Obstet Gynecol 2008;111(1):35-41.

[23] Martin JA, et al. Born a bit too early: recent trends in late preterm birth. NCHS Data Brief 2009;Nov(4):1-8.

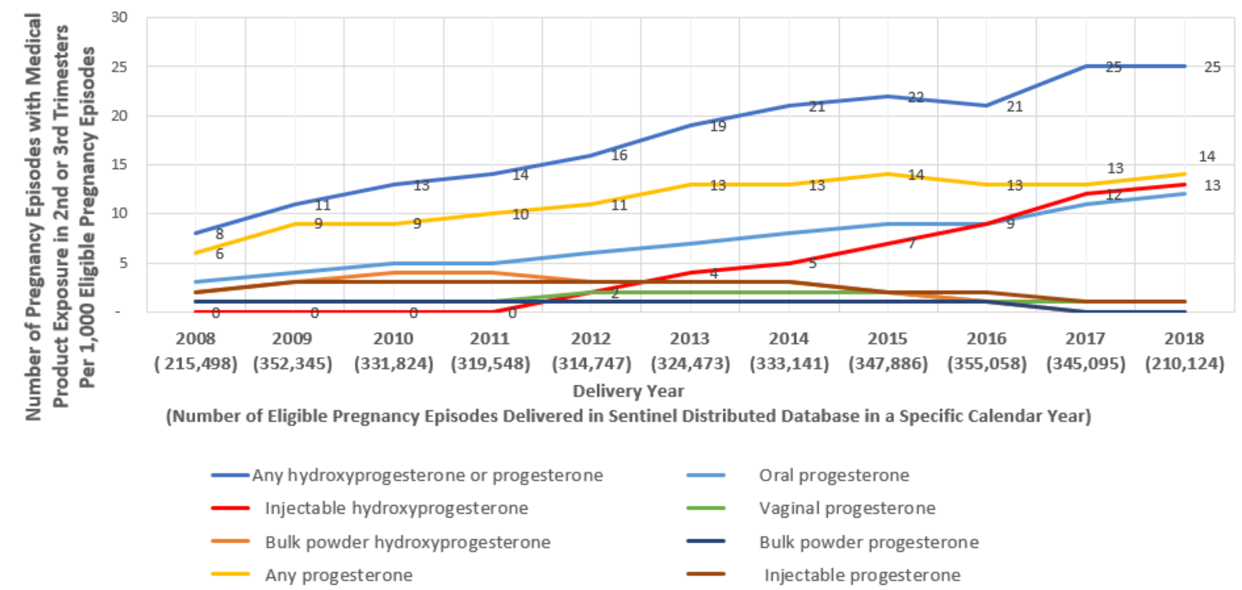
[24] Consortium on Safe Labor, Hibbard JU et al. Respiratory morbidity in late preterm birth. JAMA 2010;304(4):419-25.

singleton and multiple gestations. Progesterone use was included in this analysis because clinical guidelines recommend progesterone treatment for women at risk for preterm delivery.

Methods: This query was conducted in FDA's Sentinel Distributed Database (SDD) using electronic health care data from a distributed network of 15 data partners. The data were primarily comprised of patients with employer-based health care benefits and a small proportion of Medicaid recipients. The study population included women with a live-birth pregnancy (from the current pregnancy) between January 2008 and April 2019 (study period). The exposures of interest were HPC (injectable or bulk powder forms) and progesterone (injectable, oral, vaginal and bulk powder forms). Medical conditions related to potential reasons for HPC or progesterone use were identified by narrow and broad definitions using ICD-9 and ICD-10 diagnosis codes. Included under the narrow definition were diagnosis codes for: (1) history of preterm delivery recorded anytime until one day prior to the start of the current pregnancy, and (2) preterm labor or cervical shortening recorded during the current pregnancy. The broad definition expanded the narrow definition to add the diagnosis for (1) history of preterm labor or cervical shortening recorded anytime until one day prior to the start of the current pregnancy, and (2) preterm delivery recorded during the current pregnancy. Using the diagnostic codes, we could not determine whether the history of preterm delivery was spontaneous or indicated, or whether multiple gestations or other risk factors were present around the time of current pregnancy.

Results: We identified a total of 3,451,121 live-birth pregnancies (from 2,912,911 women) between 2008 and 2019 in FDA's SDD. Note that this number is not a total or annual number of live births in the U.S. Of these, 16,535 pregnancies (5 per 1,000 pregnancies) used injectable HPC during their second or third trimesters and 7,917 used bulk powder HPC (2 per 1,000 pregnancies). In addition, 40,144 (11 per 1,000 pregnancies) pregnancies were exposed to progesterone during the second or third trimesters. In total, approximately 18 per 1,000 pregnancies were exposed to HPC or progesterone during their second or third trimester. The number of exposed pregnancies in each year increased over the study period; the overall the number of exposed pregnancies is modest compared to total pregnancies. The use of HPC or progesterone remains low among pregnancies having a related medical condition, including history of preterm delivery (15%) (Table 3).

Figure 1: Hydroxyprogesterone or Progesterone Use in 2nd or 3rd Trimesters Among 3,449,739, Live-Birth Pregnancy Episodes With Live-Birth Deliveries in the Sentinel Distributed Database Between January 1, 2008, and December 31, 2018, by Delivery Year[1]



[1] Data from 2019 was incomplete and excluded from the figure

Table 3: Proportion of Total Pregnancy Episodes With Related Conditions and With Any Prevalent Hydroxyprogesterone or Progesterone Use During 2nd or 3rd Trimesters Among Women With Live-Birth Deliveries in Sentinel Distributed Database Between January 1, 2008, and April 30, 2019

Related Conditions	Total Number of Pregnancy Episodes with the Related Condition of Interest	Pregnancy Episodes (%) with the Related Conditions of Interest and Any Hydroxyprogesterone or Progesterone Use in the 2nd or 3rd Trimesters
	N	N (%)
Narrow Definition of Related Conditions		
History of preterm delivery[1]	82,255	12,416 (15%)
Preterm labor during the current pregnancy[2]	509,832	29,252 (6%)
Cervical shortening during the current pregnancy[2]	64,557	16,448 (26%)
Any of the narrowly defined conditions above	591,908	40,185 (7%)
Broad Definition of Related Conditions		
History of preterm labor or delivery[1] OR recorded personal history of preterm labor[2]	307,269	34,337 (11%)
Preterm labor or delivery during the current pregnancy[2]	657,719	34,809 (5%)
History of cervical shortening or cervical shortening during the current pregnancy[3]	73,899	17,857 (24%)
Any of the broadly defined conditions above[3]	860,043	51,152 (6%)

[1]Evaluated throughout available enrollment history until the day before pregnancy start date.
[2]Evaluated the day after pregnancy start date until 301 days after pregnancy start date.
[3]Evaluated throughout available enrollment history until 301 days after pregnancy start date.

Among pregnancies exposed to HPC or progesterone, 65% and 83% had at least one related medical condition by narrow and broad definitions, respectively (Table 4), most commonly preterm labor recorded during the current pregnancy. For the pregnancies exposed to injectable HPC, 73% and 98% had at least one narrowly or broadly defined medical condition, respectively.

Table 4: Proportion of Pregnancy Episodes with Related Conditions and Use of Hydroxyprogesterone or Progesterone During 2nd or 3rd Trimesters Among Women With Live-Birth Deliveries in Sentinel Distributed Database Between January 1, 2008, and April 30, 2019

	Any hydroxyprogesterone or progesterone		Hydroxyprogesterone				Progesterone							
			Injectable		Bulk powder		Any		Injectable		Oral		Vaginal	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Number of Pregnancy Episodes with Medical Product Exposure[1]	61,615		16,535		7,917		40,144		8,561		25,471		5,234	
Narrow Definition of Related Conditions														
History of preterm delivery[2]	12,416	20%	6,443	39%	2,568	32%	4,449	11%	1,646	19%	2,365	9%	318	6%
Preterm labor during the current pregnancy[3]	29,252	47%	8,137	49%	5,050	64%	17,969	45%	4,734	55%	10,337	41%	2,515	48%
Cervical shortening during the current pregnancy[3]	16,448	27%	3,228	20%	1,603	20%	12,650	32%	1,694	20%	8,404	33%	2,349	45%
Any of the narrowly defined conditions above[3]	40,185	65%	12,060	73%	6,240	79%	24,351	61%	5,717	67%	14,638	57%	3,499	67%
Broad Definition of Related Conditions														
History of preterm labor or delivery[2] <u>OR</u> recorded personal history of preterm labor during the current pregnancy[3]	34,337	56%	15,696	95%	6,387	81%	14,875	37%	5,381	63%	7,902	31%	1,285	25%
Preterm labor or delivery during the current pregnancy[3]	34,809	56%	8,861	54%	5,811	73%	22,256	55%	5,710	67%	12,875	51%	3,226	62%
History of cervical shortening or cervical shortening during the current pregnancy[4]	17,857	29%	3,982	24%	1,816	23%	13,199	33%	1,840	21%	8,745	34%	2,396	46%
Any of the broadly defined conditions above[4]	51,152	83%	16,240	98%	7,576	96%	30,268	75%	7,344	86%	18,109	71%	4,155	79%

[1] Numbers on the top row are not exclusive because a pregancy could use more than one medicaton of interest
[2] Evaluated throughout available enrollment history until the day before pregnancy start date.
[3] Evaluated the day after pregnancy start date until 301 days after pregnancy start date.
[4] Evaluated throughout available enrollment history until 301 days after pregnancy start date.

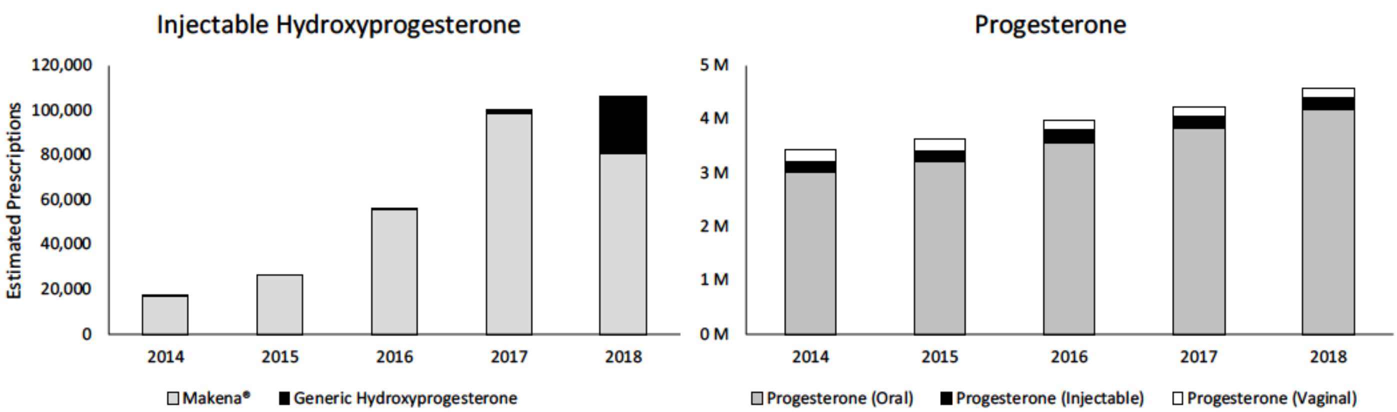
We note several study limitations. First, this analysis did not examine the timing of the related medical conditions relative to the use of HPC or progesterone. Therefore, we interpret the presence of the related medical conditions as possible reasons for use. It should be noted that this analysis captured all live-birth pregnancies in the Sentinel Distributed Database. However, we could not determine whether the recorded diagnosis for a history of preterm delivery was spontaneous or indicated, nor did we examine whether the current pregnancy was singleton or multiple gestation. Therefore, HPC exposed pregnancies may not entirely reflect the approved obstetrical indication of HPC. Second, given that women in the SDD were covered primarily by commercial insurance health plans, our findings may have limited generalizability to women without commercial health insurance. Third, we only examined HPC or progesterone use among pregnancies ending with live births. Lastly, the exposure could be under-estimated owing to the capture of pharmacy dispensing data and medication claims only (no capture of out of pocket payments). Some pharmacies create their own National Drug Codes (NDCs) for compounded HPC which would not have been captured in the analysis.

In summary, this analysis found modest use of HPC and progesterone during the second or third trimesters, even among pregnancies with a diagnostic code of a history of preterm delivery (15%). A high percentage (65% and 83% by narrow and broad definitions, respectively) of pregnancies exposed to HPC or progesterone during their second or third trimester had at least one related medical condition recorded before or during the current pregnancy.

1.4.2. Estimated Use in U.S. Outpatient Settings

FDA analyzed use patterns of injectable HPC and oral, vaginal, or injectable dosage forms of progesterone. Prescriptions for bulk powder forms were excluded due to the inability to determine the final product form and the likelihood that these are underrepresented in the data. We used the Symphony Health PHAST™ Prescription monthly database to estimate the number of prescriptions for injectable HPC and oral, vaginal, or injectable progesterone products dispensed to patients of any age from U.S. outpatient retail or mail order/specialty pharmacies, stratified by molecule and form, annually from 2014 through 2018 (Figure 2). Total prescriptions dispensed for HPC or progesterone products (products with a non-proprietary name of 'hydroxyprogesterone' or 'progesterone') increased 35% from an estimated 3.5 million prescriptions in 2014 to 4.7 million prescriptions in 2018. During this time there was an increase in HPC dispensed prescriptions from an estimated 16,600 prescriptions in 2014 to 106,000 prescriptions in 2018. In 2018, 4.6 million prescriptions (98%) dispensed were for progesterone products.

Figure 2: Estimated Annual Number of Prescriptions Dispensed for Hydroxyprogesterone or Progesterone Products*, Stratified by Molecule and Form, From U.S. Retail or Mail Order/Specialty Pharmacies, Years 2014 to 2018



Prescriptions for bulk powder forms of hydroxyprogesterone and progesterone were not included.
* Products with a non-proprietary name of 'hydroxyprogesterone' or 'progesterone'
Source: Symphony Health PHAST™ Prescription Monthly. Years 2014-2018. Extracted July 2019. File: SH Progesterone and Hydroxyprogesterone Rx 07-29-2019.xlsx

The Symphony Health IDV® Integrated Dataverse was used to obtain the estimated number of 15- to 44-year-old patients who were dispensed prescriptions for injectable HPC and oral, vaginal, or injectable progesterone products from U.S. outpatient retail and mail order/specialty pharmacies, stratified by molecule and form, annually from 2014 through 2018. The total number of patients who were dispensed HPC or progesterone increased by 17% from an estimated 479,000 patients in 2014 to 560,000 patients in 2018 (Table 17 in the Appendix). In 2018, an estimated 42,000 patients (8%) were dispensed prescriptions for HPC, and an estimated 521,000 patients (93%) were dispensed prescriptions for progesterone products. The number of patients who received a prescription for HPC increased from approximately 8,000 patients in 2014 to 25,500 patients in 2016 and 42,000 patients in 2018.

Table 18 in the Appendix provides the estimated number of drug use mentions of progesterone or HPC products among 15- to 44-year-old women, stratified by molecule and form, associated with a diagnosis as reported on U.S. office-based physician surveys from 2013 through 2018, aggregated. An estimated 50% of HPC use mentions were associated with a diagnosis of supervision of high-risk pregnancy (ICD-10 code O09), of which 78% were associated specifically with supervision of a pregnancy with a history of preterm labor (O09.21, data not shown) and 10% were associated specifically with supervision of elderly primigravida and multigravida (O09.5, data not shown). Twenty percent of HPC use mentions were associated with personal history of preterm labor (Z87.51, data not shown), 13% were associated with encounter for supervision of a normal pregnancy (Z34), and 10% were associated with preterm labor (in the current pregnancy, O60). Among progesterone products, an estimated 42% of progesterone injectable use mentions were associated with supervision of high-risk pregnancy and 41% were associated with female infertility (N97). An estimated 59% of progesterone vaginal use mentions were associated with female infertility.

Table 19 in the Appendix provides the estimated number of drug use mentions among women 15 to 44 years old associated with selected diagnoses as reported on U.S. office-based physician surveys from 2013 through 2018, aggregated. An estimated 42% of office visits with any drug use mentions that were associated with a diagnosis of history of preterm labor (O09.21 or Z87.51) mentioned Makena, and an additional 32% mentioned generic HPC products. Of office visits with drug use mentions that were associated with preterm labor in the current pregnancy, physicians mentioned Makena in 14% of visits. Of office visits associated with cervical shortening, physicians mentioned the use of progesterone products but no other products.

In summary, HPC use increased from 2014 to 2018 with the number of patients treated increasing over the same time period. However, HPC use represents a small proportion of the total use of progesterone in FDA's assessment. The primary use of HPC appeared related to obstetrical diagnoses whereas progesterone was used for both obstetrical and infertility related conditions.

2. Confirmatory Trial—Trial 003

2.1. Development of Trial 003

Please refer to Section 1.3 for a detailed discussion regarding the regulatory history of Makena. After the first non-approval of the NDA in 2006, FDA and the Applicant engaged in discussion regarding a clinical protocol to provide evidence verifying clinical benefit. In 2009, Trial 003 was initiated; the study design mirrored that of Trial 002, except that Trial 003 had coprimary endpoints of delivery prior to 35 weeks and the neonatal morbidity/mortality composite index. When Makena was approved under accelerated approval in 2011, the completion of Trial 003 became a requirement post-approval to verify and describe the clinical benefit of Makena.

Trial 003 was initiated in the United States to ensure at least 10% of subjects would be from the United States and Canada before expanding to Europe. However, after Makena's approval in

2011, enrolling U.S. subjects became increasingly difficult. Additional study sites were subsequently opened in Ukraine and Russia.

2.2. Trial Design

Trial 003 was a multicenter, randomized, double-blind, placebo-controlled clinical trial in women, aged 18 years or older, with a singleton pregnancy, and with a history of a previous singleton spontaneous preterm delivery.

2.2.1. Study Objectives

Primary objectives:

- Determine if treatment with Makena reduces the rate of preterm birth prior to 35^0 weeks of gestation.
- Determine if Makena reduces the rate of neonatal mortality or morbidity.

Secondary objectives:

- Exclude a doubling of the risk of fetal/early infant death, defined as spontaneous abortion/miscarriage (delivery from 16^0 through 19^6 weeks of gestation), early infant death (from minutes after birth until 28 days of life) occurring in livebirths prior to 24 weeks gestation, or stillbirth (antepartum or intrapartum death from 20 weeks gestation through term), in the Makena group compared to the placebo group.
- Determine if Makena reduces the rate of preterm birth prior to 32^0 and 37^0 weeks of gestation, respectively.
- Determine if Makena reduces the rate of stillbirth defined as all stillbirths/fetal deaths/in-utero fetal losses occurring from 20 weeks gestation until term.
- Determine if Makena reduces the rate of neonatal death (from minutes after birth until 28 days life) occurring in livebirths born at 24 weeks gestation or greater.

2.2.2. Trial Design and Conduct

Trial 003 was conducted in the United States, Canada, Russia, Ukraine, Hungary, Spain, Bulgaria, the Czech Republic, and Italy. Eligible subjects were randomized in a 2:1 ratio to receive either Makena or placebo and received weekly injections of study drug from randomization (16^0 through 20^6 weeks of gestation) until 36^6 weeks of gestation or delivery, whichever occurred first.

2.2.3. Eligibility Criteria

Major inclusion criteria:

1. Women aged 18 years or older.
2. Singleton gestation.
3. Estimated gestational age between 16^0 weeks and 20^6 weeks, inclusive, at the time of randomization.
4. Documented history of a previous singleton spontaneous preterm delivery. Spontaneous preterm birth was defined as delivery from 20^0 to 36^6 weeks of gestation following spontaneous preterm labor or preterm premature rupture of membranes (pPROM).

Major exclusion criteria:

1. Multifetal gestation.
2. Known major fetal anomaly or fetal demise;
3. Presence of a uterine anomaly (uterine didelphys or bicornuate uterus)
4. Maternal medical/obstetrical complications or had any significant medical disorder
5. Subjects who received a progestin during the current pregnancy AND met one of the following criteria:
    a. Progestin was administered in the 4 weeks preceding the first dose of study medication.
    b. Subjects received HPC
    c. Progestin was administered by a route other than oral or intra-vaginal.
6. Participation in an antenatal study in which the clinical status or intervention may have influenced gestational age at delivery.
7. Participation in this trial in a previous pregnancy.

2.2.4. Analysis Populations

The Applicant defined the following analysis populations:

- Intent-to-treat (ITT) population: all randomized subjects. Subjects were analyzed by the treatment group to which they were randomized, regardless of the blinded study medication (active or placebo) the subject received.
- Safety population: all subjects who received at least one dose of blinded study medication. Subjects were analyzed by the treatment that they received.
- Liveborn neonatal population: all babies of randomized women in the ITT Population who were liveborn and for whom morbidity/mortality data were available.

2.2.5. Efficacy Endpoints

There were two coprimary endpoints:

➢ Surrogate endpoint: PTB prior to 35^0 weeks of gestation
    - Scored as a 1 if any of the following events occurred: a delivery occurring from randomization up through 34^6 weeks of gestation, including a miscarriage occurring from 16^0 through 19^6 weeks of gestation, and an elective abortion.
    - Otherwise, scored as a 0.

➢ Clinical endpoint: Composite neonatal morbidity and mortality index
    - Scored as a 1 if the liveborn neonate had any of the following events occur at any time during the birth hospitalization up through discharge from the neonatal intensive care unit (NICU): neonatal death, grade 3 or 4 intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), or proven sepsis.
    - Otherwise, scored as a 0.

Key secondary endpoints:

- Neonatal death (from minutes after birth until 28 days of life) occurring in livebirths born at 24 weeks or older gestation
- Preterm birth prior to 32^0 weeks of gestation.

- Preterm birth prior to 37^0 weeks of gestation

Preterm birth endpoints were analyzed using the ITT population and neonatal endpoints were analyzed using the liveborn neonatal population.

The study was designed to detect a 30% reduction in PTB <35^0 weeks (from 30% to 21%) and 35% reduction (17% to 11%) in the neonatal composite index, based on the findings from Trial 002. An estimated sample size of 1707 provided at least 90% power to detect the hypothesized difference at alpha level 0.05, and approximately 83% power to rule out a doubling of risk of fetal/early infant death (upper bound of the 95% confidence interval of relative risk <2).

2.2.6. Statistical Analysis Methods

2.2.6.1. Primary Analyses

For each of the coprimary efficacy endpoints, the number and percentage of subjects for the event were presented by treatment groups. Statistical significance between Makena and placebo treatments for each endpoint was determined using a Cochran–Mantel–Haenszel test (CMH) stratified by gestational age at randomization (16^0 to 17^6 weeks and 18^0 to 20^6 weeks).

The interaction between treatment and gestational age at the time of randomization was assessed by a logistic regression model of preterm delivery prior to 35^0 weeks of gestation with terms for treatment, gestational age at randomization stratum, and treatment-by-gestational age at randomization stratum interaction. A similar analysis was performed for the neonatal composite index.

2.2.6.2. Exploratory Analyses

After Trial 003 failed to demonstrate efficacy with the coprimary endpoints, the Applicant conducted a series of exploratory subgroup analyses to understand the potential reasons for the negative findings in Trial 003. The Applicant analyzed the coprimary efficacy endpoints by subgroups defined in Table 5 for the overall study population in Trial 003 and its U.S. subgroup.

Table 5: Trial 003 Subgroup Categories

Subgroup	Categories
Geographic region	U.S., Non-U.S.
Gestational age at randomization	16^0-17^6 weeks, 18^0-20^6 weeks
Gestational age at qualifying delivery*	20^0-<28^0 weeks, 28^0-<32^0 weeks, 32^0-<35^0 weeks, 35^0-<37^0 Weeks
Gestational age at earliest prior PTBs	0-<20^0, 20^0-<28^0, 28^0-<32^0, 32^0-<35^0, 35^0-<37^0
Number of previous PTBs	1, 2, ≥3
Cervical length at randomization	<25 mm ≥25 mm
BMI before pregnancy (kg/m^2)	<18.5, 18.5 - <25, 25-<30, ≥30
Any substance use during pregnancy	Yes, No
Smoking	Yes, No
Alcohol	Yes, No
Illicit drugs	Yes, No
Race	Non-Hispanic black, non-Hispanic non-black
Ethnicity	Hispanic, non-Hispanic
Years of education	≤12, >12

* Qualifying delivery is the most recent preterm delivery.

Generally, FDA does not support unplanned exploratory subgroups analyses, especially when the overall result does not demonstrate efficacy. There are multiple reasons to not consider exploratory subgroup analyses to support establishing efficacy when treatment benefit in the overall population is not significant (FDA draft guidance on multiple endpoints in clinical trials,[25] E17 General Principles for Planning and Design of Multi-Regional Clinical Trials,[26] and E9 Statistical Principles for Clinical Trials[27]). The major statistical reason is inflation of type I error, that is, the heightened probability of incorrectly concluding treatment benefit. When such post-hoc subgroup analyses are used to search for evidence of benefit, there is a high probability that any observed favorable subgroup results are due to chance alone. Therefore, FDA considers exploratory analyses hypothesis-generating.

2.3. Trial Results

2.3.1. Subject Disposition

A total of 1708 subjects were randomized to either Makena (n=1130) or placebo (n=578). Almost all (99%) subjects completed the study and completed treatment (93%). Russia, Ukraine and the U.S. were the three highest enrolling countries, randomizing 621 (36%), 420 (25%) and 391 (23%) subjects, respectively, followed by Hungary, Spain, Bulgaria, Canada, the Czech Republic, and Italy, which each had less than 100 subjects (16% of all subjects).

[25] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf

[26] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM519603.pdf

[27] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf

Table 6: Trial 003 Subject Disposition

	Makena, N(%)	Placebo, N(%)
Subjects randomized (ITT population)	1130	578
Subjects who received at least one dose of study drug (safety population)	1128 (99.8)	578 (100)
Liveborn infant with morbidity data available (liveborn neonatal population)	1091 (96.5)	560 (96.9)
Subjects withdrawing from study	18 (1.6)	6 (1.0)
Subjects discontinuing study drug	80 (7.1)	43 (7.4)

Source: Applicant's study report

2.3.2. Demographics and Baseline Characteristics

The Makena and placebo groups were comparable across all demographic and baseline characteristics. The mean age was 30 years and pre-pregnancy BMI was 24.4 kg/m^2. Of the randomized subjects, 88% were white, 7% were black, and the rest included Native Hawaiian/Pacific Islanders, Asian and American Indian or Alaska native, mixed race and other. Almost all black subjects were from the United States. Approximately 10% of women were never married or divorced/widowed/separated, approximately 8% smoked, approximately 3% consumed alcohol, and 1.3% used illicit drugs.

The treatment groups were also well balanced with respect to obstetrical characteristics in the current and previous pregnancies. Slightly more subjects initiated study drug between 18^0 to 20^6 weeks of gestation (56% Makena, 58% placebo) than between 16^0 to17^6 weeks (44% Makena, 41% placebo). Overall, the median estimated gestational age at randomization was 18.1 weeks for the Makena group and 18.4 weeks for the placebo group.

2.3.3. Primary Efficacy Results

The neonatal composite index was scored as positive (value of 1) in 5.4% and 5.2% of liveborn infants in the Makena and placebo groups, respectively, with a difference of 0.2% (95% CI: -2.0%, 2.5%) as shown in Table 7. The rate of preterm births prior to 35^0 weeks gestation was 11.0% and 11.5% in the Makena and placebo groups, respectively, with a difference of -0.6% (95% CI: -3.8%, 2.6%). The treatment effect of Makena compared to placebo was not statistically significant for both coprimary endpoints.

The rates of preterm birth prior to 32 weeks gestation and prior to 37 weeks gestation were also not different between the Makena and placebo groups.

Table 7: Trial 003 Efficacy Results

Efficacy Endpoints	Makena (N=1130)	Placebo (N=578)	Difference (95% CI)*	P-value*
Neonatal composite index	5.4% (59/1091)	5.2% (29/560)	0.2% (-2.0, 2.5)	0.84
PTB <35^0 weeks (%)	11.0% (122/1113)	11.5% (66/574)	-0.6% (-3.8, 2.6)	0.72
PTB <32^0 weeks (%)	4.8% (54/1116)	5.2% (30/574)	-0.4% (-2.8, 1.7)	
PTB <37^0 weeks (%)	23.1% (257/1112)	21.9% (125/572)	1.3% (-3.0, 5.4)	

Abbreviations: N: number of randomized subjects, CI: confidence interval, PTB: preterm birth
*Difference, 95% CI and P-value were from CMH method stratified by gestational age at randomization
Source: FDA analysis

2.3.4. Exploratory Analyses Results

Applicant's subgroup analysis results: The Applicant's results for the subgroup analyses of the coprimary efficacy endpoints are presented in Table 21 and Table 22 in the Appendix.

FDA's subgroup analysis results:
FDA reviewed all results and conducted subgroup analyses by region and race because these subgroups are evaluated by FDA routinely. Also, they are important subgroups that differentiate the study populations between Trial 003 and Trial 002.

1. By geographic region (U.S. versus non-U.S.)

The Applicant asserts that the overall lower than expected rate of study outcomes substantially limited the ability of Trial 003 to assess the effects of Makena on these outcomes. The Applicant also believes that the lower rate of PTB in Trial 003 could be accounted for by significant geographic differences in PTB rates, where Russia and Ukraine enrolled more subjects but had much lower rates than the United States.

Generally, FDA does not support unplanned subgroup analyses but performed exploratory analysis by region (U.S. versus non-U.S.) to examine whether there were potentially important differences in treatment benefit between U.S. and non-U.S. patients in Trial 003.

For Trial 003, FDA calculated the rate difference between the Makena and placebo groups for each coprimary endpoint, and also the secondary endpoints of birth prior to 32 and 37 weeks gestation, using two methodologies, a stratified CMH method and shrinkage estimation through Bayesian modeling. Traditional subgroup analysis evaluates a particular subgroup category independently from other subgroup categories and relies only on the data from the subjects in that particular category, whereas the Bayesian shrinkage estimation analysis evaluates all subgroup categories jointly. In any trial, some subgroups will perform well, and others will perform poorly. The traditional subgroup analysis is likely to have an increase in the overall error of the estimates compared with the shrinkage analysis, which borrows strength across subgroups.

In the U.S. subgroup of Trial 003, both the neonatal composite index and preterm birth prior to 35 weeks endpoints showed no evidence of a treatment effect using stratified CMH and shrinkage estimation. Although the point estimates of -2.2%, based on the CMH analytic method, for the coprimary endpoints in the U.S. subgroup are in the direction of a beneficial treatment effect, the 95% confidence intervals around these point estimates include 0, indicating no evidence of effect even in these exploratory subgroup analyses. Similarly, no evidence of a treatment effect was seen for the endpoints of delivery < 37 weeks or < 32 weeks. In addition, the interaction between treatment and region for each coprimary endpoint was assessed by a logistic regression model with treatment, region and treatment-by-region interaction; no significant interaction effect was noted. This Trial 003 subgroup analysis did not show that Makena had a favorable treatment effect compared to placebo for either coprimary endpoints in either the U.S. or non-U.S. region (see Table 8). The lack of evidence of an interaction between region and treatment and the lack of evidence of a treatment effect within the U.S. subgroup in Trial 003 does not provide support for regional differences explaining the differences in results between Trial 002 and 003.

Table 8: Trial 003 Results of Efficacy Endpoints by Region (U.S. vs. non-U.S.)

			Difference (95%CI) Makena vs. Placebo	
	Makena (N=1130)	**Placebo (N = 578)**	**Stratified CMH**	**Shrinkage Estimation**
Neonatal composite index	(N=1091)	(N=560)		
U.S.	7.1% (18/252)	9.5% (12/126)	-2.2% (-8.3, 3.9)	-0.2% (-4.9, 2.8)
Non-U.S.	4.9% (41/839)	3.9% (17/434)	1.0% (-1.4, 3.3)	0.6% (-1.6, 2.8)
Preterm birth <35^0 weeks gestation	(N=1113)	(N=574)		
U.S.	15.6% (40/256)	17.6% (23/131)	-2.2% (-10.1, 5.7)	-0.8% (-6.0, 3.5)
Non-U.S.	9.6% (82/857)	9.7% (43/443)	-0.2% (-3.6, 3.2)	0.4% (-3.6, 2.8)
Preterm birth <32^0 weeks gestation	(N=1116)	(N=574)		
U.S.	5.5% (14/256)	9.2% (12/131)	-3.9% (-9.6, 1.7)	-0.6% (-8.4, 3.8)
Non-U.S.	4.7% (40/860)	4.1% (18/443)	0.6% (-1.7, 2.9)	0.5% (-1.8, 2.8)
Preterm birth <37^0 weeks gestation	(N=1112)	(N=572)		
U.S.	33.2% (85/256)	28.2% (37/131)	4.7% (-5.0, 14.3)	1.8% (-3.6, 9.0)
Non-U.S.	20.1% (172/856)	20.0 % (88/441)	0.2% (-4.4, 4.8)	0.9% (-3.5, 5.2)

Source: FDA analysis

2. By race (black/African American vs. non-black/African American)

FDA conducted a subgroup analysis by race (black and non-black) for Trial 003. This race subgroup analysis did not provide evidence that Makena had a treatment effect on either coprimary efficacy endpoints in the black or non-black subgroups.

Table 9: Trial 003 Results of Coprimary Efficacy Endpoints by Race*

	Makena (N=1130)	Placebo (N=578)	Difference (95%CI)
Neonatal composite index			
Black/African American	8.7% (6/69)	7.5% (3/40)	0.8% (-9.9,11.5)
Non-black/African American	5.2% (53/1022)	5.0% (26/520)	0.2% (-2.1, 2.5)
PTB <35^0 weeks gestation			
Black/African American	23.6% (17/72)	19.5% (8/41)	3.0% (-12.5, 18.5)
Non-black/African American	10.1% (105/1041)	10.9% (58/533)	-0.8% (-4.1, 2.4)

*This is based on the entire Trial 003 study population
Source: FDA analysis

Considering the Applicant's and FDA's subgroup analyses results, Makena did not demonstrate any favorable effect (positive finding with nominal statistical significance) over placebo in the key efficacy endpoints in any of the evaluated subgroups.

2.4. Comparisons Between Trial 003 and Trial 002

FDA does not generally support cross-study comparisons to draw efficacy conclusions. Both Trials 003 and 002 were well-controlled and well-conducted, such that each should provide evidence of efficacy on its own merit. Nevertheless, we explored the potential for significant differences in key aspects between Trials 003 and 002 that might clarify their divergent results.

Study design:
Trials 002 and 003 were nearly identical in design. However, trial 002 was conducted entirely in the United States between 1999 to 2002 with preterm birth <37 weeks as the primary efficacy endpoint. Trial 003 was a multinational trial conducted between 2009 to 2018 with coprimary endpoints of a neonatal composite index and preterm birth <35 weeks and was approximately 3.5 times larger than Trial 002. Trial 003 was powered to detect the treatment difference in the coprimary endpoints based on the effect size observed in Trial 002.

Study populations and trial outcomes:
Trial 003 had the following notable differences compared to Trial 002:

Table 10: Comparisons of Selected Characteristics Between Trial 003 and Trial 002

	Trial 003 Overall (N=1708)	Trial 003 U.S. Subgroup (N=391)	Trial 002 (N=463)
Demographics			
Black race	7%	29%	59%
Single or without a partner	10%	31%	50%
Risk factors			
Use of substance* during pregnancy	10%	28%	26%**
Gestational age of qualifying delivery (weeks)	32	33	31
History of more than one previous PTB	15%	27%	28%/41%***
Rate PTB <35 weeks in placebo group+	12%	18%	30%
Rate PTB <37 weeks in placebo group+	22%	28%	55%

*Including tobacco, alcohol, illicit drugs

**Trial 002 collected information on substance use prior to the study pregnancy and not during the pregnancy; 26% is expected to be the higher end of the estimate because it assumes that all women who used substance prior to the pregnancy continued substance use after becoming pregnant.

***HPC – 28%; Placebo – 41%

+It is assumed that the rate in the placebo group approximates that of the contemporaneous intended population

The overall study population of Trial 003 appeared to be at lower risk for factors that might affect the risk of PTB. The 003-U.S. subgroup, however, was more similar to the Trial 002 study population (see Table 10). Yet, unlike Trial 002, there was no consistent evidence of benefit of Makena over placebo in the U.S. subgroup of Trial 003 (see Table 8). As noted above, no statistically significant interaction was seen between treatment and region in Trial 003.

In its briefing document, the Applicant presented post-hoc efficacy analyses exploring a potential relationship between efficacy and the proportion of subjects in a trial with more than one of 5 selective risk factors (history of > 1 prior PTB, black race, substance use in pregnancy, ≤ 12 years of education, unmarried with no partner). The Applicant concluded that Trial 002 had the "highest" risk population (based on the observation that this trial had the highest proportion of study subjects with more than one of these 5 factors), followed by the Trial 003-U.S. subgroup, and then the overall Trial 003 population as being the relatively lowest risk population. The Applicant's analysis showed a trend toward decreasing efficacy in subpopulations the Applicant considered as lower risk. As described earlier, subgroup analyses, especially when conducted post-hoc when the study findings are known, are exploratory and cannot be relied upon for inferences of efficacy.

In addition, it is challenging to identify specific patient subpopulations that may be more responsive to treatment based on the totality of the data. FDA conducted exploratory analyses of Trial 003 using logistic regression models for each coprimary efficacy endpoint with treatment, region, each of the aforementioned 5 risk factors, and its interaction with treatment. These analyses do not provide convincing evidence of efficacy over placebo in any subpopulation and there is no statistically significant interaction between Makena and any of these risk factors. Analogous analyses in the Trial 003-U.S. subgroup produced similar results. In summary, although these risk factors may have an impact on the overall PTB or neonatal composite index rate, there was no evidence in Trial 003 that they impact the treatment effect nor was there consistent convincing evidence of an effect within a specific subpopulation across the two trials. For example, while black women in the U.S. have a higher rate of PTB compared to non-black women, there was no interaction between race (blacks vs. non-blacks) and treatment effect in Trial 002 or Trial 003, nor was there evidence of an effect in the U.S. subgroup in Trial 003. Similarly, women with > 1 prior PTB are considered at higher risk of having recurrent PTB. However, there was no consistent trend in treatment benefit in this population (see Table 22). In Trial 002, these women had a treatment benefit compared to placebo in reduced rate of delivery < 35 weeks (30% Makena vs. 44% placebo). This benefit was not observed in Trial 003, where women with > 1 PTB randomized to Makena had higher rates of birth < 35 weeks compared to placebo (Trial 003 overall: 26% Makena vs. 19% placebo; Trial 003 US subgroup: 25% Makena vs. 17% placebo). Importantly, Makena is approved in women with a singleton pregnancy and a prior sPTB, and evidence of efficacy must be based on that intended population.

In summary, Trial 003 did not demonstrate a treatment benefit of Makena on reducing the neonatal composite index or the rate of spontaneous preterm birth prior to 35 weeks gestation, nor was there evidence of a treatment benefit on the rate of spontaneous preterm birth prior to 37 weeks or 32 weeks gestation. The significant statistical limitations with exploratory subgroup analyses preclude reliable inference of efficacy based on findings from these analyses.

3. Other Evidence of Effects of Progesterone on Preterm Birth

There are published data on other progesterone formulations that have been investigated for the treatment of PTB. To explore the consistency of results, FDA evaluated pertinent published literature on the effect of progesterone on the risk of PTB from randomized, placebo-controlled trials and recent, larger meta-analyses. In its briefing document, the Applicant references several studies that evaluated 17-HPC.[28,29,30,31,32,33] However, most of these publications are not applicable to Makena's approved use because the studies assessed different clinical outcomes (early recurrent pregnancy losses or the prevention of preterm labor). There are additional publications that evaluated the effect of hydroxyprogesterone caproate intramuscular injections on pregnancy outcomes (with dosing regimens ranging from 500 mg weekly or twice weekly to

[28] Levine L. Habitual abortion. A controlled study of progestational therapy. West J Surg Obstet Gynecol. 1964;72:30-36.

[29] Papiernik-Berkhauser E. Double blind study of an agent to prevent pre-term delivery among women at increased risk. Edition Schering. 1970;Serie IV(fiche 3):65-68.

[30] Johnson JWC, et al. Efficacy of 17α-hydroxyprogesterone caproate in the prevention of premature labor. New Engl J Med. 1975;293:675-680.

[31] Yemini M, et al. Prevention of premature labor by 17 alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 1985:151(5):574-577.

[32] Suvonnakote T. Prevention of pre-term labour with progesterone. J Med Assoc Thailand. 1986;69(10):537-542.

[33] Saghafi N, et al. Efficacy of 17α-hydroxyprogesterone caproate in the prevention of preterm delivery. J Obstet Gynaecol Res. 2011;37(10):1342-1345.

1000 mg weekly); however, they are not discussed further here because of the smaller sample size (80 subjects)[34] or the absence of a concurrent control group.[35,36,37,38]

3.1. Randomized, Placebo-Controlled Clinical Trials

The following six placebo-controlled trials evaluated the treatment effect of progesterone on preterm birth and included pregnant women with a history of a prior sPTB. Note that all these trials evaluated vaginal progesterone.

- The 2003 da Fonseca et al. publication reported findings from a single center trial in Brazil that randomized 142 women with a current singleton pregnancy and a history of previous PTB, cerclage, or uterine malformation in a 1:1 ratio to daily vaginal progesterone insert (100 mg) or placebo.[39] Study drug was applied from 24 to 34 weeks of gestation. The majority (>90%) of women enrolled had previous PTB (mean gestational age at delivery 33 weeks). The rate of PTB <37 weeks was 14% in the progesterone group compared to 29% with placebo (p=0.03).
- The 2007 O'Brien et al. publication reported findings from an international trial that randomized 659 women with a singleton pregnancy and a prior singleton sPTB (delivery between 20^0 and 35^0 weeks of gestation) in a 1:1 ratio to daily vaginal progesterone (8% gel, 90 mg) or placebo starting at 18 to 22^6 weeks until 37 weeks or delivery.[40] Both treatment groups had normal cervical length at randomization (3.7 cm). The primary endpoint, the rate of PTB ≤32 weeks, was not statistically different between the two study groups (10% progesterone vs. 11% placebo, odds ratio: 0.9). Similar results were seen for rate of PTB <37 weeks (42% progesterone vs. 41% placebo, odds ratio: 1.08) and ≤35 weeks (23% progesterone vs. 27% placebo., odds ratio: 0.9). No differences were seen in neonatal outcome (Apgar score, birth weight, NICU admission, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and death).

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[34] Hauth JC, et al. The effect of 17 alpha- hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. Am J Obstet Gynecol. 1983;146(2):187-190.

[35] Katz Z, et al. Teratogenicity of progestogens given during the first trimester of pregnancy. Obstet Gynecol. 1985;65(6):775-780.

[36] Rozenberg P, Chauveaud A, Deruelle P, et al. Prevention of preterm delivery after successful tocolysis in preterm labor by 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Am J Obstet Gynecol. 2012;206(3):206 e1-9.

[37] Senat MV, Porcher R, Winer N, et al. Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. Am J Obstet Gynecol. 2013;208(3):194 e1-8.

[38] Winer N, Bretelle F, Senat MV, et al. 17 alpha-hydroxyprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: a randomized controlled trial. Am J Obstet Gynecol. 2015;212(4):485 e481-485 e410.

[39] Da Fonseca EB, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2003 Feb;188(2):419-24

[40] O'Brien JM, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007;30: 687 – 696

- The 2007 Fonseca et al. publication reported findings from an international trial that randomized, in a 1:1 ratio, 250 women with a singleton (N=226) or twin (N=24) pregnancy and a short cervix to daily 200 mg micronized progesterone capsule or placebo.[41] The qualifying risk factor was a cervical length ≤15 mm identified incidentally on routine anatomy ultrasound performed at 20 to 24 weeks of gestation, irrespective of history of PTB; the majority of women (>50%) were nulliparous, approximately a third had no prior PTBs, and 15% had a history of one or more PTB. The study medication was used from 24 to 33^6 weeks of gestation. The primary endpoint was spontaneous delivery <34 weeks. The rate of PTB <34 weeks was 19% in the progesterone group compared to 34% in the placebo group, and this difference was statistically significant (relative risk: 0.56; p=0.007). There was no between-group difference for birthweight, fetal/neonatal death, admission to the NICU or major adverse neonatal outcomes before discharge. Among women with a history of PTB (N=38), progesterone administration did not reduce the incidence of PTB before 34 weeks (95% confidence for relative risk included 1).
- In 2011, Hassan et al. reported results of an international (23 U.S. and 21 non-U.S. sites) trial that randomized 465 asymptomatic women with a singleton pregnancy and a shortened cervix (cervical length between 10 to 20 mm) to daily vaginal progesterone (8% gel, 90 mg) or placebo in a 1:1 ratio.[42] Enrollment was stratified by presence/absence of a history of PTB. Women received study drug from 20 to 23^6 weeks until 36^6 weeks or delivery. The primary endpoint was delivery <33 weeks of gestation. The progesterone group had a significantly lower rate of delivery <33 weeks of gestation compared with the placebo (9% vs. 16%, respectively, p=0.02). In women with a history of PTB (13% of the study population) <35 weeks gestation, vaginal progesterone gel administration was not associated with a reduction in the rate of delivery <33 weeks compared to placebo (relative risk: 0.77, 95% CI 0.29-2.06).
- Published in 2016, the OPPTINUM trial was conducted primarily in the United Kingdom and randomized 1228 women with a singleton pregnancy and at risk for PTB in a 1:1 ratio to daily vaginal progesterone (200 mg) or placebo from 22-24 weeks to 34 weeks of gestation.[43] Eligible women had the following risk factors: previous sPTB at ≤34 weeks gestation, a cervical length ≤25 mm, or a positive fetal fibronectin test combined with other clinical risk factors for preterm birth. Three primary outcomes were defined: fetal death or birth <34 weeks (obstetric), a composite of death, brain injury, or bronchopulmonary dysplasia (neonatal), and a standardized cognitive score at 2 years of age (childhood). After adjusting for multiplicity (i.e. overall type I error for multiple outcomes) progesterone was not found to have a significant benefit on the three primary outcomes. In the subgroup of women with a history of sPTB (N=903), there were no

[41] Fonseca EB, et al. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462-9.

[42] Hassan SS, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2011; 38: 18–31.

[43] Norman JE, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet 2016; 387: 2106–16.

significant differences in the rate of sPTB prior to 34 weeks gestation between the progesterone and placebo groups (odds ratio: 0.82, 95% confidence interval 0.58 to 1.16).

- The 2017 Crowther et al. publication reported findings of the PROGRESS trial, an international trial that randomized 787 women with a singleton or twin pregnancy and a history of sPTB <37 weeks gestation in a 1:1 ratio to vaginal progesterone pessary (100 mg) or placebo.[44] Women were asked to self-administer a vaginal pessary (equivalent to 100 mg vaginal progesterone as active substance) daily from 20 weeks gestation until 34 weeks or delivery. Progesterone treatment had no benefit on the primary outcome of neonatal respiratory distress syndrome (RDS) or other neonatal and maternal morbidities related to preterm birth. Progesterone treatment also had no effect on the incidence of PTB at <37 weeks gestation, a secondary outcome (37% in both treatment groups).

These randomized, placebo-controlled clinical trials enrolled women with varying risk factors for PTB, evaluated different vaginal progesterone doses and formulations, and assessed different outcome measures. Overall, the evidence from these publications does not suggest that vaginal progesterone is beneficial in reducing the risk of preterm birth in women with a history of PTB. Note that FDA has not approved vaginal progesterone for indications related to preterm birth.

3.2. Meta-Analyses

Two published meta-analyses of clinical trials studied the efficacy of progesterone on reducing the risk of PTB: Romero et al. (2018)[45] and Dodd et al. (2013)[46] (Table 11). This section summarizes the meta-analyses, discusses the limitations of each meta-analysis and the regulatory utility of these meta-analyses in supporting the efficacy of Makena. To be consistent with the coprimary endpoint used in Trial 003, we focus on PTB <35 weeks and neonatal composite index.[47]

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[44] Crowther et al. Vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS study): A multicentre, randomised, placebo-controlled trial. PLoS Med 2017 Sep 26;14(9):e1002390.

[45] Romero R, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. Am J Obstet Gynecol 2018;218(2): 161-180.

[46] Dodd, Jodie M., et al. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database of Systematic Reviews*7 (2013).

[47] The components of neonatal composite index include neonatal death prior to discharge, grade 3/4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and proven sepsis.

Table 11: Comparison of Study Designs

	Trial 003	Romero et al.	Dodd et al.
Number of subjects (Number of studies)	HPC (Makena): 1,130 Vehicle: 578 (1 RCT)	Progesterone: 498 Placebo: 476 (5 RCTs)	Progesterone: 1,029 Placebo: 869 (11 RCTs)
Study population	Women with singleton birth and history of spontaneous PTB	Women with singleton birth and short cervix	Women with singleton birth and history of spontaneous PTB
Dose	250 mg weekly	90-100 or 200 mg daily	<500 mg weekly or ≥500 mg weekly
Administration	Intramuscular	Intravaginal	Intramuscular, intravaginal, oral, intravenous
Number of subjects from the United States	HPC (Makena): 258 Placebo: 133	Progesterone: 115 Placebo: 117	No U.S. subjects

Source: Reviewer's table

Romero et al. (2018) assessed whether vaginal progesterone prevents PTB and improves perinatal outcomes in women with a singleton gestation and a mid-second trimester, sonographic short cervix (cervical length ≤25 mm). The authors defined a composite neonatal morbidity and mortality[48] outcome. The doses were either 90-100 mg/day or 200 mg/day by intravaginal administration. The authors performed a meta-analysis and estimated the pooled relative risk (RR) with an associated 95% confidence interval (CI). An additional post-hoc subgroup analysis was conducted using an interaction test to examine whether intervention effects differ between the country of enrollment (United States versus other countries). When the heterogeneity of treatment effect was substantial (I^2 >30%), the results were pooled using a random-effect model. Otherwise, a fixed-effect model was used.

The authors' meta-analysis included 5 studies (498 progesterone subjects versus 476 placebo subjects). The meta-analysis showed that vaginal progesterone significantly reduced the risk of PTB <35 weeks (RR [95% CI] = 0.72 [0.58–0.89]) and the risk of composite neonatal morbidity and mortality (RR [95% CI] = 0.59 [0.38–0.91]). A subgroup analysis compared the risk of PTB <33 weeks (PTB <35 weeks and composite neonatal morbidity and mortality not available) between women enrolled from the United States (RR [95% CI] = 0.73 [0.42–1.27]) and women from other countries (RR [95% CI] = 0.59 [0.43–0.80]). The interaction test for subgroup difference did not show significant difference (p = 0.51). Romero et al. included similar proportions of Caucasian subjects (37.2% vs. 39.7%, progesterone and placebo, respectively) and black subjects (36.3% vs. 37.0%, progesterone and placebo, respectively). The subgroup analysis for reduction of PTB among black subjects had a 95% confidence interval that crossed 1 (RR [95% CI] = 0.86 [0.58–1.26]), whereas that of Caucasian subjects had a 95% confidence interval that excluded 1 (RR [95% CI] = 0.45 [0.28–0.73]).

This meta-analysis included subjects with various dose levels (90-100 or 200 mg per day) and the analysis was mainly driven by 3 large studies. In addition, the meta-analysis was underpowered to evaluate interactions. Although both Trial 003 and Romero et al. included

[48] The only difference between neonatal composite index and composite neonatal morbidity and mortality is whether the intraventricular hemorrhages are restricted to grade 3/4 or all grades, respectively.

women with a singleton pregnancy, subjects of Trial 003 had a high prevalence of spontaneous PTB history (100%) with a low prevalence of short cervix (1.6%), while 30% of subjects in the Romero et al. meta-analysis had a history of sPTB history with a high prevalence of short cervix (100%). Romero et al. does not provide information for the approved dose of 250 mg per week administered by intramuscular injection. Because of the difference in study population, formulation, dose levels, and route of administration in Romero et al., the characteristics of the trials in this meta-analysis are not comparable to Trial 003 and the meta-analysis findings do not inform the efficacy of Makena.

Dodd et al. (2013) assessed the benefits and risks of progesterone for the prevention of PTB for women considered to be at increased risk of PTB. This article did not provide a composite neonatal outcome. However, components of the neonatal composite index, except bronchopulmonary dysplasia, were available. The authors performed a meta-analysis and estimated the pooled RR with an associated 95% CI. A random-effect model was employed when the heterogeneity of treatment effect was substantial (I^2 >30%). Otherwise, a fixed-effect model was used.

We focused on the results from the indicated population, women with a singleton pregnancy and history of spontaneous PTB. The authors dichotomized the weekly cumulative dose to either <500 mg or ≥500 mg per week, and the drug was administered through multiple routes: intramuscular, intravaginal, oral, and intravenous. The authors used a total of 11 clinical studies (1,029 progesterone subjects versus 869 placebo subjects) to conduct a meta-analysis in the indicated population. Not all 11 studies were used to analyze the outcomes. Because the result using an outcome of PTB <35 weeks of gestation was not available, we used the authors' outcome of PTB <34 weeks, which concluded that progesterone significantly reduced the risk of PTB (5 studies; RR [95% CI] = 0.31 [0.14–0.69]). The authors reported that neonatal death (6 studies; RR [95% CI] = 0.45 [0.27–0.76]) and necrotizing enterocolitis (3 studies; RR [95% CI] = 0.30 [0.10–0.89]) showed significant risk reduction.

The analysis using 5 studies to estimate the risk of PTB <34 weeks included subjects treated with multiple dose levels and routes of administration. Therefore, the treatment effect of the indicated dose (250 mg) and administration route is unclear. The I^2 from the five studies indicated substantial heterogeneity (I^2 = 56%), raising concerns of whether the trials were too different to be incorporate into the meta-analysis.

Compared to Trial 003, Dodd et al. neither studied the approved dose (250 mg weekly) nor used the intramuscular injection only for administration. Therefore, this meta-analysis is not directly comparable to Trial 003, providing limited inference from the pooled estimate of the treatment effect. None of the five pooled studies that estimated PTB<34 weeks were conducted in the United States; study sites were Iran, Turkey, Brazil, and India.

The two meta-analyses combined different patient populations, formulations, doses and routes of administration. Thus, these studies did not investigate Makena's indicated population, dose, and route of administration and are not comparable to Trial 003. In addition, we do not have access to the patient-level data, individual study protocols and study reports. Because of issues with the relevancy and the unknown quality of these meta-analyses, the utility of these meta-analyses is limited in addressing the efficacy of Makena.

4. Safety

In Trial 002, total fetal/neonatal deaths included miscarriages (delivery from 16^0 up through 19^6 weeks, stillbirths ([antepartum or intrapartum death] from 20 weeks gestation through term) and neonatal deaths (death of a liveborn born from 20 weeks gestation through term). Of concern was the numerically higher rate of miscarriages and stillbirths in Trial 002. The number of these events were small, and no clear conclusions about the effect of HPC on this safety concern could be made. Trial 003 was powered to exclude a doubling of the risk of fetal/early infant deaths, the primary safety outcome. Fetal/early infant deaths were comprised of the following:

- Spontaneous abortion/miscarriage (delivery from 16^0 up through 19^6 weeks), and
- Stillbirth (antepartum or intrapartum death) from 20 weeks gestation through term, and
- Early fetal death (from minutes after birth until 28 days of life) occurring in livebirths born at < 24 weeks gestation

Fetal and early infant death data from Trial 002 and Trial 003 are juxtaposed in Table 12 and pooled results from both trials are shown in Table 13. Note that the "early fetal death," as defined in 003, was not analyzed as such in Trial 002. The results for "early fetal death" for Trial 002 in Table 12 and Table 13 were analyzed post-hoc for this efficacy supplement. As shown in Table 12, Trial 003 excluded a doubling of the risk of fetal/early infant deaths for Makena (upper bound of 95% was 1.81). When the data from Trial 002 and 003 were pooled, there was no difference in the overall incidence of fetal/early infant deaths with Makena compared to placebo in either trial. There appeared to be a trend toward an increase in stillbirths in both trials; however, the numbers are small, precluding reliable determination of risk. The pooled data from Trials 002 and 003 showed similar results.

Table 12: Fetal and Early Infant Deaths in Trial 002 and Trial 003 (Safety Population)

	Trial 002			Trial 003		
Safety Outcomes N[a], n[b] (%)	**Makena N=310**	**Placebo N=153**	**RR[c] (95% CI)**	**Makena N=1130**	**Placebo N=578**	**RR 95% CI**
Total fetal/early infant deaths[e]	15 (4.8%)	6 (3.9%)	1.22 (0.48, 3.1)	19 (1.7%)	11 (1.9%)	0.87 (0.42, 1.81)
Miscarriages (<20 weeks)	5 (2.4%)	0	N/A	4 (0.5%)	6 (1.3%)	0.32 (0.09, 1.14)
Stillbirths (≥20 weeks)	6 (2.0%)	2 (1.3%)	1.52 (0.31, 7.52)	12 (1.1%)	3 (0.5%)	2.07 (0.59, 7.29)
Early infant deaths	4 (1.3%)	4 (2.6%)	0.49 (0.13, 1.92)	3 (0.3%)	2 (0.4%)	0.73 (0.12, 4.48)

Abbreviations: RR = relative risk, calculated for 17-HPC relative to placebo; CI = confidence interval

[a]N = number of subjects in the Intent to Treat Population in the specified treatment group. The safety population consists of all subjects who received any amount of study medication.

[b]n = number of subjects within a specific category. Percentages are calculated as 100x (n/N)

[c]Relative risk of fetal/early infant death for Makena relative to placebo and is for the Cochran-Mantel-Haenszel test adjusted for gestational age at randomization

[e] Defined as spontaneous abortion/miscarriage, stillbirth, and early fetal death (from minutes after birth until 28 days of life) occurring in livebirths born at <24 weeks gestation

Source: Applicant's analysis (submitted September 25, 2019)

Table 13: Fetal and Early Infant Deaths in Trial 002 and Trial 003 Subjects Combined (Safety Population)

Safety outcomes N[a], n[b] (%)	Trials 002 and 003 Combined		
	Makena N = 1438	**Placebo N = 731**	**RR (95% CI)**
Total fetal/neonatal deaths[e]	34 (2.4%)	17 (2.3%)	1.01 (0.57, 1.79)
Miscarriages (<20 weeks)	n = 1075 9 (0.8%)	n = 555 6 (1.1%)	0.73 (0.26, 2.04)
Stillbirths (≥20 weeks)	n = 1429 18 (1.3%)	n = 724 5 (0.7%)	1.86 (0.69, 4.99)
Early infant deaths	n = 1411 7 (0.5%)	n = 720 6 (0.8%)	0.58 (0.20, 1.73)

Source: Applicant's analysis (submitted September 25, 2019)

Birth at 24 weeks is traditionally considered to be the threshold for viability for a preterm neonate, and the Applicant counted only deaths in livebirths born < 24 weeks (early infant death) in the primary safety outcome. FDA, however, considers deaths occurring from minutes after birth until 28 days of life in livebirths born ≥ 20 weeks gestation (neonatal deaths) to be an important safety measurement. These results on fetal and neonatal deaths from Trial 002 and Trial 003 are juxtaposed in Table 14 and pooled results from both trials are shown in Table 15. Overall, these findings are consistent with those above.

Table 14: Fetal and Neonatal Deaths in Trial 002 and Trial 003 (Safety Population)

	Trial 002			Trial 003		
Safety Outcomes N[a], n[b] (%)	**Makena N=310**	**Placebo N=153**	**RR[c] (95% CI)**	**Makena N=1130**	**Placebo N=578**	**RR 95% CI**
Total fetal/neonatal deaths[c]	19 (6.1%)	11 (7.2%)	0.83 (0.41, 1.70)	22 (2.0%)	13 (2.2%)	0.85 (0.43, 1.67)
Miscarriages (<20 weeks)	5 (2.4%)	0	N/A	4 (0.5%)	6 (1.3%)	0.32 (0.09, 1.14)
Stillbirths (≥20 weeks)	6 (2.0%)	2 (1.3%)	1.52 (0.31, 7.52)	12 (1.1%)	3 (0.5%)	2.07 (0.59, 7.29)
Neonatal deaths	8 (2.7%)	9 (6.0%)	0.44 (0.18, 1.12)	6 (0.5%)	4 (0.7%)	0.73 (0.21, 2.58)

[a]N = number of subjects in the Intent to Treat Population in the specified treatment group. The safety population consists of all subjects who received any amount of study medication.

[b]n = number of subjects within a specific category. Percentages are calculated as 100x (n/N)

[c] Defined as spontaneous abortion/miscarriage, stillbirth, and neonatal death (from minutes after birth until 28 days of life) occurring in livebirths born ≥ 20 weeks gestation

Source: Applicant's analysis (submitted September 27, 2019)

Table 15: Fetal and Neonatal Deaths in Trial 002 and Trial 003 Subjects Combined (Safety Population)

Safety outcomes N[a], n[b] (%)	Trials 002 and 003 Combined		
	Makena N = 1438	**Placebo N = 731**	**RR (95% CI)**
Total fetal/neonatal deaths[c]	41 (2.9%)	24 (3.3%)	0.85 (0.52, 1.40)
Miscarriages (<20 weeks)	n = 1075 9 (0.8%)	n = 555 6 (1.1%)	0.73 (0.26, 2.04)
Stillbirths (≥20 weeks)	n = 1429 18 (1.3%)	n = 724 5 (0.7%)	1.86 (0.69, 4.99)
Neonatal deaths	n = 1411 14 (1.0%)	n = 720 13 (1.8%)	0.54 (0.25, 1.31)

[a]N = number of subjects in the Intent to Treat Population in the specified treatment group. The safety population consists of all subjects who received any amount of study medication.

[b]n = number of subjects within a specific category. Percentages are calculated as 100x (n/N)

[c] Defined as spontaneous abortion/miscarriage, stillbirth, and neonatal death (from minutes after birth until 28 days of life) occurring in livebirths born ≥ 20 weeks gestation

Source: Applicant's analysis (submitted September 27, 2019)

In Trial 003, the same proportion of subjects in each treatment group (3%) experienced serious treatment-emergent adverse event (TEAE) or maternal pregnancy complications (MPC). The most frequently reported serious TEAE or MPC for subjects treated with Makena were premature separation of placenta (5 subjects, 0.4%), placental insufficiency (4 subjects, 0.4%), and pneumonia (3 subjects, 0.3%). The most frequently reported serious TEAE or MPC for subjects treated with placebo were cholestasis (3 subjects, 0.5%) and premature separation of placenta (2 subjects, 0.3%).

Table 16: Most Common (≥ 2 subjects Overall) Serious TEAE and MPC by Preferred Term in Trial 003 (Safety Population)

Preferred Term	Makena N = 1128 N (%)	Placebo N = 578 N (%)
Subjects with at least one serious TEAE/MPC	**34 (3%)**	**18 (3%)**
Cholestasis	0 (0)	3 (0.5)
Endometritis	1 (0.1)	1 (0.2)
Escherichia sepsis	2 (0.2)	0 (0)
Migraine	1 (0.1)	1 (0.2)
Placental insufficiency	4 (0.4)	1 (0.2)
Pneumonia	3 (0.3)	0 (0)
Premature separation of placenta	5 (0.4)	2 (0.3)
Pyelonephritis	2 (0.2)	1 (0.2)
Wound infection	2 (0.2)	0 (0)

Although the number of fetal and neonatal deaths are too low to draw definitive conclusions, the findings of this safety outcome appear to be similar between placebo and Makena. Otherwise, the safety profile of Makena remains unchanged.

5. Appendix

Table 17: Estimated Annual Number of 15- to 44-Year-Old Patients With Dispensed Prescriptions for Hydroxyprogesterone or Progesterone Products, Stratified by Molecule and Form, From U.S. Retail or Mail Order/Specialty Pharmacies 2014-2018

	2014		2015		2016		2017		2018	
	Patients (N)	**%**	**Patients (N)**	**%**	**Patients (N)**	**%**	**Patients (N)**	**%**	**Patients (N)**	**%**
Total Patients (Hydroxyprogesterone and Progesterone)*	478,567	100%	492,992	100%	513,900	100%	546,499	100%	559,985	100%
All Hydroxyprogesterone	8,039	2%	12,581	3%	25,477	5%	38,744	7%	42,320	8%
Makena®	8,035	100%	12,581	100%	25,126	99%	37,581	97%	31,684	75%
Generic Hydroxyprogesterone Caproate	0	0%	0	0%	117	<1%	769	2%	12,325	29%
All Progesterone Products	471,252	98%	481,858	98%	491,869	96%	510,955	93%	520,992	93%
Progesterone (Oral)	341,067	72%	358,172	74%	377,479	77%	403,335	79%	427,085	82%
Progesterone (Injectable)	94,578	20%	96,532	20%	100,647	20%	102,199	20%	113,736	22%
Progesterone (Vaginal)	117,579	25%	107,735	22%	96,986	20%	89,305	17%	77,378	15%

* Prescriptions for bulk powder forms of hydroxyprogesterone and progesterone were not included.
Source: Symphony Health IDV® Integrated Dataverse. Data years 2014-2018. Extracted August 2019. File: SH UPC Progesterone and Hydroxyprogesterone Pt 08-07-2019.xlsx.
Unique patient counts should not be added across time periods or drug categories due to the possibility of double counting those patients who received multiple products within the same calendar year or over multiple periods in the study. Generic hydroxyprogesterone caproate use in 2016 and 2017 were generic Delalutin products.

Table 18: Diagnoses Associated With the Estimated Number of Progesterone or Hydroxyprogesterone Use Mentions Among 15- to 44-Year-Old Women From U.S. Office-Based Physician Surveys, 2013 Through 2018, Aggregated

January 2013 - December 2018	Uses (000)	95% CI (000)	% Share
Total Progesterone and Hydroxyprogesterone	**3,786**	**3,401-4,172**	**100%**
Hydroxyprogesterone Inj	**1,592**	**1,342-1,842**	**42%**
O09 Supervision of high-risk pregnancy	797	620-973	50%
Z87.51 Personal history of preterm labor	324	211-437	20%
Z34 Encounter for supervision of normal pregnancy	211	120-302	13%
O60 Preterm labor in current pregnancy	158	79-237	10%
O34 Maternal care for abnormality of pelvic organs	28	<0.5-61	2%
All Others	75	21-130	5%
Progesterone (all forms)	**2,194**	**1,901-2,488**	**58%**
Progesterone oral	**677**	**514-840**	**31%**
O20 Hemorrhage in early pregnancy	80	24-136	12%
N97 Female infertility	79	23-134	12%
Z34 Encounter for supervision of normal pregnancy	68	17-120	10%
N91 Absent, scanty and rare menstruation	68	16-119	10%
O26 Maternal care for pregnancy-related conditions	64	14-114	9%
All Others	318	206-430	47%
Progesterone injectable	**416**	**288-543**	**19%**
O09 Supervision of high-risk pregnancy	173	91-256	42%
N97 Female infertility	169	87-250	41%
O20 Hemorrhage in early pregnancy	41	1-81	10%
O60 Preterm labor in current pregnancy	17	<0.5-43	4%
O34 Maternal care for abnormality of pelvic organs	9	<0.5-28	2%
All Others	7	<0.5-23	2%
Progesterone vaginal	**1,054**	**851-1,258**	**48%**
N97 Female infertility	622	466-779	59%
O09 Supervision of high-risk pregnancy	125	55-195	12%
O20 Hemorrhage in early pregnancy	121	52-190	11%
O26 Maternal care for pregnancy-related conditions	105	41-170	10%
N96 Recurrent pregnancy loss	45	3-87	4%
All Others	36	<0.5-73	3%

Source: Syneos Health Research and Insights, TreatmentAnswers™ with Pain Panel. Data years 2013-2018. Extracted July 2019. File: Progesterone and Hydroxyprogesterone products by diagnosis 07-22-2019.xlsx. Diagnosis data are not directly linked to dispensed prescriptions but obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity one day a month. Drug use mentions below 100,000 may not represent reliable estimates of use and should be interpreted with caution because the sample size may be very small with corresponding large confidence intervals.

Table 19: Estimated Drug Use Mentions Among 15- to 44-Year-Old Women Associated With Selected Diagnoses From U.S. Office-Based Physician Surveys, 2013-2018, Aggregated

January 2013 through December 2018	Uses (000)	95% CI Uses (000)	Share %
Current/history preterm labor or cervical shortening	**2,364**	**2,059-2,668**	**100%**
History of preterm labor (O09.21X, Z87.51)	1,277	1,054-1,501	54%
Makena	539	394-685	42%
17-Alpha Hydroxyprogesterone	290	184-397	23%
Hydroxyprogesterone	112	46-178	9%
Prenatal OTC	88	29-146	7%
Prenatal Rx	73	19-126	6%
All Others	175	92-258	14%
Preterm labor in current pregnancy (O60.XXX)	936	744-1,127	40%
Nifedipine	172	90-254	18%
Makena	135	62-207	14%
Procardia	132	60-203	14%
Terbutaline Inj	85	27-143	9%
Betamethasone Inj	75	21-129	8%
All Others	338	223-453	36%
Cervical shortening (O26.87X)	151	74-228	6%
Progesterone vaginal	73	20-127	48%
Prometrium	60	11-109	40%
Prochieve	11	<0.5-32	7%
Crinone	7	<0.5-23	5%

Source: Syneos Health Research and Insights, TreatmentAnswers™ with Pain Panel. Data years 2013-2018. Extracted July 2019. File: Progesterone and Hydroxyprogesterone products by diagnosis 07-22-2019.xlsx. Diagnosis data are not directly linked to dispensed prescriptions but obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity one day a month. Drug use mentions below 100,000 may not represent reliable estimates of use and should be interpreted with caution because the sample size may be very small with corresponding large confidence intervals.

Table 20: Comparison of Demographics and Baseline Characteristics: Studies 002 and 003

	Trial 003		Trial 003 U.S. subset		Trial 002	
Variable	**Makena (N=1130)**	**Placebo (N=578)**	**Makena (N=258)**	**Placebo (N=133)**	**Makena (N=310)**	**Placebo (N=153)**
Gestational age of qualifying delivery, weeks	31.3 ± 4.4	31.6 ± 4.2	32.5 ± 3.9	32.5 ± 3.9	30.6 ± 4.6	31.3 ± 4.2
Number of previous preterm deliveries						
1 previous PTB, N (%)	964 (85)	494 (86)	187 (72)	97 (73)	224 (72)	90 (59)
>1 previous PTB, N (%)	166 (15)	82 (14)	71 (28)	36 (27)	86 (28)	63 (41)
Number with cervical length <25 mm at randomization, N (%)	18 (2)	9 (2)	13 (5)	3 (2)	NA	NA
Age, years	30 ± 5	30 ± 5	28 ± 5	27 ± 5	26 ± 6	27 ± 5
Race, N (%)						
Black or African American/African Heritage	73 (6)	41 (7)	72 (28)	41 (31)	183 (59)	90 (59)
White	1004 (89)	504 (87)	170 (66)	84 (63)	79 (25)	34 (22)
Asian	23 (2)	22 (4)	4 (2)	2 (2)	2 (1)	1 (1)
Other	30 (3)	11 (2)	12 (5)	6 (5)	3 (1)	2 (1)
Ethnicity, N (%)						
Hispanic or Latino	101 (9)	54 (9)	31 (12)	23 (17)	43 (14)**	26 (17)**
Non-Hispanic or Latino	1029 (91)	524 (91)	227 (88)	110 (83)	267 (86)	127 (83)
Marital Status, N (%)						
Married or living with partner	1013 (90)	522 (90)	180 (70)	91 (68)	159 (51)	71 (46)
Never married	86 (8)	40 (7)	61 (24)	33(25)	119 (38)	64 (42)
Divorced, widowed or separated	31 (3)	16 (3)	17 (7)	9 (7)	32 (10)	18 (12)
BMI before pregnancy	24.3 ± 7.1	24.7 ± 8.7	27.4 ± 11.8	29.3 ± 15.3	26.9 ± 7.9	26.0 ± 7.0
Years of education	13 ± 2	13 ± 2	13 ± 2	13 ± 2	12 ± 2	12 ± 2
Any substance use during pregnancy, N (%)	105 (9)	51 (9)	69 (27)	40 (30)	85 (27)	36 (24)
Smoking	92 (8)	40 (7)	58 (22)	31 (23)	70 (23)	30 (20)
Alcohol	23 (2)	18 (3)	20 (8)	16 (12)	27 (9)	10 (7)
Illicit drugs	15 (1)	8 (1)	15 (6)	8 (6)	11 (4)	4 (3)

**Hispanic or Latino included in both race and ethnicity category for Study 002

Table 21: Summary of Neonatal Composite Index by Subgroups

	Trial 003		Trial 003 U.S. subset		Trial 002	
Neonatal Composite Index, Subgroup	**Makena (N=1091)**	**Placebo (N=560)**	**Makena (n=252)**	**Placebo (n=126)**	**Makena (N=295)**	**Placebo (N=151)**
GA at randomization (weeks)						
16^0-17^6	25/481 (5.2)	12/230 (5.2)	4/93 (4.3)	4/36 (11.1)	12/97 (12.4)	11/47 (23.4)
18^0-20^6	34/610 (5.6)	17/330 (5.2)	14/159 (8.8)	8/90 (8.9)	23/198 (11.6)	15/104 (14.4)
Overall	59/1091 (5.4)	29/560 (5.2)	18/252 (7.1)	12 /126 (9.5)	35/295 (11.9)	26/151 (17.2)
GA of qualifying delivery* (weeks)						
20^0 - <28^0	17/221 (7.7)	3/97 (3.1)	3/30 (10.0)	2/17 (11.8)	11/74 (14.9)	9/29 (31.0)
28^0 - <32^0	14/198 (7.1)	13/102 (12.7)	3/37 (8.1)	4/18 (22.2)	5/65 (7.7)	5/30 (16.7)
32^0 - <35^0	15/339 (4.4)	9/182 (4.9)	3/73 (4.1)	5/39 (12.8)	11/79 (13.9)	9/54 (16.7)
35^0 - <37^0	13/330 (3.9)	4/176 (2.3)	9/110 (8.2)	1/51 (2.0)	8/77 (10.4)	3/38 (7.9)
GA of earliest prior PTB** (weeks)						
0 - <20^0	24/445 (5.4)	11/228 (4.8)	5/75 (6.7)	3/35 (8.6)	6/46 (13.0)	1/16 (6.3)
20^0 - <28^0	13/153 (8.5)	2/71 (2.8)	4/27 (14.8)	1/18 (5.6)	10/47 (21.3)	9/23 (39.1)
28^0 - <32^0	9/112 (8.0)	7/59 (11.9)	2/29 (6.9)	3/13 (23.1)	4/39 (10.3)	4/20 (20.0)
32^0 - <35^0	7/198 (3.5)	6/99 (6.1)	2/59 (3.4)	4/29 (13.8)	8/55 (14.5)	6/34 (17.6)
35^0 - <37^0	6/183 (3.3)	3/102 (2.9)	5/62 (8.1)	1/31 (3.2)	5/40 (12.5)	2/26 (7.7)
Previous PTB, N (%)						
1	43/933 (4.6)	22/478 (4.6)	11/184 (6.0)	8/92 (8.7)	18/210 (8.6)	10/89 (11.2)
>1[‡]	16/158 (10.1)	7/80 (8.8)	7/78 (9.0)	4/34 (11.8)	17/85 (10.0)	16/62 (25.8)
2	14/125 (11.2)	5/66 (7.6)	6/52 (11.5)	4/28 (14.3)	12/55 (21.8)	8/45 (17.8)
≥3	2/33 (6.1)	2/14 (14.3)	1/16 (6.3)	0/6 (0.0)	5/30 (16.7)	8/17 (47.1)
Cervical length at randomization***, N (%)						
<25 mm	2/17 (11.8)	2/9 (22.2)	1/13 (7.7)	1/3 (33.3)	NA	NA
≥25 mm	44/890 (4.9)	23/444 (5.2)	11/110 (10.0)	10/63 (15.9)	NA	NA
BMI before pregnancy (kg/m^2)						
Underweight (<18.5)	4/80 (5.0)	3/37 (8.1)	0/11 (0)	0/2 (0)	4/25 (16.0)	2/10 (20.0)
Normal (18.5 - <25)	34/629 (5.4)	12/328 (3.7)	7/112 (6.3)	2/49 (4.1)	13/116 (11.2)	14/73 (19.2)
Overweight (25 - <30)	10/249 (4.0)	9/125 (7.2)	6/63 (9.5)	6/34 (17.6)	6/56 (10.7)	5/30 (16.7)
Obese (≥30)	11/133 (8.3)	5/69 (7.2)	5/66 (7.6)	4/41 (9.8)	10/86 (11.6)	5/34 (14.7)

Neonatal Composite Index, Subgroup	Trial 003 Makena (N=1091)	Trial 003 Placebo (N=560)	Trial 003 U.S. subset Makena (n=252)	Trial 003 U.S. subset Placebo (n=126)	Trial 002 Makena (N=295)	Trial 002 Placebo (N=151)
Any substance use during pregnancy, N (%)						
Yes	8/101 (7.9)	5/49 (10.2)	5/67 (7.5)	4/38 (10.5)	12/82 (14.6)	6/35 (17.1)
No	51/990 (5.2)	24/511 (4.7)	13/185 (7.0)	8/88 (9.1)	23/213 (10.8)	20/116 (17.2)
Smoking						
Yes	8/89 (9.0)	4/39 (10.3)	5/57 (8.8)	3/29 (10.3)	10/67 (14.9)	6/29 (20.7)
No	51/1002 (5.1)	25/521 (4.8)	13/195 (6.7)	9/97 (9.3)	25/228 (11.0)	20/122 (16.4)
Alcohol						
Yes	0/23 (0)	4/17 (23.5)	0/19 (0)	3/15 (20.0)	3/26 (11.5)	0/10 (0)
No	59/1068 (5.5)	25/543 (4.6)	18/233 (7.7)	9/111 (8.1)	32/269 (11.9)	26/141 (18.4)
Illicit drugs						
Yes	1/14 (7.1)	1/7 (14.3)	1/13 (7.7)	1/7 (14.3)	2/10 (20.0)	0/4 (0)
No	58/1077 (5.4)	28/553 (5.1)	17/239 (7.1)	11/119 (9.2)	33/285 (11.6)	26/147 (17.7)
Race						
Non-Hispanic black	6/69 (8.7)	3/39 (7.7)	5/68 (7.4)	3/39 (7.7)	22/176 (12.5)	20/89 (22.5)
Non-Hispanic non-black	50/923 (5.4)	23/468 (4.9)	13/153 (8.5)	7/64 (10.9)	8/81 (9.9)	6/36 (16.7)
Ethnicity						
Hispanic	3/99 (3.0)	3/53 (5.7)	0/31 (0)	2/23 (8.7)	5/38 (13.2)	0/26 (0)
Non-Hispanic	56/992 (5.6)	26/507 (5.1)	18/221 (8.1)	10/103 (9.7)	30/257 (11.7)	26/125 (20.8)
Years of education						
≤12	28/458 (6.1)	18/249 (7.2)	9/116 (7.8)	9/69 (13.0)	29/213 (13.6)	18/101 (17.8)
>12	31/632 (4.9)	11/311 (3.5)	9/135 (6.7)	3/57 (5.3)	6/82 (7.3)	8/50 (16.0)

* If more than one prior delivery was sPTB, qualifying delivery was the most recent.
** The earliest PTB may be indicated or spontaneous.
***Cervical length measurement was not captured for all subjects in a treatment group.
GA = gestational age
NA = not available
Source: Applicant Analysis; ǂFDA Analysis.

Table 22: Summary of PTB <35^0 Weeks by Subgroups

Stratification Groups, n/N (%)	Trial 003 Makena (N=1130)	Trial 003 Placebo (N=578)	Trial 003 U.S. Subset Makena (N=258)	Trial 003 U.S. Subset Placebo (N=133)	Trial 02 Makena (N=310)	Trial 02 Placebo (N=153)
GA at randomization (weeks)						
16^0-17^6	61/493 (12.4)	31/238 (13.0)	16/96 (16.7)	9/40 (22.5)	22/103 (21.4)	21/47 (44.7)
18^0-20^6	61/620 (9.8)	35/336 (10.4)	24/160 (15.0)	14/91 (15.4)	41/203 (20.2)	26/106 (24.5)
Overall	122/1113 (11.0)	66/574 (11.5)	40/256 (15.6)	23/131 (17.6)	63/306 (20.6)	47/153 (30.7)
GA of qualifying delivery* (weeks)						
20^0 - <28^0	29/229 (12.7)	9/101 (8.9)	7/31 (22.6)	3/18 (16.7)	21/82 (25.6)	13/29 (44.8)
28^0 - <32^0	24/201 (11.9)	20/104 (19.2)	9/37 (24.3)	4/18 (22.2)	12/65 (18.5)	6/30 (20.0)
32^0 - <35^0	36/344 (10.5)	24/186 (12.9)	9/75 (12.0)	10/40 (25.0)	12/81 (14.8)	18/55 (32.7)
35^0 - <37^0	32/336 (9.5)	13/180 (7.2)	14/111 (12.6)	6/54 (11.1)	18/78 (23.1)	10/39 (25.6)
GA of earliest prior PTB** (weeks)						
0 - <20^0	53/459 (11.5)	26/234 (11.1)	13/78 (16.7)	5/36 (13.9)	9/46 (19.6)	3/16 (18.8)
20^0 - <28^0	21/156 (13.5)	7/73 (9.6)	7/27 (25.9)	3/19 (15.8)	21/55 (38.2)	11/23 (47.8)
28^0 - <32^0	15/113 (13.3)	12/60 (20.0)	8/30 (26.7)	3/13 (23.1)	7/39 (17.9)	5/20 (25.0)
32^0 - <35^0	18/201 (9.0)	12/100 (12.0)	5/59 (8.5)	6/29 (20.7)	9/56 (16.1)	13/35 (37.1)
35^0 - <37^0	15/184 (8.2)	9/106 (8.5)	7/62 (11.3)	6/34 (17.6)	10/40 (25.0)	5/26 (19.2)
Previous PTD, N (%)						
1	80/949 (8.4)	51/491 (10.4)	22/185 (11.9)	17/96 (17.7)	37/220 (16.8)	19/90 (21.1)
>1[‡]	42/164 (25.6)	15/81 (18.5)	18/71 (25.3)	6/35 (17.1)	26/86 (30.2)	28/63 (44.4)
2	29/127 (22.8)	10/67 (14.9)	13/52 (25.0)	4/29 (13.8)	18/56 (32.1)	17/46 (37.0)
≥3	13/37 (35.1)	5/14 (35.7)	5/19 (16.3)	2/6 (33.3)	8/30 (26.7)	11/17 (64.7)
Cervical length at randomization***, N (%)						
<25 mm	4/18 (22.2)	4/9 (44.4)	2/13 (15.4)	1/3 (33.3)	NA	NA
≥25 mm	92/907 (10.1)	45/455 (9.9)	21/112 (18.8)	13/66 (19.7)	NA	NA
BMI before pregnancy						
Underweight (<18.5)	13/83 (15.7)	4/38 (10.5)	0/11 (0)	0/3 (0)	5/25 (20.0)	6/10 (60.0)
Normal (18.5 - <25)	59/637 (9.3)	33/335 (9.9)	20/112 (17.9)	10/51 (19.6)	23/131 (17.6)	26/77 (33.8)
Overweight (25 - <30)	29/255 (11.4)	16/127 (12.6)	9/66 (13.6)	6/34 (17.6)	14/60 (23.3)	10/32 (31.3)
Obese (≥30)	21/138 (15.2)	13/74 (17.6)	11/67 (16.4)	7/43 (16.3)	21/90 (23.3)	5/34 (14.7)

Stratification Groups, n/N (%)	Trial 003		Trial 003 U.S. Subset		Trial 02	
	Makena (N=1130)	Placebo (N=578)	Makena (N=258)	Placebo (N=133)	Makena (N=310)	Placebo (N=153)
Any substance use during pregnancy, N (%)						
Yes	19/105 (18.1)	13/51 (25.5)	11/69 (15.9)	10/40 (25.0)	16/85 (18.8)	16/36 (44.4)
No	103/1008 (10.2)	53/523 (10.1)	29/187 (15.5)	13/91 (14.3)	47/221 (21.3)	31/117 (26.5)
Smoking						
Yes	18/92 (19.6)	11/40 (27.5)	10/58 (17.2)	8/30 (26.7)	13/70 (18.6)	15/30 (50.0)
No	104/1021 (10.2)	55/534 (10.3)	30/198 (15.2)	15/101 (14.9)	50/236 (21.2)	32/123 (26.0)
Alcohol						
Yes	1/23 (4.3)	5/18 (27.8)	1/19 (5.3)	4/16 (25.0)	5/27 (18.5)	2/10 (20.0)
No	121/1090 (11.1)	61/556 (11.0)	39/237 (16.5)	19/115 (16.5)	58/279 (20.8)	45/143 (31.5)
Illicit drugs	2/15 (13.3)	3/8 (37.5)	2/14 (14.3)	3/8 (37.5)	2/11 (18.2)	0/4 (0)
Yes						
No	120/1098 (10.9)	63/566 (11.1)	38/242 (15.7)	20/123(16.3)	61/295 (20.7)	47/149 (31.5)
Race						
Non-Hispanic black	17/72 (23.6)	8/40 (20.0)	16/71 (22.5)	8/40 (20.0)	39/183 (21.3)	32/90 (35.6)
Non-Hispanic non-black	92/940 (9.8)	50/480 (10.4)	19/154 (12.3)	10/68 (14.7)	28/127 (22.0)	15/63 (23.8)
Ethnicity						
Hispanic	13/101 (12.9)	8/54 (14.8)	5/31 (16.1)	5/23 (21.7)	10/41 (24.4)	4/26 (15.4)
Non-Hispanic	109/1012 (10.8)	58/520 (11.2)	35/225 (15.6)	18/108 (16.7)	53/265 (20.0)	43/127 (33.9)
Years of education						
≤12	64/474 (13.5)	40/256 (15.6)	24/120 (20.0)	18/74 (24.3)	49/223 (22.0)	32/103 (31.1)
>12	58/639 (9.1)	26/318 (8.2)	16/136 (11.8)	5/57 (8.8)	14/83 (16.9)	15/50 (30.0)

* If more than one prior delivery was sPTB, qualifying delivery was the most recent.
** The earliest PTB may be indicated or spontaneous.
***Cervical length measurement was not captured for all subjects in a treatment group.
GA = gestational age
NA = not available
Source: Applicant Analysis. ‡FDA Analysis.

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) Roster

Chairperson
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*** Consumer Representative (vacant)**
**** Industry Representative (non-voting)**

Updated: September 23, 2019

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
October 29, 2019

AGENDA

The committee will discuss supplemental new drug application (sNDA 021945/S-023) for MAKENA (hydroxyprogesterone caproate injection, 250 milligrams per milliliter) manufactured by AMAG Pharmaceuticals. In 2011, MAKENA received approval under the accelerated approval pathway (21 CFR part 314, subpart H, and section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)) for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. MAKENA was shown in the preapproval clinical trial to reduce the proportion of women who delivered at less than 37 weeks gestation, a surrogate endpoint that FDA determined was reasonably likely to predict a clinical benefit of preterm birth prevention, such as improved neonatal mortality and morbidity. As required under 21 CFR 314.510, the Applicant conducted a postapproval confirmatory clinical trial to verify and describe clinical benefit. AMAG Pharmaceuticals has disclosed that this completed confirmatory trial did not demonstrate a statistically significant difference between the treatment and placebo arms for the co-primary endpoints of reducing the risk of recurrent preterm birth or improving neonatal mortality and morbidity. The committee will consider the trial's findings and the sNDA in the context of AMAG Pharmaceuticals' confirmatory study obligation.

8:15 a.m.	Call to Order and Introduction of Committee	**Vivian Lewis, MD** Chairperson, BRUDAC
8:25 a.m.	Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Designated Federal Officer, BRUDAC
8:30 a.m.	FDA Opening Remarks	**Christine Nguyen, MD** Deputy Director for Safety Division of Bone, Reproductive and Urologic Products (DBRUP) Office of Drug Evaluation III (ODE III) Office of New Drugs (OND), CDER, FDA
8:45 a.m.	APPLICANT PRESENTATIONS	**AMAG Pharmaceuticals, Inc.**
	Introduction	**Julie Krop, MD** Chief Medical Officer Executive Vice President, Development & Regulatory Affairs AMAG Pharmaceuticals, Inc.
	Clinical Background and Unmet Need	**Michelle Owens, MD** Professor and Medical Director School of Medicine Department of Obstetrics and Gynecology The University of Mississippi Medical Center

AGENDA (cont.)

	APPLICANT PRESENTATIONS (CONT.)	
	Meis Study Design and Results	**Baha Sibai, MD** Professor Department of Obstetrics, Gynecology, and Reproductive Sciences Investigator, MFMU University of Texas Health Science Center of Houston MFMU[1] Network
	PROLONG: Efficacy and Safety	**Laura Williams, MD, MPH** Sr. Vice President, Clinical Development & Biostatistics AMAG Pharmaceuticals, Inc.
	Prevention of Preterm Birth: Clinical Perspective	**Sean Blackwell, MD** Professor and Chair Department of Obstetrics, Gynecology, and Reproductive Sciences Principal Investigator, MFMU University of Texas Health Science Center of Houston MFMU[1] Network
	Conclusion	**Julie Krop, MD**
10:00 a.m.	Clarifying Questions to Applicant	
10:25 a.m.	**BREAK**	
10:35 a.m.	**FDA PRESENTATIONS**	
	Clinical Overview	**Barbara Wesley, MD, MPH** Medical Officer DBRUP, ODEIII, OND, CDER, FDA
	Efficacy in Confirmatory Trial 003	**Jia Guo, PhD** Statistical Reviewer Division of Biometrics 3 (DB3) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA
	Hydroxyprogesterone Caproate (HPC) Utilization in the United States	**Huei-Ting Tsai, PhD** Epidemiologist Division of Epidemiology II (DEPI-II) Office of Pharmacovigilance and Epidemiology (OPE) Office of Surveillance and Epidemiology (OSE) CDER, FDA

AGENDA (cont.)

FDA PRESENTATIONS (CONT.)

	Summary Remarks	**Christina Chang, MD, MPH** Clinical Team Leader DBRUP, ODEIII, OND, CDER, FDA
11:40 a.m.	Clarifying Questions to FDA	
12:00 p.m.	**LUNCH**	
1:00 p.m.	**OPEN PUBLIC HEARING**	
2:00 p.m.	Clarifying Questions to Applicant or FDA	
2:20 p.m.	**BREAK**	
2:30 p.m.	Questions to the Committee/Committee Discussion and Voting	
5:00 p.m.	**ADJOURNMENT**	

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
October 29, 2019

MEETING ROSTER

DESIGNATED FEDERAL OFFICER (Non-Voting)

Kalyani Bhatt, BS, MS
Division of Advisory Committee and Consultant Management
Office of Executive Programs, CDER, FDA

BONE, REPRODUCTIVE AND UROLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Douglas C. Bauer, MD
Professor of Medicine and Epidemiology & Biostatistics
University of California, San Francisco
San Francisco, California

Matthew T. Drake, MD, PhD
Associate Professor of Medicine
Chair, Metabolic Bone Disease Core Group
Division of Endocrinology
Mayo Clinic College of Medicine
Rochester, Minnesota

Vivian Lewis, MD
(Chairperson)
Vice Provost for Faculty Development & Diversity
Professor, Obstetrics and Gynecology
University of Rochester
Rochester, New York

Pamela Shaw, PhD
Associate Professor
Department of Biostatistics and Epidemiology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

TEMPORARY MEMBERS (Voting)

Jonathan M. Davis, MD
Vice-Chair of Pediatrics
Chief of Newborn Medicine
The Floating Hospital for Children at Tufts Medical Center
Professor of Pediatrics
Tufts University School of Medicine
Boston, Massachusetts

Ahizechukwu Eke, MD, MPH
Assistant Professor
Division of Maternal Fetal Medicine
Department of Gynecology & Obstetrics
Johns Hopkins University School of Medicine
Baltimore, Maryland

Annie Ellis
(Patient Representative)
White Plains, New York

Daniel Gillen, PhD
Professor and Chair, Statistics
University of California, Irvine
Irvine, California

TEMPORARY MEMBERS (Voting) (cont.)

Kimberly Hickey, MD
Colonel, Medical Corps, US Army
Chief, Maternal Fetal Medicine
Walter Reed National Military Medical Center
Deputy Director, National Capital Consortium
Uniformed Services University of the Health Sciences
Bethesda, Maryland

Sally Hunsberger, PhD
Mathematical Statistician
Division of Clinical Research
National Institute of Allergy and Infectious Disease
National Institute of Health
Rockville, Maryland

Michael K. Lindsay, MD, MPH
Luella Klein Associate Professor
Chief, Gynecology and Obstetrics Service Grady Health Systems
Director, Division of Maternal Fetal Medicine
Emory University
Atlanta, Georgia

Michele Orza, ScD
(Acting Consumer Representative)
Chief of Staff
Patient-Centered Outcomes Research Institute (PCORI)
Washington, District of Columbia

Uma M. Reddy, MD, MPH
Professor, Department of Obstetrics, Gynecology and Reproductive Sciences
Division Chief, Maternal Fetal Medicine
Section Chief, Maternal Fetal Medicine of Yale New Haven Hospital
Program Director, Maternal-Fetal Medicine Fellowship
Department of Obstetrics, Gynecology and Reproductive Sciences
Yale School of Medicine
New Haven, Connecticut

Brian Smith MD, MPH, MHS
Samuel L. Katz Professor of Pediatrics
Division of Neonatal-Perinatal Medicine
Duke University Medical Center
Durham, North Carolina

Kelly Wade, MD, PhD, MSCE
Attending Neonatologist
Children's Hospital of Philadelphia (CHOP)
Associate Professor of Clinical Pediatrics
University of Pennsylvania
CHOP Newborn Care
Philadelphia, Pennsylvania

Deborah A. Wing, MD, MBA
Senior Client Partner
Los Angeles, California
Formerly, Professor of Obstetrics-Gynecology
Division of Maternal Fetal Medicine
University of California, Irvine
Orange, California

MEETING ROSTER (cont.)

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE (Non-Voting)

Venkateswar Jarugula, PhD
(Acting Industry Representative)
Executive Director
Translation Medicine
Novartis Institutes for Biomedical Research
East Hanover, New Jersey

FDA PARTICIPANTS (Non-Voting)

Christine Nguyen, MD
Deputy Director for Safety
Division of Bone, Reproductive and Urologic Products (DBRUP)
Office of Drug Evaluation III (ODE III)
Office of New Drugs (OND), CDER, FDA

Christina Chang, MD, MPH
Clinical Team Leader
DBRUP, ODEIII, OND, CDER, FDA

Barbara Wesley, MD, MPH
Medical Officer
DBRUP, ODEIII, OND, CDER, FDA

Jia Guo, PhD
Statistical Reviewer
Division of Biometrics 3 (DB3)
Office of Biostatistics (OB)
Office of Translational Sciences (OTS), CDER, FDA

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
October 29, 2019

QUESTIONS

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1. **DISCUSSION:** Discuss the effectiveness of Makena on recurrent preterm birth and neonatal morbidity and mortality.

2. **DISCUSSION:** If a new confirmatory trial were to be conducted, discuss the study design, including control, dose(s) of study medication, efficacy endpoints and the feasibility of completing such a trial.

3. **DISCUSSION:** Discuss the potential consequences of withdrawing Makena on patients and clinical practice.

4. **VOTE:** Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal outcomes?

   Provide rationale for your vote.

5. **VOTE**: Based on the findings from Trial 002 and Trial 003, is there substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth?

   Provide rationale for your vote.

6. **VOTE:** FDA approval, including accelerated approval, of a drug requires substantial evidence of effectiveness, which is generally interpreted as clinically and statistically significant findings from two adequate and well-controlled trials, and sometimes from a single adequate and well-controlled trial. For drugs approved under the accelerated approval pathway based on a surrogate endpoint, the Applicant is required to conduct adequate and well-controlled postapproval trial(s) to verify clinical benefit. If the Applicant fails to conduct such postapproval trial(s) or if such trial(s) do not verify clinical benefit, FDA may, following an opportunity for a hearing, withdraw approval.

   Should FDA:

   A. Pursue withdrawal of approval for Makena
   B. Leave Makena on the market under accelerated approval and require a new confirmatory trial
   C. Leave Makena on the market without requiring a new confirmatory trial

   Provide rationale for your vote and discuss the following:

   - Vote (A) (withdraw approval) may be appropriate if you believe the totality of evidence does not support Makena’s effectiveness for its intended use.

     - Discuss the consequences of Makena removal (if not previously discussed in Discussion point 3)

QUESTIONS (cont.)

- Vote (B) (require a new confirmatory trial) may be appropriate if you believe the totality of evidence supports Makena's effectiveness in reducing the risk of recurrent preterm birth, but that there is no substantial evidence of effectiveness on neonatal outcomes AND you believe that a new confirmatory trial is necessary and feasible.

    - Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth, based on the surrogate endpoint of gestational age at delivery.

    - Also discuss key study elements, including study population, control, dose(s), and efficacy endpoints of the new confirmatory trial (if not previously discussed in Discussion point 2) and approaches to ensure successful completion of such a trial.

- Vote (C) (leave Makena on the market without a new confirmatory trial) may be appropriate if you believe Makena is effective for reducing the risk of recurrent preterm birth and that it is not necessary to verify Makena's clinical benefit in neonates.

    - Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth and why it is not necessary to verify Makena's clinical benefits in neonates.

Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
October 29, 2019

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland.

Topic: The committee discussed supplemental new drug application (sNDA 021945/S 023) for MAKENA (hydroxyprogesterone caproate injection, 250 milligrams per milliliter) manufactured by AMAG Pharmaceuticals. In 2011, MAKENA received approval under the accelerated approval pathway (21 CFR part 314, subpart H, and section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)) for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. MAKENA was shown in the preapproval clinical trial (Trial 002) to reduce the proportion of women who delivered at less than 37 weeks gestation, a surrogate endpoint that FDA determined was reasonably likely to predict a clinical benefit of preterm birth prevention, such as improved neonatal mortality and morbidity. As required under 21 CFR 314.510, the Applicant conducted a post approval confirmatory clinical trial (Trial 003) to verify and describe clinical benefit. AMAG Pharmaceuticals has disclosed that this completed confirmatory trial did not demonstrate a statistically significant difference between the treatment and placebo arms for the co-primary endpoints of reducing the risk of recurrent preterm birth at less than 35 weeks gestation or improving neonatal mortality and morbidity. The committee considered the trial’s findings and the sNDA in the context of AMAG Pharmaceuticals’ confirmatory study obligation.

These summary minutes for the Ocotber 29, 2019, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration were approved on November 22, 2019.

I certify that I attended the November 22, 2019, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/	**/S/**
Kalyani Bhatt, BS, MS *Designated Federal Officer, BRUDAC*	Vivian Lewis, MD *Chairperson, BRUDAC*

Summary Minutes of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
October 29, 2019

The Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on October 29, 2019, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and AMAG Pharmaceuticals. The meeting was called to order by Vivian Lewis, MD (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS (Designated Federal Officer). There were approximately 175 people in attendance. There were sixteen (16) Open Public Hearing (OPH) presentations.

A verbatim transcript will be available, in most instances, approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed supplemental new drug application (sNDA 021945/S-023) for MAKENA (hydroxyprogesterone caproate injection, 250 milligrams per milliliter) manufactured by AMAG Pharmaceuticals. In 2011, MAKENA received approval under the accelerated approval pathway (21 CFR part 314, subpart H, and section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)) for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. MAKENA was shown in the preapproval clinical trial (Trial 002) to reduce the proportion of women who delivered at less than 37 weeks gestation, a surrogate endpoint that FDA determined was reasonably likely to predict a clinical benefit of preterm birth prevention, such as improved neonatal mortality and morbidity. As required under 21 CFR 314.510, the Applicant conducted a post approval confirmatory clinical trial (Trial 003) to verify and describe clinical benefit. AMAG Pharmaceuticals has disclosed that this completed confirmatory trial did not demonstrate a statistically significant difference between the treatment and placebo arms for the co-primary endpoints of reducing the risk of recurrent preterm birth at less than 35 weeks gestation or improving neonatal mortality and morbidity. The committee considered the trial’s findings and the sNDA in the context of AMAG Pharmaceuticals’ confirmatory study obligation.

Attendance:
Bone, Reproductive and Urologic Drugs Advisory Committee Members Present (Voting): Douglas C. Bauer, MD; Matthew T. Drake, MD, PhD; Vivian Lewis, MD (Chairperson); Pamela Shaw, PhD

Bone, Reproductive and Urologic Drugs Advisory Committee Members Not Present (Voting): Toby Chai, MD; James Q. Clemens, MD, FACS, MSCI; ; Beatrice Edwards, MD, MPH, FACP; Margery Gass, MD; Christian P. Pavlovich, MD; Gloria Richard Davis, MD, MBA, NCMP, FACOG

Bone, Reproductive and Urologic Drugs Advisory Committee Member Not Present (Non-Voting): Gerard G. Nahum, MD, FACOG (Industry Representative)

Temporary Members (Voting): Jonathan M. Davis, MD; Ahizechukwu Eke, MD, MPH; Annie Ellis (Patient Representative); Daniel Gillen, PhD; Kimberly Hickey, MD; Sally Hunsberger, PhD; Michael K. Lindsay, MD, MPH; Michele Orza, ScD (Acting Consumer Representative); Uma M. Reddy, MD, MPH; Brian Smith MD, MPH, MHS; Kelly Wade, MD, PhD, MSCE; Deborah A. Wing, MD, MBA

Acting Industry Representative to the Committee (Non-voting): Venkateswar Jarugula, PhD (Acting Industry Representative)

FDA Participants (Non-Voting): Christine Nguyen, MD; Barbara Wesley, MD, MPH; Christina Chang, MD, MPH; Jia Guo, PhD

Open Public Hearing Speakers: Meena M. Aladdin, PhD (Public Citizen); Adam C. Urato, MD (MetroWest Medical Center); Stephanie Fox-Rawlings, PhD (National Center for Health Research); Washington Clark Hill, MD, FACOG (Florida Department of Health, Sarasota County); John R. Barton, MD, MS (Baptist Health Lexington); Danielle Boyce (statement read by Robin Osman); Mary Norton, MD (Society for Maternal-Fetal Medicine); Anabel Jimenez-Gomez (statement read by Amelia Chiaverini); Kelle Moley, MD (March of Dimes); Allison Johnson; Glory M. Joseph (statement read by Allison Johnson); Marc Jackson, MD, MBA (The American College of Obstetricians and Gynecologists); Amelia Chiaverini; Michael Randell, MD, MBA; Steven Caritis, MD (University of Pittsburgh School of Medicine); Elizabeth Thom, PhD (George Washington University)

The agenda was as follows:

Call to Order and Introduction of Committee	**Vivian Lewis, MD** Chairperson, BRUDAC
Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Designated Federal Officer, BRUDAC
FDA Opening Remarks	**Christine Nguyen, MD** Deputy Director for Safety Division of Bone, Reproductive and Urologic Products (DBRUP) Office of Drug Evaluation III (ODE III) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**AMAG Pharmaceuticals, Inc.**
Introduction	**Julie Krop, MD** Chief Medical Officer Executive Vice President, Development & Regulatory Affairs

	AMAG Pharmaceuticals, Inc.
Clinical Background and Unmet Need	**Michelle Owens, MD** Professor and Medical Director School of Medicine Department of Obstetrics and Gynecology The University of Mississippi Medical Center
Meis Study Design and Results	**Baha Sibai, MD** Professor Department of Obstetrics, Gynecology, and Reproductive Sciences Investigator, MFMU University of Texas Health Science Center of Houston MFMU[1] Network
PROLONG: Efficacy and Safety	**Laura Williams, MD, MPH** Sr. Vice President, Clinical Development & Biostatistics AMAG Pharmaceuticals, Inc.
Prevention of Preterm Birth: Clinical Perspective	**Sean Blackwell, MD** Professor and Chair Department of Obstetrics, Gynecology, and Reproductive Sciences Principal Investigator, MFMU University of Texas Health Science Center of Houston MFMU[1] Network
Conclusion	**Julie Krop, MD**
Clarifying Questions to Applicant	

BREAK

FDA PRESENTATIONS

Clinical Overview	**Barbara Wesley, MD, MPH** Medical Officer DBRUP, ODEIII, OND, CDER, FDA
Efficacy in Confirmatory Trial 003	**Jia Guo, PhD** Statistical Reviewer Division of Biometrics 3 (DB3) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA

Hydroxyprogesterone Caproate (HPC) Utilization in the United States	**Huei-Ting Tsai, PhD** Epidemiologist Division of Epidemiology II (DEPI-II) Office of Pharmacovigilance and Epidemiology (OPE) Office of Surveillance and Epidemiology (OSE) CDER, FDA
Summary Remarks	**Christina Chang, MD, MPH** Clinical Team Leader DBRUP, ODEIII, OND, CDER, FDA

Clarifying Questions to FDA

LUNCH

OPEN PUBLIC HEARING

Clarifying Questions to Applicant or FDA

BREAK

Questions to the Committee/Committee Discussion and Voting

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the effectiveness of Makena on recurrent preterm birth and neonatal morbidity and mortality.

   Committee Discussion: *There was general consensus among committee members that neither Trial 002 nor Trial 003 showed a treatment benefit of Makena on neonatal morbidity or mortality. The committee members further agreed that the data regarding preterm birth rates were conflicting, but there was a range of opinion as to which of the two trials better informed the efficacy of Makena for this outcome. Certain committee members opined that Trial 003 was large enough to show that there were no effect modifiers that could explain the differences in efficacy findings between 002 and 003. Further, the members could not identify a subgroup of patients where the efficacy results were consistent between Trials 002 and 003. Several members of the committee questioned the high rate of preterm birth in the placebo arm in Trial 002. Several commented on the smaller size of the US cohort in Trial 003 (23% of the total), making it difficult to interpret findings. Others were encouraged by the trend of positive treatment effect in the US subgroup in Trial 003, although the findings were not statistically significant. See the transcript for details of the committee discussion.*

2. **DISCUSSION:** If a new confirmatory trial were to be conducted, discuss the study design, including control, dose(s) of study medication, efficacy endpoints and the feasibility of completing such a trial.

   Committee Discussion: *The committee members agreed that, given the years to complete Trial 003, the number of sites used, and professional societies' guidelines, a new placebo-controlled trial would be extremely challenging and likely not feasible. Several committee members commented that pharmacokinetic studies should be performed to assess dosing, timing of drug administration and drug metabolism. Committee members also noted that studies should include an "enriched" population, such as pregnant women who are obese, with family histories of preterm birth, with substance abuse history, and recurrent preterm birth. Some committee members also recommended inclusion of other populations that might benefit, such as patients of different ages and racial groups. Some members recommended a study to look at "responders" vs "non-responders" and perhaps study pharmacogenetics. Other study design alternatives noted by committee members included comparing Makena to vaginal progesterone, a dose escalation study, a dose-response study, or creating a registry of women who used Makena. Some members noted that only a randomized control trial, and not observational studies, could provide the data needed. See the transcript for details of the committee discussion.*

3. **DISCUSSION**: Discuss the potential consequences of withdrawing Makena on patients and clinical practice.

   Committee Discussion: *Several members noted that Makena withdrawal from the US market would lead to resumption of use of compounded (hydroxyprogesterone caproate) HPC and use of other progesterone products. Some expressed concerns over unknown risks of compounded HPC from a safety perspective and quality perspective. Committee members also noted that the greatest burden could be felt by the most vulnerable groups (e.g., lower socioeconomic groups). Committee members also commented on the emotional burden for patients, and their providers, who are desperate for a treatment. On the other hand, some members commented on the potential positive consequences of Makena's withdrawal. These included the opportunity to bring the discussion of Makena's efficacy back to equipoise to allow the conduct of an adequate and well-controlled trial to inform Makena's efficacy in a defined population. See the transcript for details of the committee discussion.*

4. **VOTE:** Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal outcomes?

   Provide rationale for your vote.

   Vote Result: Yes: 0 No: 16 Abstain: 0

   Committee Discussion: *The committee unamiously agreed that the findings from Trial 003 do not verify the clinical benefit of Makena on neonatal outcomes. The committee* *members noted that there were no other data that supported the clinical benefit on the neonate. A neonatogist commented that significantly adverse neonatal outcomes in infants born after 32 – 34 weeks gestation are relatively rare. To detect treatment effect of Makena on these outcomes would likely require a trial larger than Trial 003. See the transcript for details of the committee discussion.*

5. **VOTE**: Based on the findings from Trial 002 and Trial 003, is there substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth?

   Vote Result: Yes: 3 No: 13 Abstain: 0

   Committee Discussion: *The majority of the committee members agreed that, based on the findings from Trial 002 and Trial 003, there is not substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth. The committee members who voted "No" based their vote on the statutory and scientific definition of "substantial evidence of effectiveness," because Trial 003 did not substantiate the positive findings on preterm birth seen in Trial 002. These members also noted there was no treatment effect seen in any of the Trial 003 subgroups analyzed, and that there was no evidence of an interaction between the treatment effect of Makena and risk factors for preterm birth to explain the differences in the efficacy findings between Trials 003 and 002. Because no subgroup could be identified to have benefitted from Makena in both Trials 002 and 003, the appropriate patient population could not be determined. Those who voted "Yes" stated that the findings from Trial 002 were compelling and the positive trend seen in the U.S. subgroup in Trial 003 was encouraging. Although there was no evidence of effectiveness of Makena in Trial 003, they opined that the study's population, a majority of whom were from Russia and Ukraine, was not relevant to the U.S. and that the population's low-risk of pre-term birth may have obscured the evidence of effectiveness in U.S. women. See the transcript for details of the committee discussion.*

6. **VOTE:** FDA approval, including accelerated approval, of a drug requires substantial evidence of effectiveness, which is generally interpreted as clinically and statistically significant findings from two adequate and well-controlled trials, and sometimes from a single adequate and well-controlled trial. For drugs approved under the accelerated approval pathway based on a surrogate endpoint, the Applicant is required to conduct adequate and well-controlled post approval trial(s) to verify clinical benefit. If the Applicant fails to conduct such post approval trial(s) or if such trial(s) do not verify clinical benefit, FDA may, following an opportunity for a hearing, withdraw approval.

   Should FDA:

   A. Pursue withdrawal of approval for Makena
   B. Leave Makena on the market under accelerated approval and require a new confirmatory trial
   C. Leave Makena on the market without requiring a new confirmatory trial

   Provide rationale for your vote and discuss the following:

- Vote (A) (withdraw approval) may be appropriate if you believe the totality of evidence does not support Makena's effectiveness for its intended use.
    - o Discuss the consequences of Makena removal (if not previously discussed in Discussion point 3)
- Vote (B) (require a new confirmatory trial) may be appropriate if you believe the totality of evidence supports Makena's effectiveness in reducing the risk of recurrent preterm birth, but that there is no substantial evidence of effectiveness on neonatal outcomes AND you believe that a new confirmatory trial is necessary and feasible.
    - o Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth, based on the surrogate endpoint of gestational age at delivery.
    - o Also discuss key study elements, including study population, control, dose(s), and efficacy endpoints of the new confirmatory trial (if not previously discussed in Discussion point 2) and approaches to ensure successful completion of such a trial.
- Vote (C) (leave Makena on the market without a new confirmatory trial) may be appropriate if you believe Makena is effective for reducing the risk of recurrent preterm birth and that it is not necessary to verify Makena's clinical benefit in neonates.
    - o Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth and why it is not necessary to verify Makena's clinical benefits in neonates.

Vote Result: A: 9 B: 7 C: 0

Committee Discussion: *The committee members who voted "A" noted that the totality of evidence did not provide substantial evidence of effectiveness of Makena in the reducing the risk of recurrent preterm birth. Furthermore, there is no evidence from Trials 002 and 003 that Makena benefits the neonate, which is the goal of treatment. These members stated that the only way to definitely determine whether Makena is effective would be to conduct a well-designed, prospective, randomized clinical trial. They expressed that the withdrawal of Makena would facilitate the conduct of such a trial in the US and that professional societies should take a leadership role in communicating the importance of gathering this information. Some of these committee members, however, expressed concerns over Makena's withdrawal, because of potential clinical and societal repurcussions.*

The committee members who voted "B" acknowledged the efficacy data for reducing the risk of recurrent preterm birth are conflicting and not particularly persuasive. They also *recognized the need for more data, especially to identify subpopulations that might benefit from Makena. However, these members did not believe another randomized, controlled trial would be feasible under any circumstance, including after withdrawal of Makena's approval. They were concerned that prescribers and patients would insist on receiving treatment, regardless of the evidence of efficacy, and would resort to compounded products or other progesterone products with even less evidence. Some members indicated that withdrawal of Makena would be warranted only if the drug was unsafe.*

None of the committee members voted "C."

See the transcript for details of the committee discussion.

The meeting adjourned at approximately 4:30 p.m.

17 α-Hydroxyprogesterone Caproate (Makena®) for Women with Singleton Pregnancy and Prior Spontaneous Preterm Birth

FDA Advisory Committee Meeting

Division of Bone, Reproductive and Urologic Products

AMAG Pharmaceuticals, Inc.

October 29, 2019

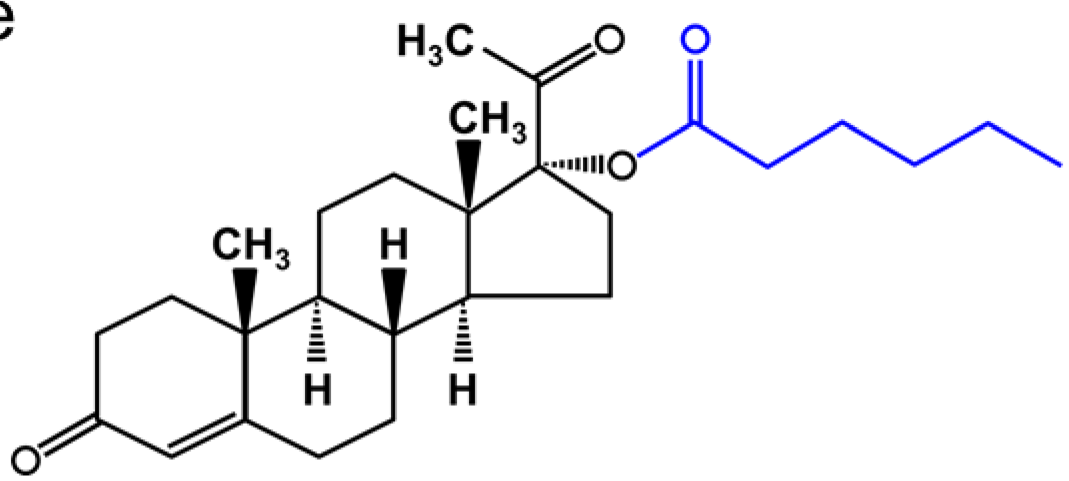
Introduction

Julie Krop, MD
Chief Medical Officer
EVP Clinical Development and Regulatory Affairs
AMAG Pharmaceuticals, Inc.

Makena and Generic 17P Formulations: Only FDA-Approved Therapy to Reduce Recurrent Preterm Birth

- Synthetic progestin
- Active pharmaceutical ingredient: 17 α-hydroxyprogesterone caproate
  - Not same as progesterone
- Proposed MOA
  - Decreases inflammation
  - Inhibits uterine activity
- Not metabolized into androgens, estrogen, or corticosteroids

17P



17P is an Orphan Drug

- Indicated for women with singleton pregnancy and prior spontaneous preterm birth
- Subset of all preterm birth
  - Affects ~ 3% (130,000) of all pregnancies
- Orphan Drug designation received

17P's Prolonged Half-Life Allows Once-Weekly Administration

- 17P treatment
  - Begins between 16^0 and 20^6 weeks pregnancy
  - Continued until 37 weeks or delivery
- Previously only available through pharmacy compounding

17P Approved Under Subpart H Accelerated Approval Pathway in 2011

- Subpart H applies to therapies that
  - Treat serious or life-threatening conditions with unmet need
  - Demonstrate efficacy on surrogate endpoint reasonably likely to predict clinical benefit
- Preterm birth (PTB) < 37 weeks accepted surrogate endpoint
  - Multiple studies established preterm infants at high risk of morbidity and mortality
- Required confirmatory trial of clinically relevant endpoints

FDA 21CFR314

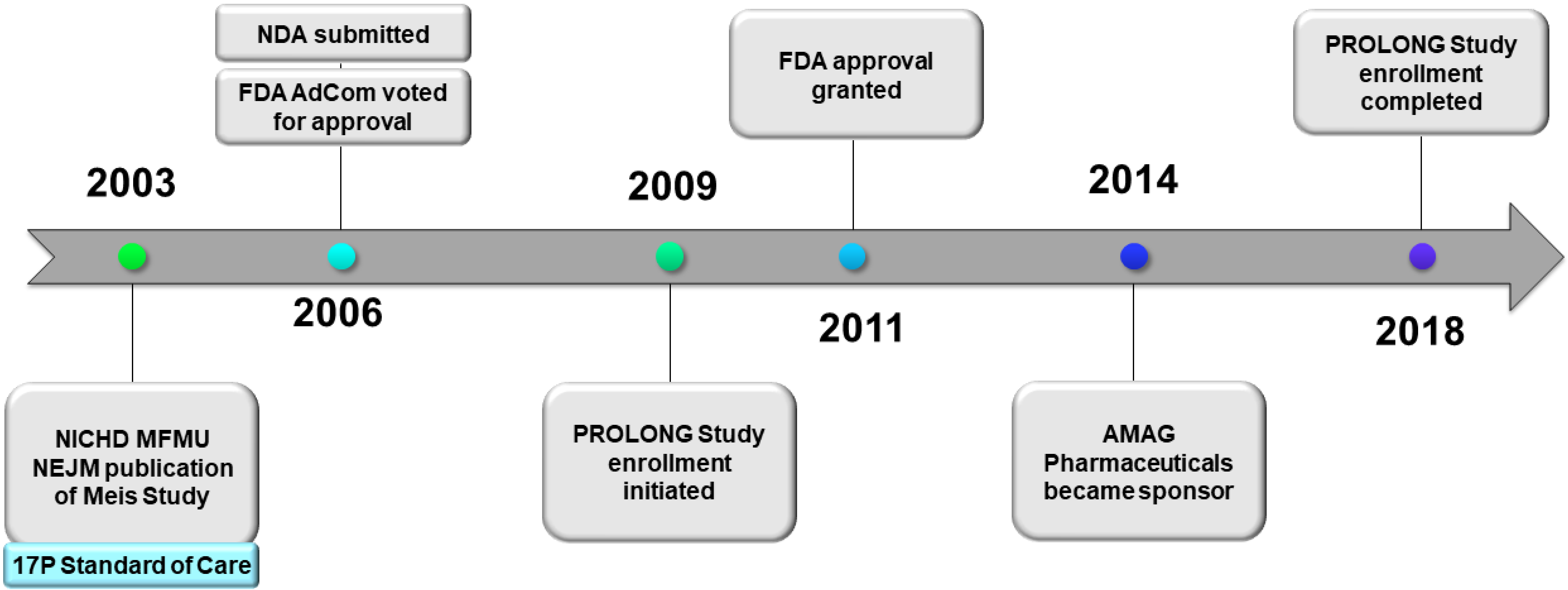
17P Approved Based on Compelling Results of Study 002 (Meis)

- Meis study conducted through NICHD MFMU
  - All US population
- Established substantial evidence of 17P efficacy
  - Highly statistically significant reduction in PTB rate vs. placebo < 37 weeks (p=0.0003)
  - Also reduced PTB < 35 weeks and < 32 weeks
    - Associated with highest incidence of neonatal complications

Meis, NEJM, 2003

NICHD = National Institute of Child Health and Human Development Health; MFMU = Maternal Fetal Medicine Units

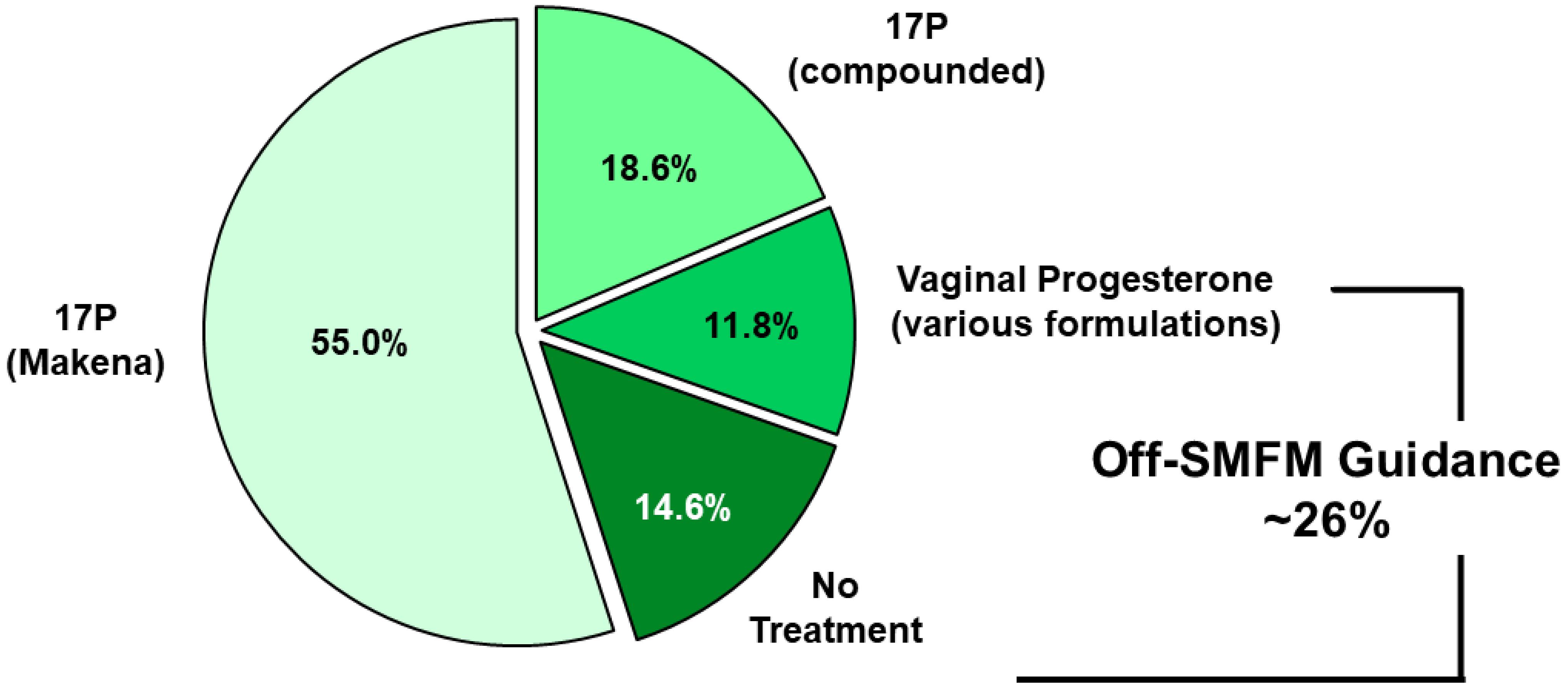
Key Events in 17P Approval Pathway



Preterm Birth is Major US Public Health Concern

- Leading cause of infant morbidity and mortality
- Can lead to serious long-term health complications
- Recurrent PTB represents only a small proportion of all PTBs

~75% of Indicated Patients Treated with 17P in 2017



Gallagher AJP Reports, 2018

Generalizability of PROLONG Efficacy Data to US is Challenging

- Key differences in study populations and background rates
- Meis trial enrolled in US inner city academic medical centers
  - ~30% background rate of PTB < 35 weeks
- PROLONG enrolled population with low PTB rate
  - ~11% background rate of PTB < 35 weeks
- Strong efficacy from Meis and other clinical trials along with favorable safety profile

Agenda

Clinical Background / Unmet Need	**Michelle Y. Owens, MD** Professor and Medical Director School of Medicine Department of Obstetrics and Gynecology The University of Mississippi Medical Center
Meis Study Design and Results	**Baha M. Sibai, MD** Professor Department of Obstetrics, Gynecology and Reproductive Sciences McGovern Medical School-UTHealth Principal Investigator, MFMU
PROLONG Efficacy and Safety	**Laura A. Williams, MD, MPH** Sr Vice President, Clinical Development AMAG
Clinical Perspective / Benefit / Risk	**Sean C. Blackwell, MD** Professor and Chair Department of Obstetrics, Gynecology, and Reproductive Sciences McGovern Medical School-UTHealth Principal Investigator, MFMU
AMAG Actions Following PROLONG	**Julie Krop, MD** CMO, EVP Clinical Development and Regulatory Affairs, AMAG

Additional Expert Consultants

Hugh Miller, MD	Principal Investigator, PROLONG Founder, Watching Over Mothers & Babies (WOMB)
Anita Das, PhD	Statistician AD Stat Consulting
Eugene Poggio, PhD	Statistician Biostatistical Consulting

Clinical Background and Need

Michelle Y. Owens, MD
Professor and Medical Director
School of Medicine Department of Obstetrics and Gynecology
The University of Mississippi Medical Center

Preterm Birth: Significant Problem in US

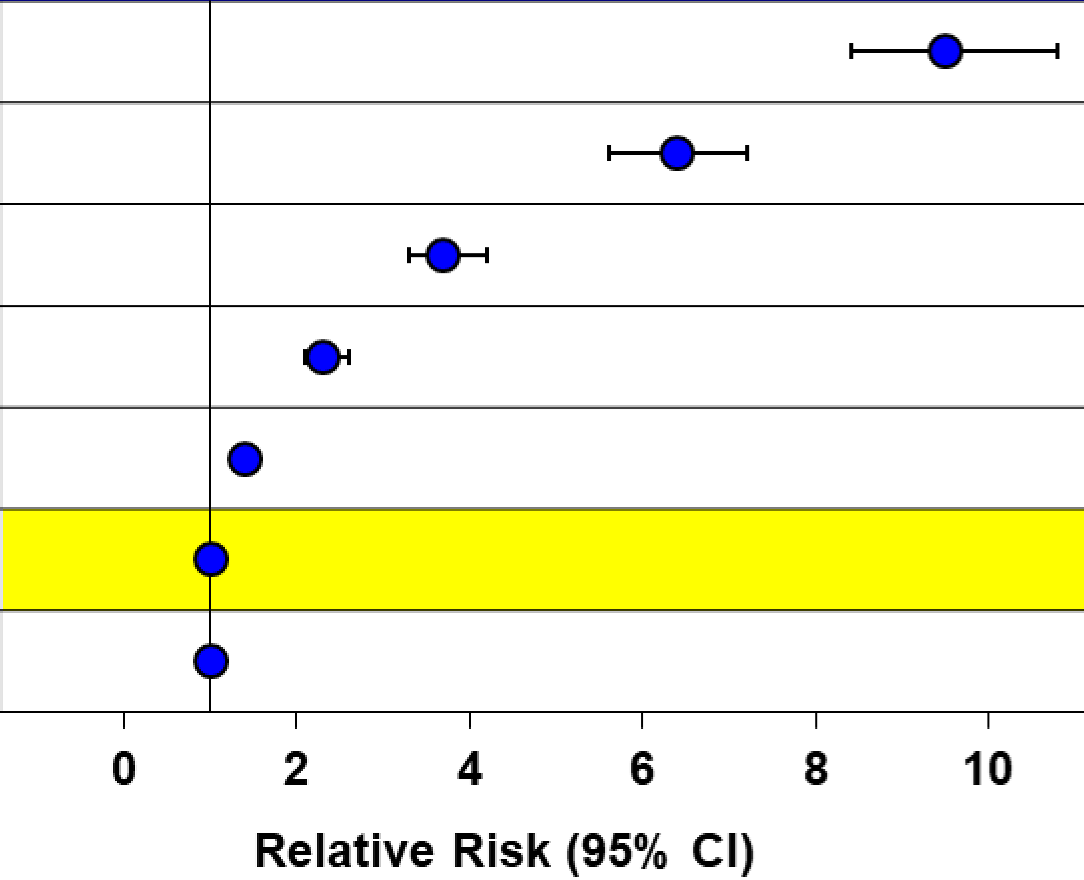
- 1 in 10 babies born prematurely in US
- Disadvantaged women – socioeconomically, educationally, limited healthcare access
- PTB puts infant at substantial risk
- Critical to have access to FDA-approved 17P for subset of women with prior PTB

What is at Stake: The Health of Infants

Photo: https://nyuwinthrop.org/newsroom/cornerstone/winter-spring-2018/nyu-winthrop-neonatal-breakthroughs/

Neonatal and Infant Mortality Significantly Higher for Babies Born at 34 – 36 Weeks Gestation

Gestational Age (weeks)	Death Within First 28 Days	Relative Risk (95% CI)
34		9.5 (8.4 – 10.8)
35		6.4 (5.6 – 7.2)
36		3.7 (3.3 – 4.2)
37		2.3 (2.1 – 2.6)
38		1.4 (1.3 – 1.5)
39 (Reference)		1.0
40		1.0 (0.9 – 1.1)



Reddy, et al., Pediatrics 2009

Preterm Birth and Complications
#1 Cause of Death of Babies in US

Short-Term Complications

- Respiratory distress syndrome (RDS)
- Bronchopulmonary dysplasia (BPD)
- Intraventricular hemorrhage (IVH)
- Periventricular leukomalacia (PVL)
- Necrotizing enterocolitis (NEC)
- Apnea
- Jaundice
- Anemia
- Infections

Long-Term Consequences

- Chronic respiratory problems
- Rehospitalization
- Metabolic disorders
- Neurodevelopmental problems
    - Cerebral palsy
    - Cognitive deficits
    - Hearing and vision impairment
    - Learning disorders

Spong CY. Obstet Gynecol 2003, Stoll, et al, Pediatrics, 2010, Gyamfi-Bannerman, NEJM, 2016

Babies Born at Lower Gestational Ages Have Higher Rates of Neonatal Morbidity and Mortality

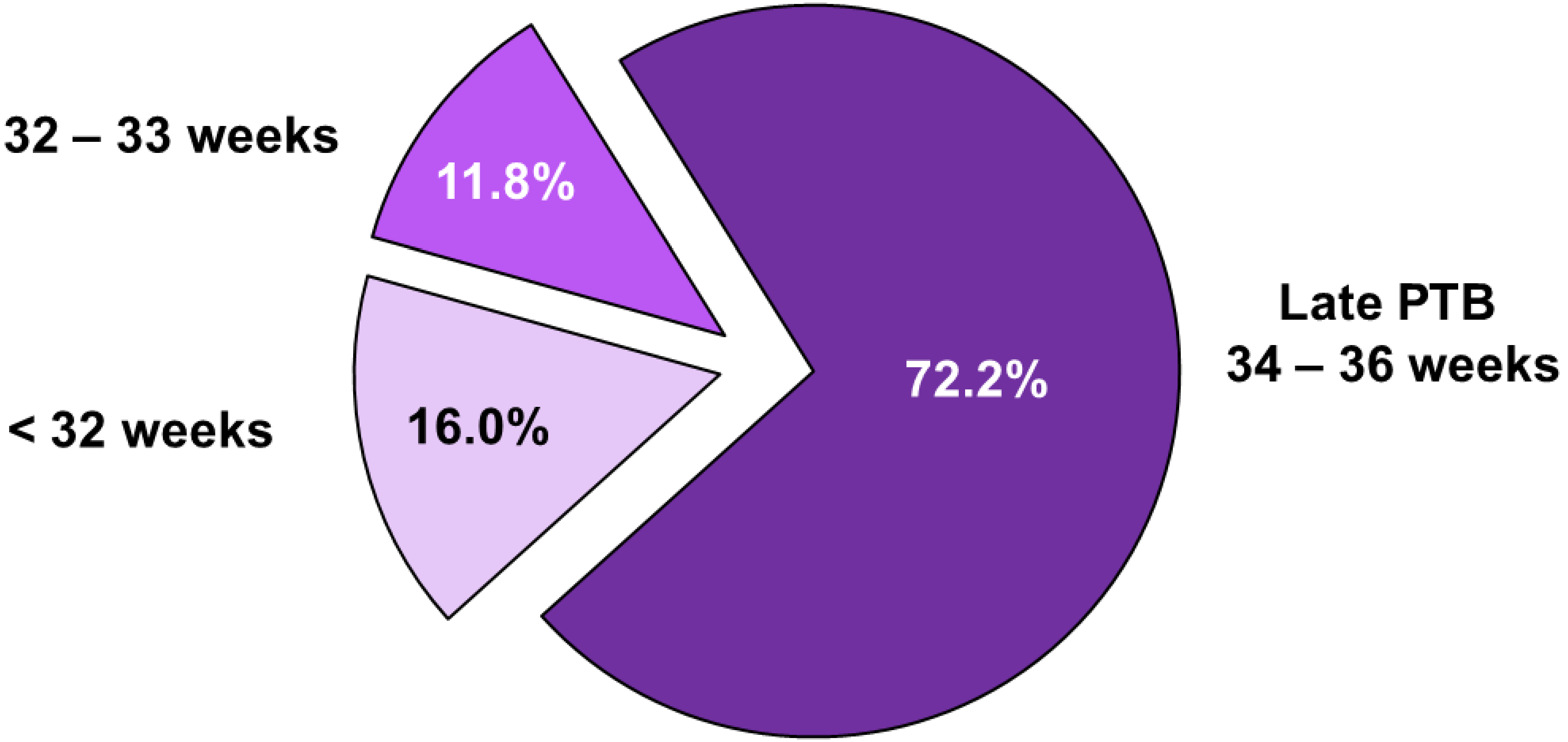
Delivery Gestational Age (Weeks)	Death n (%)	Major Morbidity n (%)	Death or Major Morbidity n (%)
< 32	117 (3)	448 (11)	565 (14)
< 35	119 (2)	560 (9)	679 (11)
36	0 (0)	55 (2)	55 (2)

Major morbidities

- Persistent pulmonary hypertension
- IVH grade 3 / 4
- Seizures
- Hypoxic-ischemic encephalopathy
- NEC stage II / III
- Bronchopulmonary dysplasia

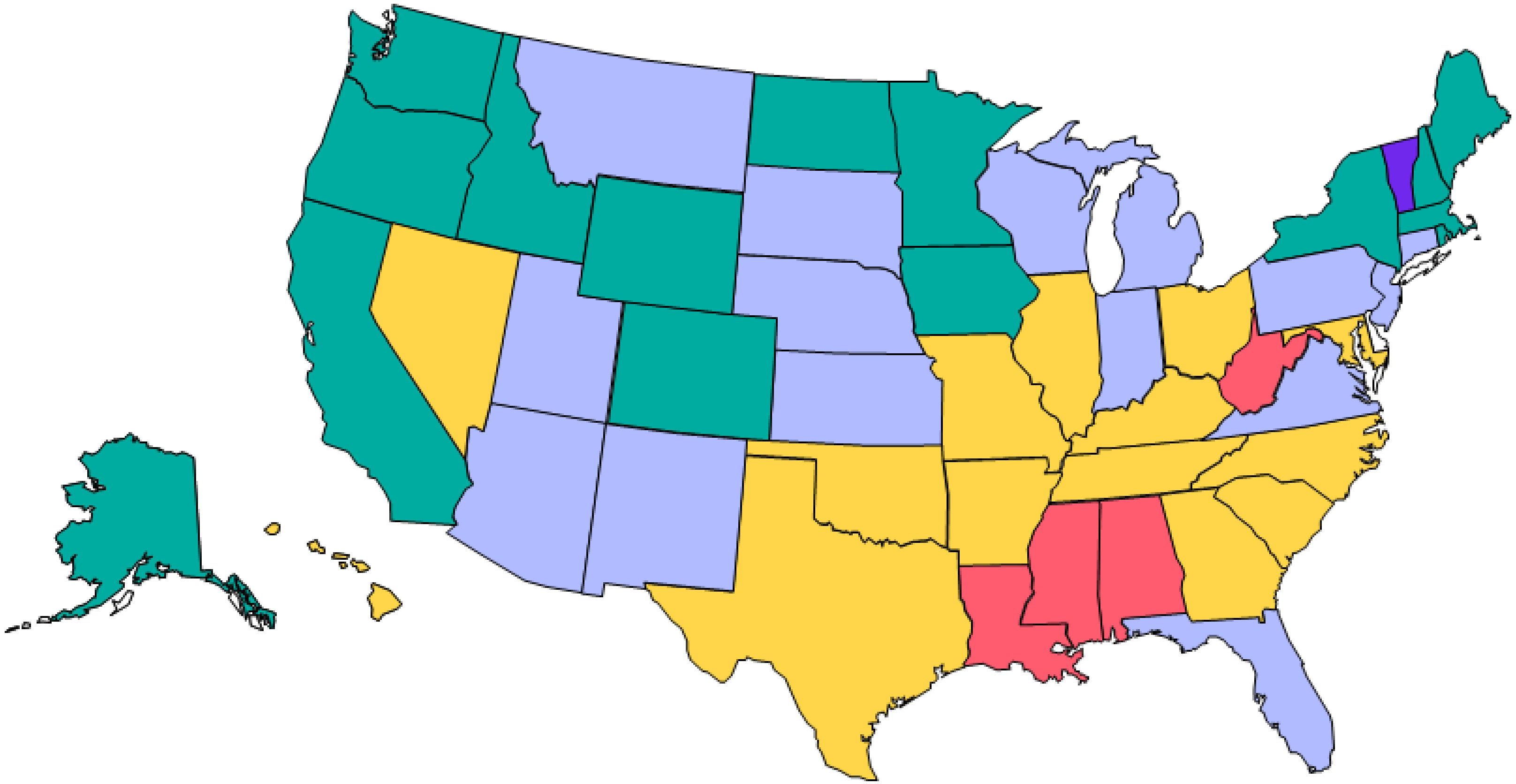
Manuck, AJOG 2016

Preterm Birth by Gestational Age



National Vital Statistics Reports "Births: Final Data for 2017"

US Ranks 131st of 184 Countries for Preterm Birth



Preterm Birth Rate

- Grade A: ≤ 8.1%
- Grade B: 8.2 – 9.2%
- Grade C: 9.3 – 10.3%
- Grade D: 10.4 – 11.4%
- Grade F: ≥ 11.5%

March of Dimes, 2018 Premature Birth Report Card
National Vital Statistics Reports "Births: Preliminary Data for 2015"

Risk Factors for Singleton Preterm Birth

Maternal Characteristics

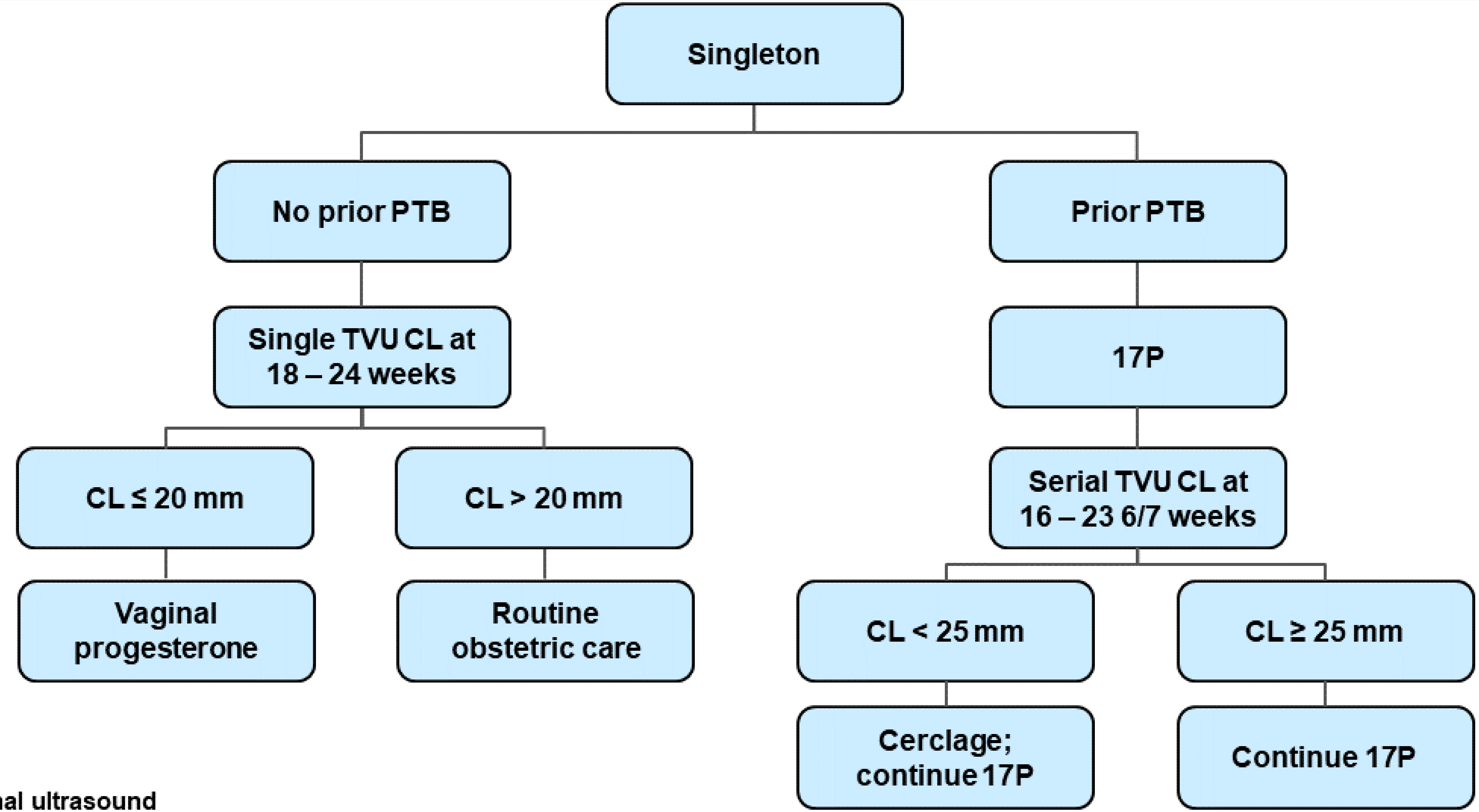
- **History of SPTB < 37 weeks**
- Short cervix
- African American
- Genitourinary infections
- Short intervals between pregnancies
- Advanced maternal age
- Low pre-pregnancy BMI

Social Determinants of Health

- Low socioeconomic status (i.e., education, income, marital status, nutrition)
- Stress (e.g., domestic violence, housing instability)
- Nicotine, alcohol, or drug use

Goldenberg Lancet 2008
ACOG Committee Opinion #729 2018

SMFM 2012 Clinical Guidelines



TVU = transvaginal ultrasound
SMFM Publications Committee, with assistance of Vincenzo Berghella AJOG 2012

Preterm Birth is Major US Public Health Concern, Disproportionately Affecting Lower SES Groups

- Infants spend weeks or months in NICU
- Must reduce preterm birth rate and prevent complications
- Physicians and patients need continued access to 17P

Meis Study Design and Results

Baha Sibai, MD

Professor, Department of Obstetrics, Gynecology and Reproductive Sciences

McGovern Medical School-UTHealth

Investigator, MFMU Network

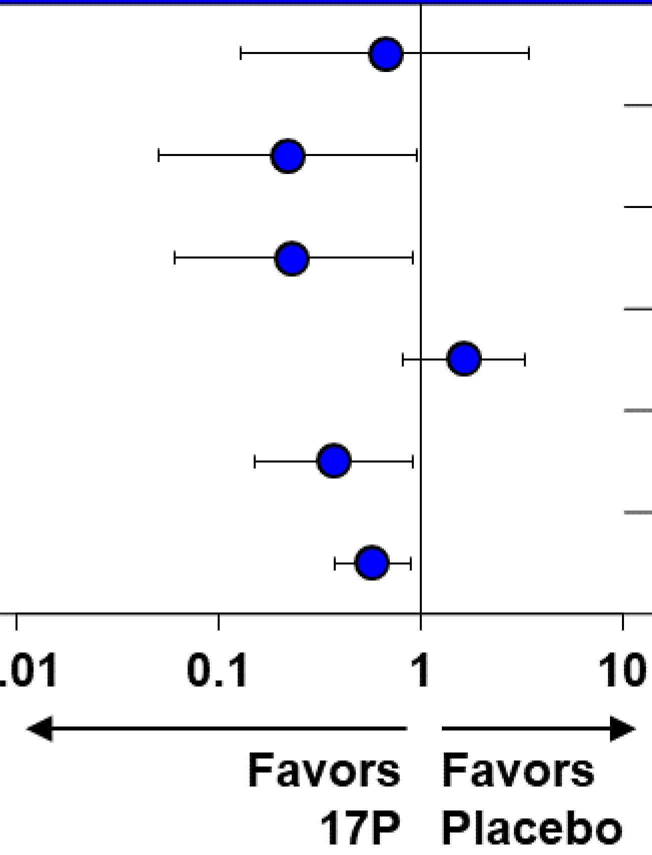
MFMU Network Established to Promote Rigorous Clinical Trials in Pregnancy

- Primary aim to reduce rate of preterm birth
- Rigorous process to select centers and studies
  - Network centers with ≥ 40% high-risk obstetric population
  - Diverse patient populations

MFMU established in 1986 by NICHD

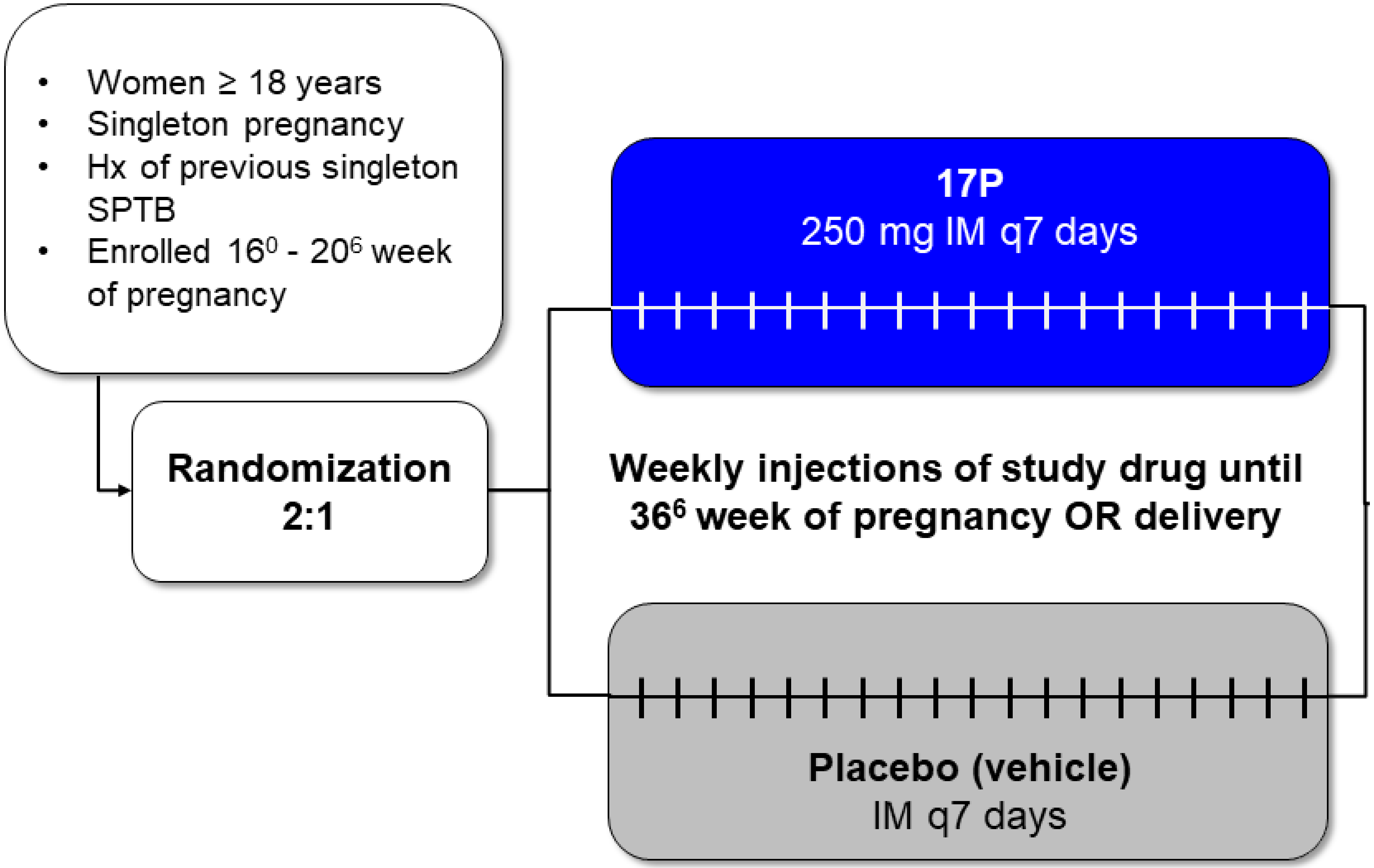
Meta-Analysis of 17P Demonstrated 42% Reduction in Recurrent PTB

Study	17P n/N	Placebo n/N	17P vs. Placebo Relative Risk (95% CI)
LeVine (1964)	2/15	3/15	0.67 (0.13 – 3.44)
Papiernick-Berkhauer (1970)	2/50	9/49	0.22 (0.05 – 0.96)
Johnson (1975)	2/18	12/25	0.23 (0.06 – 0.91)
Hartikainen-Sorri (1980)	15/39	9/38	1.62 (0.81 – 3.25)
Yemini (1985)	5/39	14/40	0.37 (0.15 – 0.92)
Meta-Analysis	26/161	47/167	0.58 (0.38 – 0.90)



Adapted from Keirse, BJOG 1990

Meis Study Designed to Evaluate 17P in Women with History of SPTB



Meis, et al. NEJM. 2003

Meis Study High-Risk Population for Preterm Birth

Demographics and baseline characteristics	17P (N=310)	Vehicle (N=153)
Age (years), mean ± SD	26.0 ± 5.6	26.5 ± 5.4
> 1 Previous PTB	27.7%	41.2%
Black or African American	59.0%	58.8%
White	25.5%	22.2%
Non-Hispanic or Latino	86.1%	83.0%
Married or living with partner	51.3%	46.4%
BMI before pregnancy (kg/m^2), mean ± SD	26.9 ± 7.9	26.0 ± 7.0
Educational level (years), mean ± SD	11.7 ± 2.3	11.9 ± 2.3
Gestational age of qualifying delivery (weeks), mean ± SD	30.6 ± 4.6	31.3 ± 4.2
Any substance use* during pregnancy	27.4%	23.5%

2 – 4% of patients were Asian, 2 – 3% were Other (Native Hawaiian/Pacific Islander, American Indian or Alaska native, mixed race and other)
*Smoking, alcohol or illicit drugs

Meis et al. NEJM 2003

Meis Study Primary Outcome: Preterm Delivery < 37 Weeks

- < 37 weeks gestation current definition of prematurity
- Sample size N = 500 women
  - Based on expected recurrent PTB rate of 37% in placebo group
  - Expected 1/3 reduction of recurrence with 17P

Meis, et al. NEJM 2003

Meis Study:
High Rate of Completion and Compliance

	17P (N=310)	Vehicle (N=153)
Completed study, %	98.7%	100%
Number of injections (mean)	14.1	13.7
Full compliance (< 10 days between doses)	91.5%	91.5%

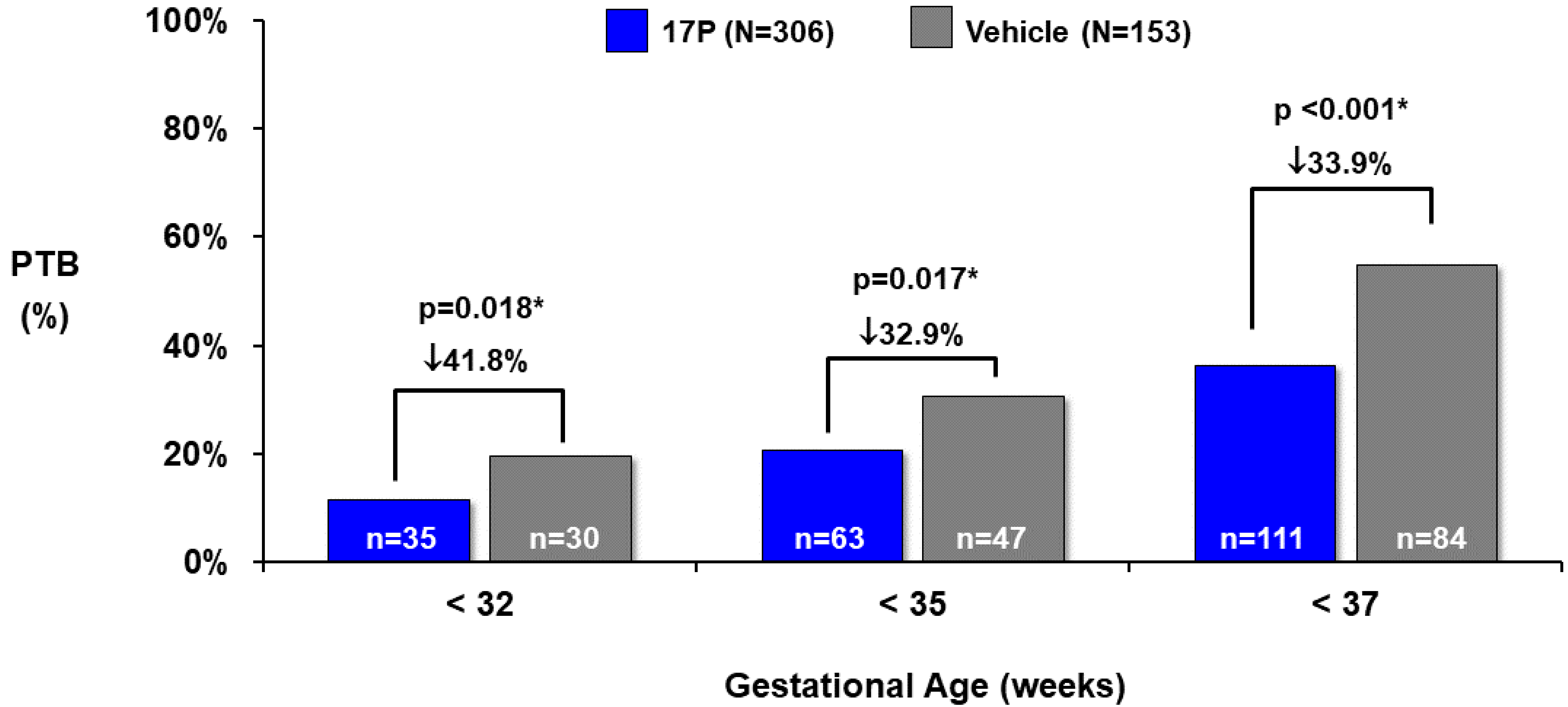
Meis, et al. NEJM 2003

Meis Study Stopped Early Due to Clear Evidence of 17P Benefit

- Study conducted from 1999 – 2002
- Planned interim analysis with pre-specified stopping criterion for efficacy (p=0.015)
  - Study halted at second interim analysis
  - Data available for 93% of planned sample (463/500)

Meis, et al. NEJM 2003

Meis Study Demonstrated Significant Reduction of PTB with 17P Compared to Vehicle

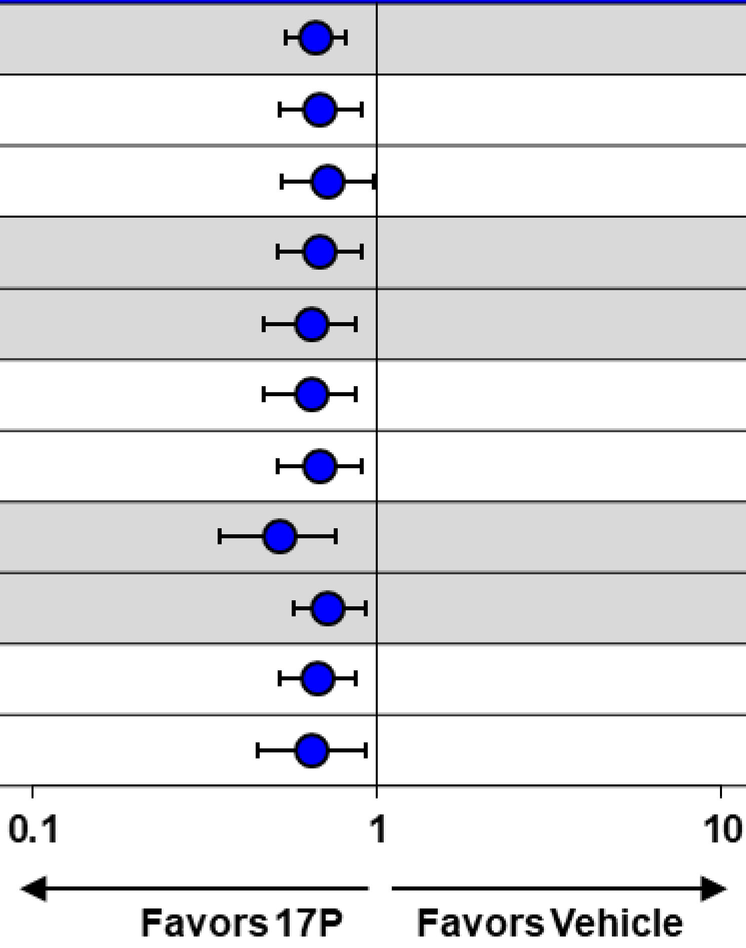


*p-values unadjusted for imbalance in prior PTBs

Meis, et al. NEJM 2003

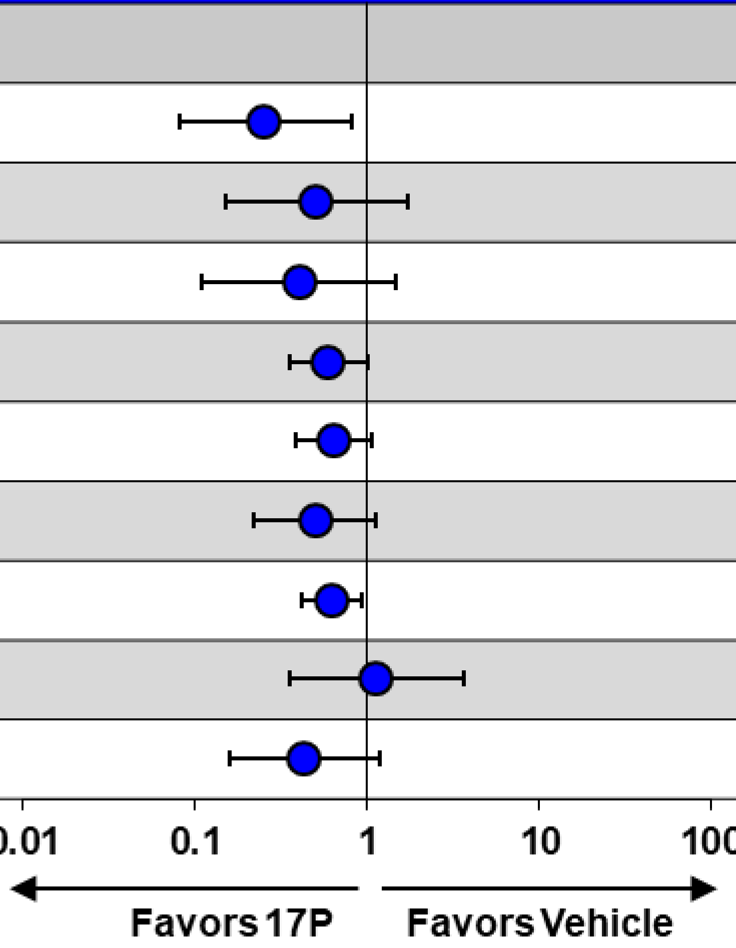
Meis Study: Consistent Reduction in PTB < 37 Weeks with 17P Across Subgroups

Subgroup	17P (n/N)	Vehicle (n/N)	Relative Risk (95% CI)
All patients	111/310	84/153	0.66 (0.54, 0.81)
> 1 Prior PTB	41/86	44/63	0.68 (0.52, 0.90)
Only 1 prior PTB	70/220	40/90	0.72 (0.53, 0.97)
Black	64/181	47/90	0.68 (0.51, 0.90)
Non-Black	47/125	37/63	0.64 (0.47, 0.87)
Unmarried	50/150	43/82	0.64 (0.47, 0.86)
Married	61/156	41/71	0.68 (0.51, 0.90)
Smoke or substance use	28/85	23/36	0.52 (0.35, 0.76)
No smoke or substance use	83/221	61/117	0.72 (0.57, 0.92)
Education ≤ 12 years	80/223	55/103	0.67 (0.52, 0.86)
Education > 12 years	31/83	29/50	0.64 (0.45, 0.93)



17P Reduced Neonatal Complications vs. Placebo

Subgroup	17P (n/N)	Vehicle (n/N)	Relative Risk (95% CI)
Necrotizing enterocolitis	0/305	4/152	0 (p<0.05)
IVH Any Grade	4/305	8/153	0.25 (0.08, 0.82)
Retinopathy	5/305	5/152	0.50 (0.15, 1.70)
Bronchopulmonary dysplasia	4/305	5/152	0.40 (0.11, 1.46)
Ventilatory support	26/303	22/151	0.59 (0.35, 1.00)
Respiratory distress syndrome	29/305	23/152	0.63 (0.38, 1.05)
Transient tachypnea	11/305	11/152	0.50 (0.22, 1.12)
Supplemental oxygen	45/303	36/151	0.62 (0.42, 0.92)
Proven sepsis	9/305	4/152	1.12 (0.35, 3.58)
Patent ductus arteriosus	7/305	8/151	0.43 (0.16, 1.17)



Meis, et al., NEJM 2003

Reduced Neonatal Intensive Care Unit (NICU) Admissions and Days With 17P Compared to Vehicle

	17P	Vehicle	17P vs Vehicle
Admitted to NICU, n/N (%)	82/295 (27.8%)	55/151 (36.4%)	Relative Risk = 0.76 95% CI (0.58, 1.01)
Number of NICU days, mean ± SD	23.9 ± 32.4	29.2 ± 37.6	Δ = -5.3 95% CI (-17.5, 6.9)

Perinatal Death in Meis Study

Complication	17P (N=306)[1] n (%)	Vehicle (N=153) n (%)
Total deaths	19 (6.2)	11 (7.2)
Neonatal deaths	8 (2.6)	9 (5.9)
Miscarriages < 20 weeks gestation [2]	5 (2.4)	0
Stillbirth	6 (2.0)	2 (1.3)

1. 4 patients in the 17P group were lost to follow-up and perinatal death status could not be determined
2. Percentage adjusted for the number at risk (17P n=209, Vehicle n=107) enrolled at <20 weeks gestation.

Follow-Up Observational Study of Meis Trial Babies Confirmed Long-Term Safety of 17P

Ages and Stages Questionnaire (ASQ) Scored below cutoff on	17P (N=193)	Vehicle (N=82)	p-value
At least one area	27%	28%	0.9
Communication	11%	11%	0.9
Gross motor	3%	4%	0.7
Fine motor	21%	18%	0.6
Problem solving	10%	11%	0.9
Personal-social	4%	1%	0.4
Preschool Activities Inventory (PAI)			
Mean score for boys	67	67	0.3
Mean score for girls	33	32	0.5

Northen et al., Am J Obstet Gynecol, 2007

Median age (48 months, 41.8 to 55.0, 25th to 75th percentile)

Meis Results Considered Significant Advance in Obstetrics

- Relative risk
  - 0.66 (95% CI, 0.54 to 0.81)
- Absolute difference in preterm
  - 18.6%
- Number Need to Treat
  - 5.4 women to prevent 1 PTB


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2003 VOL. 348 NO. 24

Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate

Paul J. Meis, M.D., Mark Klebanoff, M.D., Elizabeth Thom, Ph.D., Mitchell P. Dombrowski, M.D., Baha Sibai, M.D., Atef H. Moawad, M.D., Catherine Y. Spong, M.D., John C. Hauth, M.D., Menachem Miodovnik, M.D., Michael W. Varner, M.D., Kenneth J. Leveno, M.D., Steve N. Caritis, M.D., Jay D. Iams, M.D., Ronald J. Wapner, M.D., Deborah Conway, M.D., Mary J. O'Sullivan, M.D., Marshall Carpenter, M.D., Brian Mercer, M.D., Susan M. Ramin, M.D., John M. Thorp, M.D., and Alan M. Peaceman, M.D., for the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

Meis, NEJM 2003

Meis Study Established Substantial Evidence of 17P Efficacy and Formed Foundation of PTB Prevention

- Clinicians have relied on 17P since 2003
- Only FDA-approved treatment to reduce risk of recurrent PTB since 2011
- Patients and clinicians need 17P as available option to prevent recurrent PTB

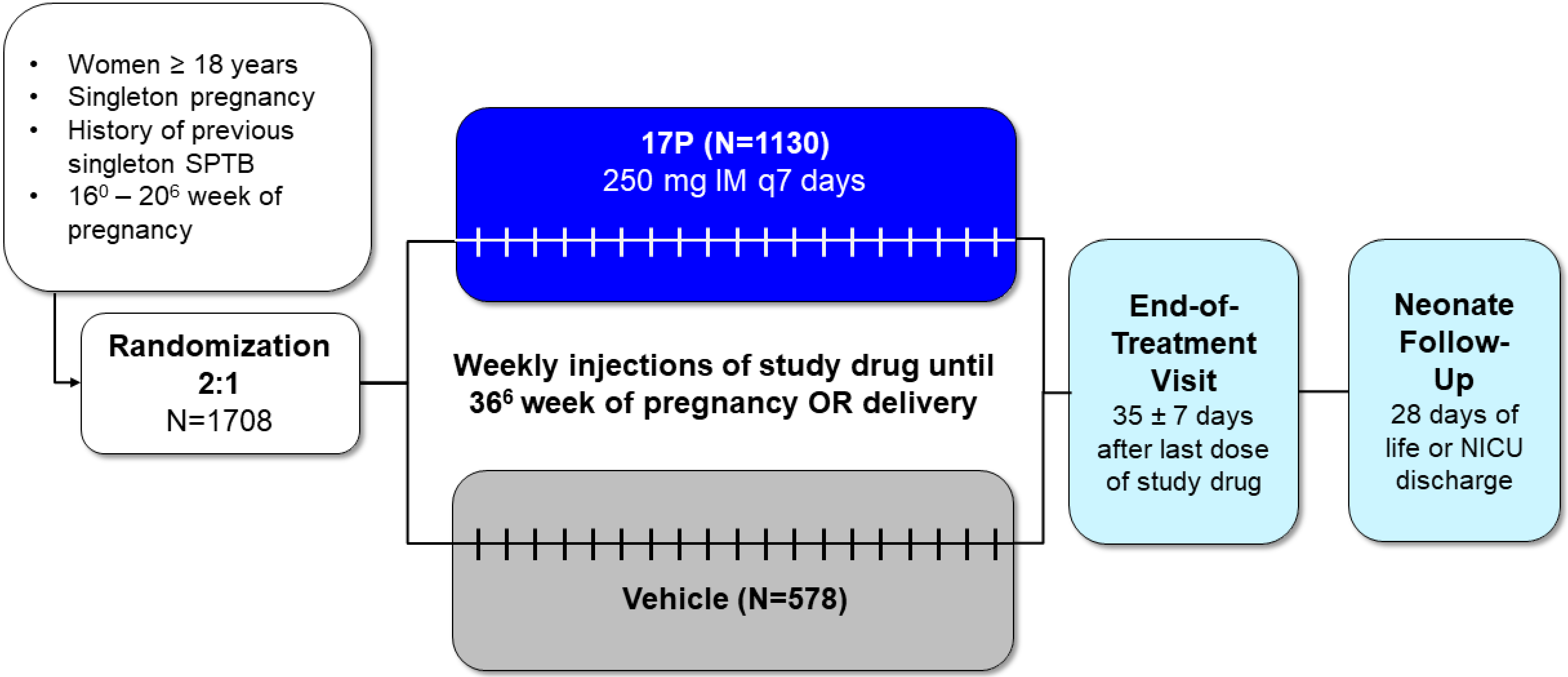
PROLONG: Efficacy and Safety

Laura A. Williams, MD, MPH
Senior Vice President, Clinical Development & Biostatistics
AMAG Pharmaceuticals, Inc.

PROLONG Designed to Mirror Meis Trial

- PROLONG did not meet its co-primary outcomes
  - Lower background PTB rates in PROLONG compared to Meis

PROLONG: Double-Blind, Vehicle-Controlled, Multi-Center, Randomized Study



PROLONG: Co-Primary Outcomes

- Reduction of PTB < 35 weeks gestation
- Reduction in composite neonatal morbidity and mortality index
  - Respiratory distress syndrome
  - Bronchopulmonary dysplasia
  - Grade 3 or 4 intraventricular hemorrhage
  - Necrotizing enterocolitis
  - Proven sepsis
  - Neonatal death

PROLONG: Key Secondary Efficacy and Primary Safety Outcomes

Secondary Outcomes

- Reduction of PTB by gestational age at delivery

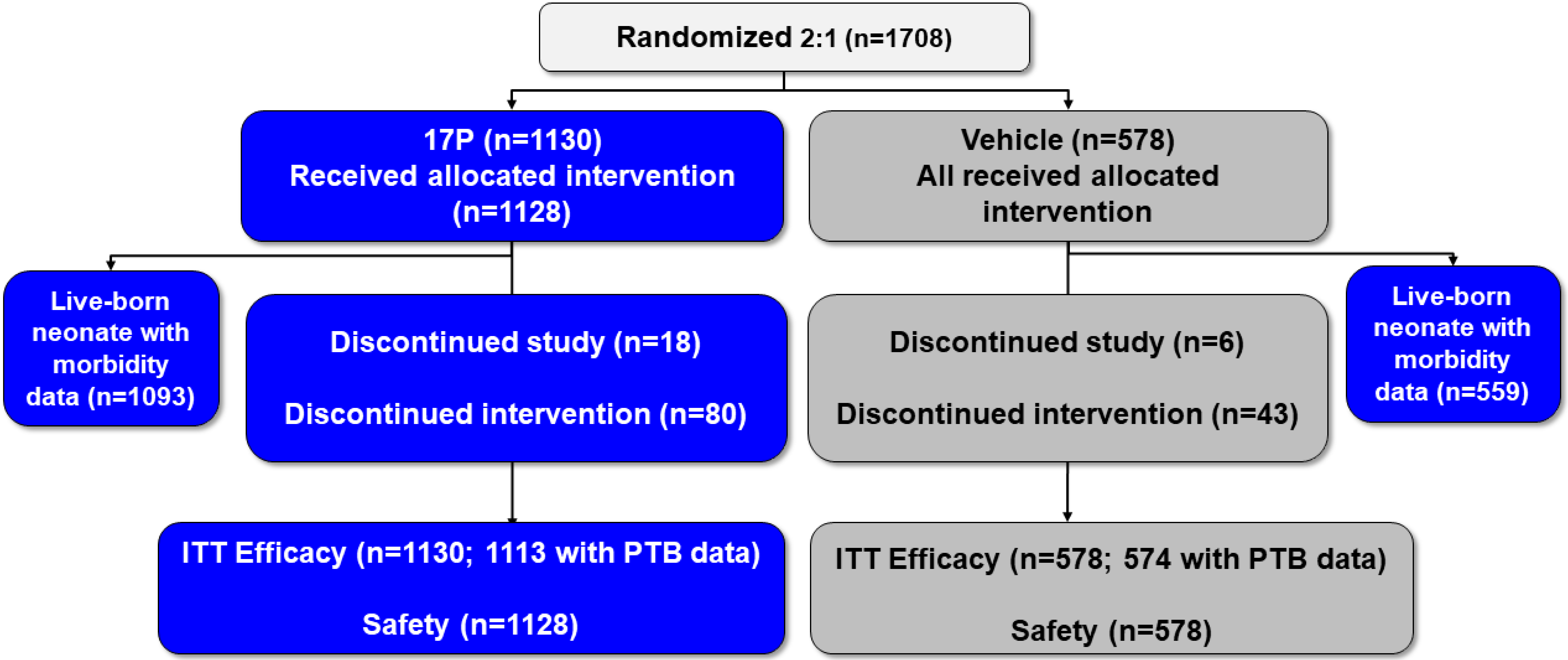
Primary Safety Outcome

- Exclude doubling in risk of fetal or early infant death

PROLONG: Sample Size and Powering Based on Conservative Estimates of Meis Results

- Sample size of 1707 provide
  - 98% power to detect 30% reduction in PTB < 35 weeks
  - 90% power to detect 35% reduction in neonatal composite index
  - 83% power to rule out doubling in risk of fetal/early infant death

PROLONG Patient Disposition: ~ 99% of Patients Completed Study



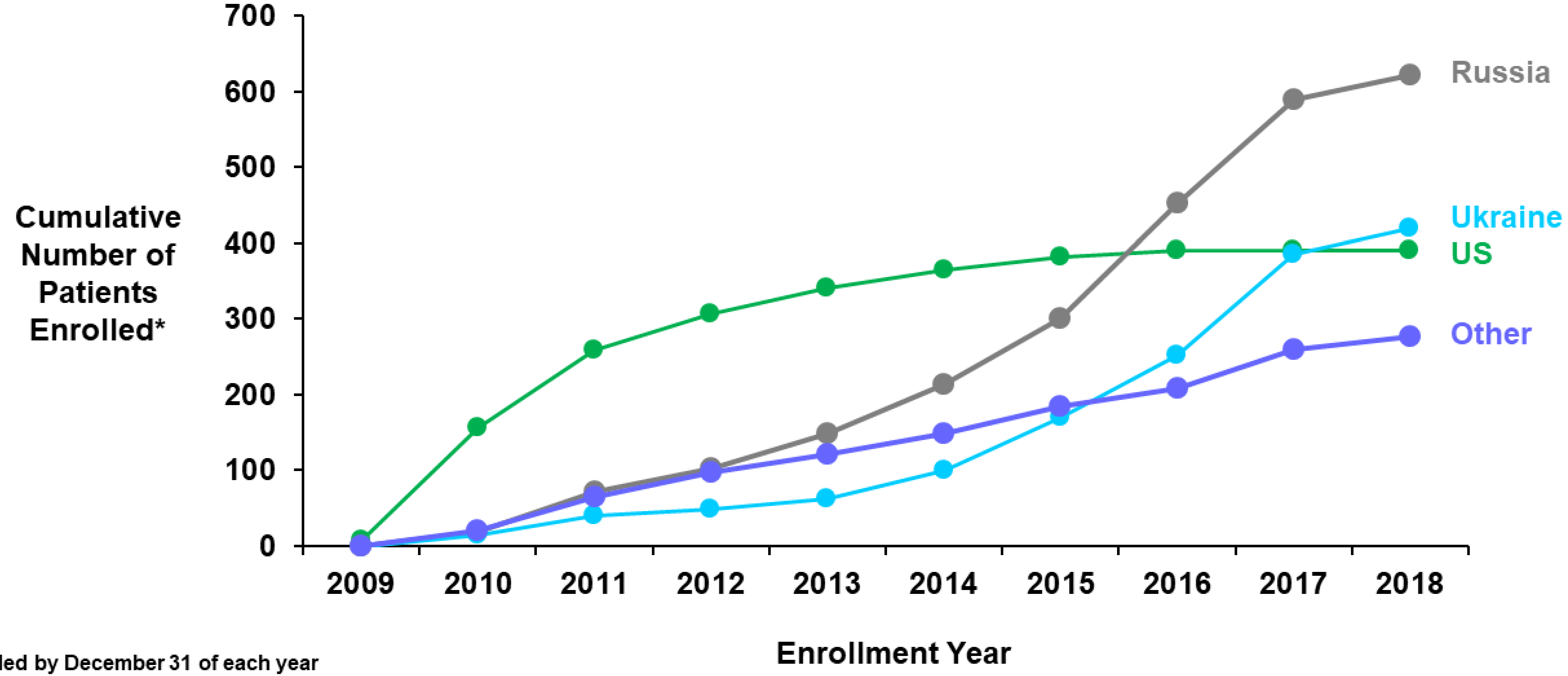
PROLONG: Enrollment by Geographic Region ~ 75% of Patients Enrolled Ex-US

Country	Number of Patients (N=1708) n (%)
United States	391 (22.9)
Ex-US	1,317 (77.1)
Russia	621 (36.4)
Ukraine	420 (24.6)
Hungary	91 (5.3)
Spain	85 (5.0)
Bulgaria	50 (2.9)
Canada	31 (1.8)
Czech Republic	14 (0.8)
Italy	5 (0.3)

61% of patients from Russia/Ukraine

16% (n=276 total) from other Ex-US Countries

PROLONG: Enrollment (Year End)



*Enrolled by December 31 of each year
Other: Bulgaria, Canada, Czech Republic, Hungary, Italy, Spain

PROLONG: Demographics and Baseline Characteristics Similar Across Treatment Groups

Demographics & Baseline Characteristics	17P (N=1130)	Vehicle (N=578)
Age (years), mean ± SD	30.0 ± 5.17	29.9 ± 5.22
Race / ethnicity		
White	88.8%	87.2%
Black, African American / African heritage	6.5%	7.1%
Non-Hispanic or Latino	91.1%	90.7%
Married or living with partner	89.6%	90.3%
BMI before pregnancy (kg/m^2), mean ± SD	24.3 ± 7.1	24.7 ± 8.7
Educational level (years), mean ± SD	13 ± 2.4	13 ± 2.4
Transvaginal cervical length < 25 mm at ≤ 20 weeks	1.2%	1.9%
Any substance use* during pregnancy	9.3%	8.8%

2 – 4% of patients were Asian, 2 – 3% were Other (Native Hawaiian/Pacific Islander, American Indian or Alaska native, mixed race and other) *Smoking, alcohol or illicit drugs

PROLONG: Prior Pregnancy History Similar Across Treatment Groups

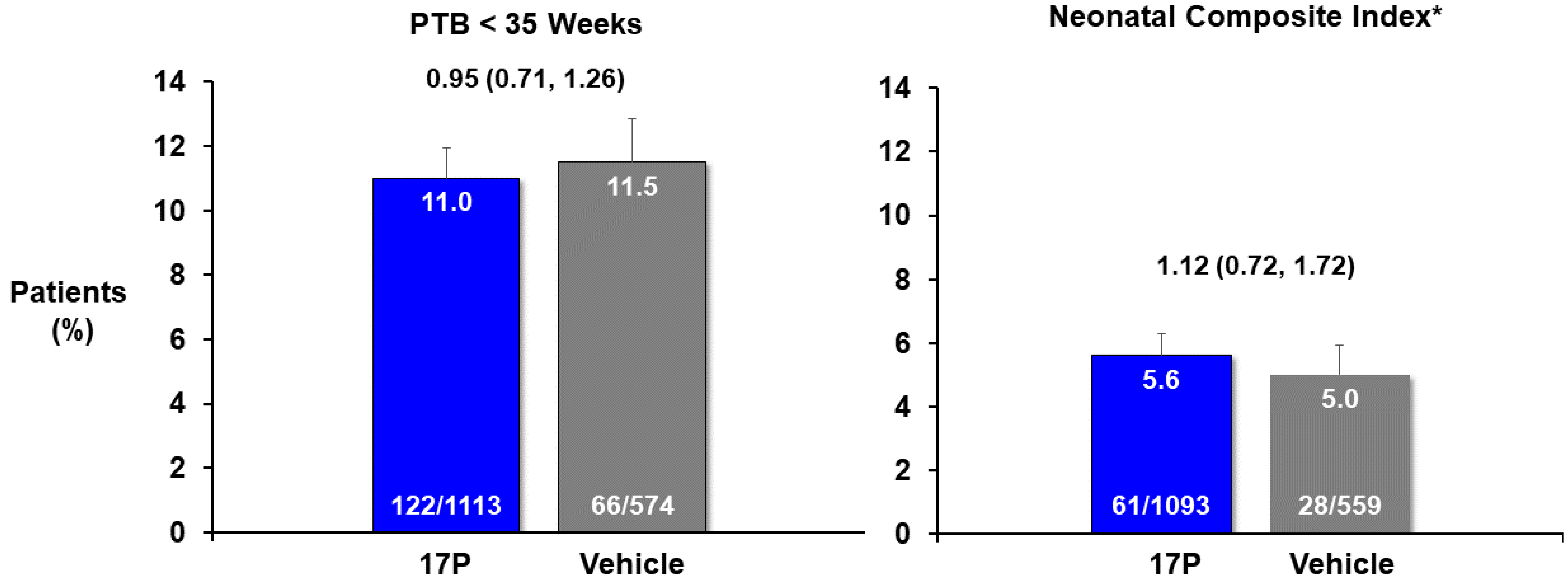
Pregnancy Characteristics	17P (N=1130)	Vehicle (N=578)
Prior SPTB – median (min, max)	1.0 (1, 7)	1.0 (0*, 5)
> 1 previous SPTB n (%)	148 (13.1)	70 (12.1)
Gestational age of prior qualifying delivery (weeks) mean ± SD median (min, max)	 31.3 ± 4.35 32 (20, 36)	 31.6 ± 4.16 33 (20,36)

*1 patient in vehicle arm did not have SPTD (protocol deviation)

PROLONG: Comparable Study Drug Compliance Across Treatment Groups

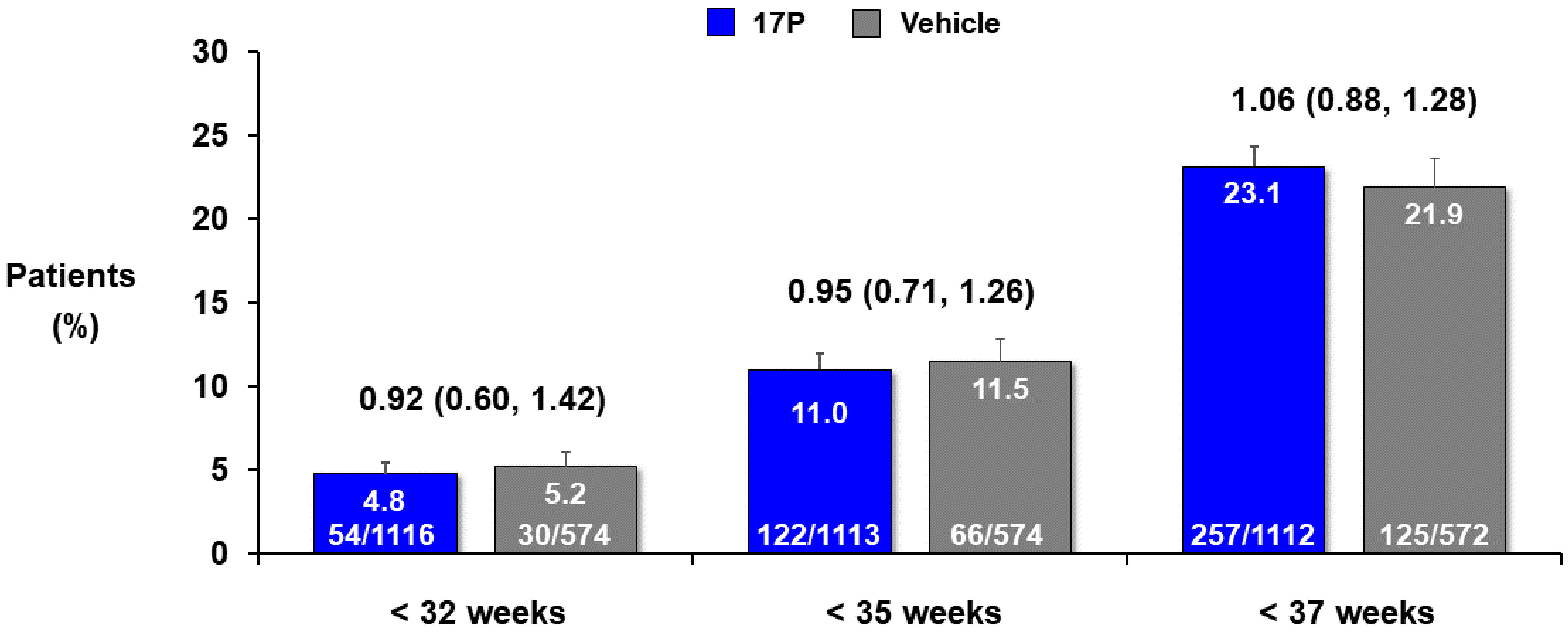
Study Drug Exposure	17P (N=1128)	Vehicle (N=578)
Injections received		
Mean (SD)	17.6 (3.65)	17.5 (3.81)
Median	18	18
Min, Max	(1, 22)	(1, 22)
Patients with full compliance	91.4%	92.4%

PROLONG: Co-Primary Endpoint Results PTB < 35 Weeks and Neonatal Composite Index



*Composite included: Death, RDS, BPD, Grade 3 or 4 IVH, NEC and proven sepsis

PROLONG: Key Secondary Endpoint Results (PTB by Gestational Age at Delivery)



PROLONG: Co-Primary Efficacy Outcome Event Rates Higher in US Compared to Ex-US

Preterm Birth < 35 weeks

	17P (N=1130)	Vehicle (N=578)
US, n/N (%)	40/256 (15.6)	23/131 (17.6)
Ex-US, n/N (%)	82/857 (9.6)	43/443 (9.7)

Neonatal Composite Index

	17P (N=1093)	Vehicle (N=559)
US, n/N (%)	18/252 (7.1)	11/125 (8.8)
Ex-US, n/N (%)	43/841 (5.1)	17/434 (3.9)

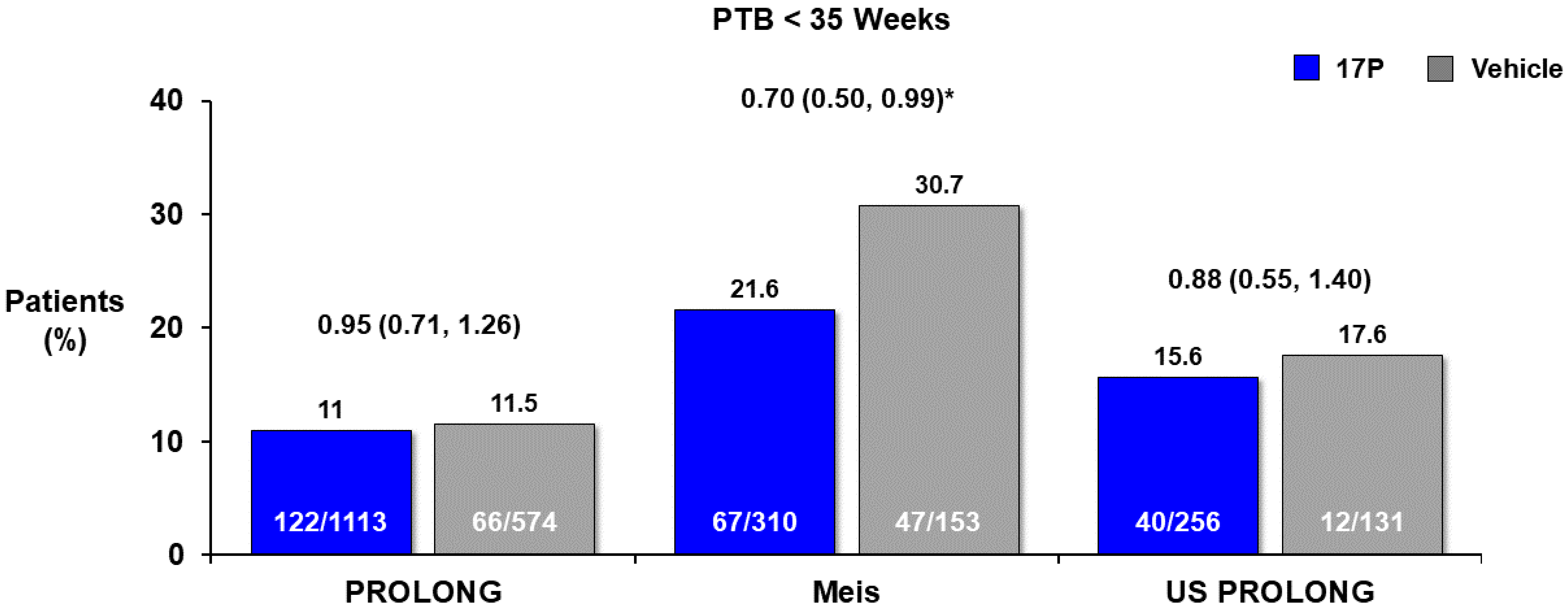
Differences Between PROLONG and Meis Study Populations Less Notable in US PROLONG Subset

Demographics/Baseline Characteristics	PROLONG (N=1708) %	Meis (N=463) %	US PROLONG (N=391) %
Age (years), mean ± SD	30.0 ± 5.2	26.2 ± 5.6	27.6 ± 5.1
> 1 previous SPTB	14.5	28.9	27.4
Black / African American	6.7	59.0	28.9
Hispanic or Latino	9.1	14.9	13.8
Unmarried with no partner	10.1	50.3	30.7
Educational status (≤ 12 years)	43.7	71.3	50.5
Any substance use during pregnancy	9.3	26.1	28.4
Smoking	7.8	21.6	22.8
Alcohol	2.5	8.0	9.2
Illicit drugs	1.4	3.2	5.9

Multifactorial Causes of PTB Make it Challenging to Identify Markers of Response

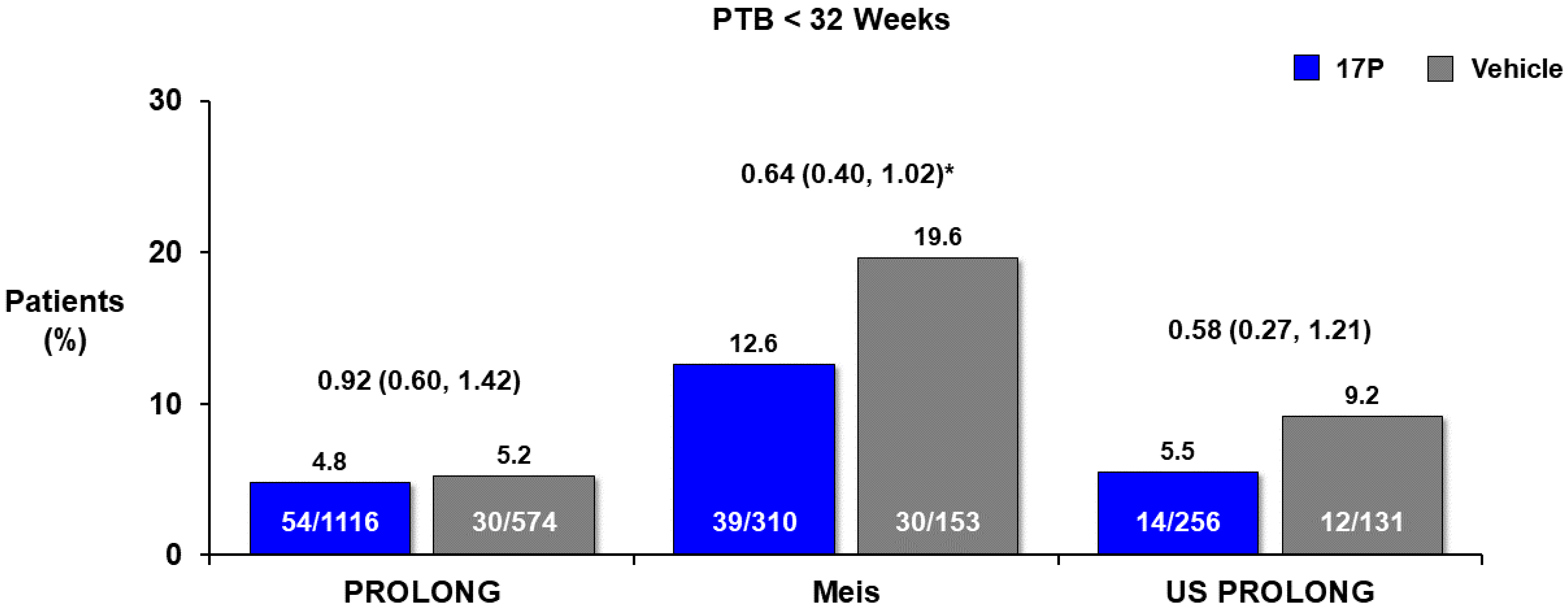
- Additional post hoc analyses conducted
- US PROLONG subset more similar demographics and background characteristics to Meis

Trends for Reductions in PTB Rates at < 35 Weeks in US PROLONG Align (Directionally) with Meis



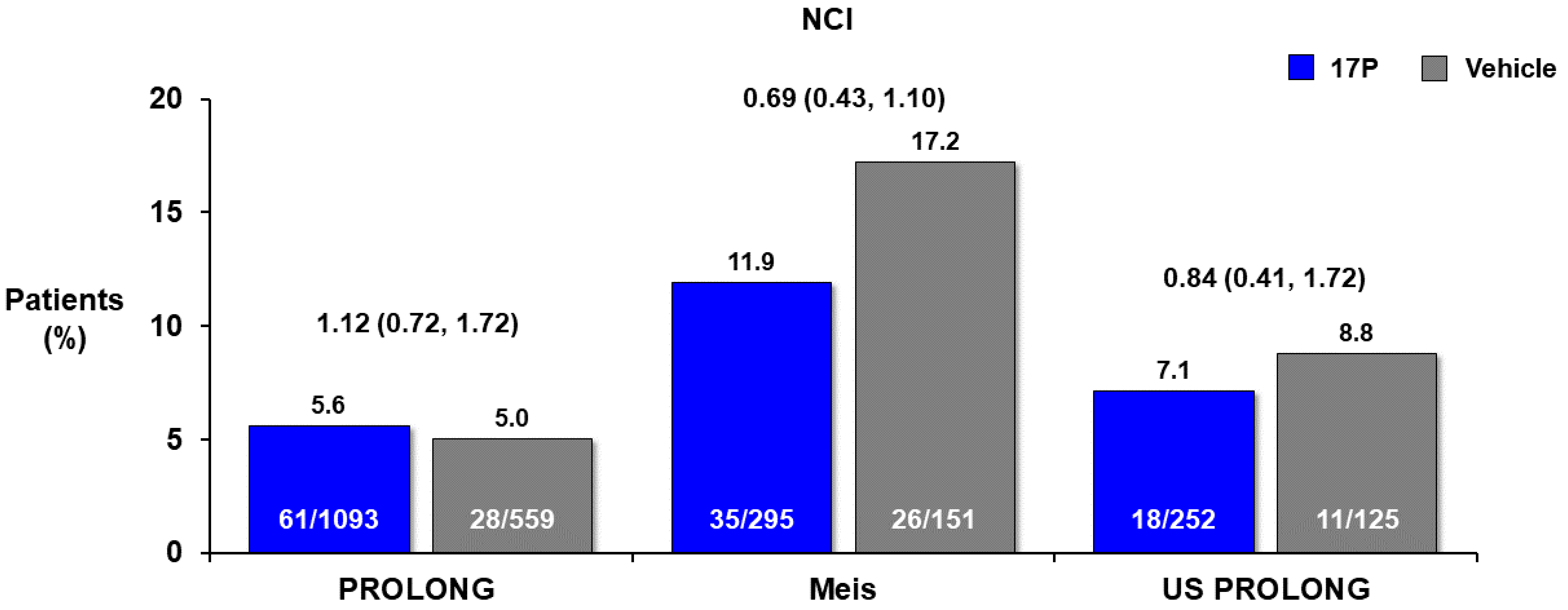
*The CI is a 96.5% CI to adjust for the interim analyses.
Relative risks (RR) and confidence intervals (CI) for the PROLONG study are adjusted for gestational age at randomization stratum.

Trends for Reductions in PTB Rates at < 32 Weeks in US PROLONG Align (Directionally) with Meis



*The CI is a 96.5% CI to adjust for the interim analyses.
Relative risks (RR) and confidence intervals (CI) for the PROLONG study are adjusted for gestational age at randomization stratum.

Trends for Reductions in Neonatal Composite Index* Rates in US PROLONG Align (Directionally) with Meis



*Composite included: Death, RDS, BPD, Grade 3 or 4 IVH, NEC and proven sepsis

PROLONG Efficacy Summary

- Study did not meet co-primary endpoints
  - Findings do not refute robust efficacy seen in Meis
  - Lower background PTB rates in PROLONG compared to Meis
- Trends for benefit favoring 17P seen in smaller subset study population (US PROLONG)

PROLONG Safety

PROLONG: Primary Safety Outcomes

- **Exclude doubling in risk of fetal or early infant death in 17P group vs. vehicle, defined as**
  - Spontaneous abortion/miscarriage (delivery $16^0 – 19^6$)
  - Stillbirth at ≥ 20 weeks
  - Early infant death at ≤ 24 weeks (occurring minutes after birth until 28 days of life)
- **Overall perinatal death most relevant outcome**

PROLONG: Overall Rates of Perinatal Death Low and Similar Across Treatment Groups

Fetal or Early Infant Deaths		17P (N=1128)	Vehicle (N=578)	RR (95% CI)[1]
Non-Liveborn	Miscarriages (< 20 weeks)	4/866 (0.5)	7/448 (1.3)	0.28 (0.08, 0.94)
	Stillbirths (≥ 20 weeks)	12/1124 (1.1)	3/571 (0.5)	2.07 (0.59, 7.29)
Liveborn	Early Infant Deaths (≥ 20 to ≤ 24 weeks)	3/1112 (0.3)	1/568 (0.2)	1.48 (0.14, 15.24)
Total Fetal/Early Infant Deaths		19/1128 (1.7)	11/578 (1.9)	0.87 (0.42, 1.81)

1. Relative risk for 17P relative to Vehicle (Placebo) and is from the Cochran-Mantel-Haenszel test adjusted for gestational age at randomization.

PROLONG: Overall Incidence of Treatment Emergent Adverse Events (TEAEs) Comparable Between 17P and Vehicle

Summary of TEAEs	17P (N=1128) n (%)	Vehicle (N=578) n (%)
Any AEs	646 (57.3)	334 (57.8)
Any maternal pregnancy complication (MPC)	115 (10.2)	64 (11.1)
Any AEs leading to study drug withdrawal	11 (1.0)	5 (0.9)
Any SAEs	34 (3.0)	18 (3.1)
Maternal deaths	0	0

PROLONG: No Clinically Meaningful Differences in AEs or Maternal Pregnancy Complications (MPCs)* Between Treatment Groups

AEs and MPCs (≥3%) Preferred Term	17P (N=1128) / n (%)	Vehicle (N=578) / n (%)
Patients with ≥1 TEAE or MPC	653 (57.9)	336 (58.1)
Anemia	104 (9.2)	56 (9.7)
Headache	68 (6.0)	28 (4.8)
Nausea	55 (4.9)	26 (4.5)
Back pain	50 (4.4)	20 (3.5)
After birth pain	48 (4.3)	24 (4.2)
Urinary tract infection	44 (3.9)	23 (4.6)
Abdominal pain	40 (3.5)	27 (4.7)
Vomiting	42 (3.7)	19 (3.3)
Injection site pruritis	42 (3.7)	23 (4.0)
Vaginal infection	41 (3.6)	21 (3.6)
Nasopharyngitis	39 (3.5)	27 (4.7)
Constipation	38 (3.4)	17 (2.9)
Dyspepsia	37 (3.3)	25 (4.3)
Insomnia	36 (3.2)	13 (2.2)
Injection site pain	36 (3.2)	24 (4.2)
Vaginitis bacterial	35 (3.1)	21 (3.6)
Gestational diabetes	35 (3.1)	22 (3.8)
Cervical incompetence*	34 (3.0)	16 (2.8)

*MPC = maternal pregnancy complication

PROLONG: TEAEs and MPCs* Leading to Premature Discontinuation of Study Medication

TEAE/MPC Leading to Discontinuation Preferred Term	17P (N=1128)	Vehicle (N=578)
Patients with ≥ 1 TEAE/MPC leading to discontinuation	11 (1.0)	5 (0.9)
Hypothyroidism*	1 (0.1)	0
Nausea/vomiting[1]	1 (0.1)	0
Injection site AEs (erythema, nodule, pruritus, rash, reaction)	4 (0.4)	1 (0.2)
Cholestasis*	0	2 (0.3)
Headache	0	1 (0.2)
Fetal growth restriction*	1 (0.1)	0
Preeclampsia*	0	1 (0.2)
Mood altered[1]	1 (0.1)	0
Shortened cervix*	1 (0.1)	0
Vaginal hemorrhage	1 (0.1)	0
Dermatitis allergic	1 (0.1)	0
Dry skin	1 (0.1)	0

*MPC [1]AE occurred in same patient

PROLONG: Most Commonly Reported Serious Adverse Events (SAEs) and MPCs*

SAEs and MPCs (≥ 2 patients) Preferred Term	17P (N=1128) n (%)	Vehicle (N=578) n (%)
Patients ≥ 1 SAE/MPC	34 (3.0)	18 (3.1)
Cholestasis*	0	3 (0.5)
Endometritis	1 (0.1)	1 (0.2)
Escherichia coli sepsis	2 (0.2)	0
Migraine	1 (0.1)	1 (0.2)
Placental insufficiency*	4 (0.4)	1 (0.2)
Pneumonia	3 (0.3)	0
Premature separation of placenta*	5 (0.4)	2 (0.3)
Pyelonephritis	2 (0.2)	1 (0.2)
Wound infection	2 (0.2)	0

2 patients each had 1 SAE considered possibly related to study drug: 1 in 17P group hospitalized for mild nephrolithiasis; 1 in vehicle group with severe cholestasis

Post-Marketing Surveillance: Safety Consistent with Clinical Trial Data

- Cumulative exposure of 294,781 patients since approval
- Post-marketing data consistent with safety data obtained from Meis and PROLONG
  - No new or unexpected safety findings
- Most frequent AE reports consistent with registration studies
  - Injection site pain and/or other injections site localized reactions (e.g., pruritus, nodule, swelling)

Post-Marketing Surveillance: Makena SAEs Around Perinatal Mortality

SAE: Death		Estimated Post-marketing Reporting Rate*
Non-Liveborn	Abortion spontaneous	0.1%
	Stillbirth	0.1%
Liveborn	Death Neonatal	0.003%
Total Perinatal Deaths		0.2%

**Reporting Rate is computed based on cumulative patient exposure of 294,781 as of Aug 2019*

PROLONG Reaffirmed Safety of 17P Demonstrated in Meis Study

- No new or unexpected safety findings
- No clinically meaningful difference in safety profile between treatment arms
- Consistent, favorable maternal and fetal safety comparable to vehicle
- Consistent findings in post-marketing surveillance data

Prevention of Preterm Births: Clinical Perspective

Sean C. Blackwell, MD

Professor and Chair, Department of Obstetrics, Gynecology, and Reproductive Sciences

McGovern Medical School-UTHealth

3 Key Clinical Questions

1. Why did PROLONG efficacy results differ from Meis results?

2. Is it feasible to do <u>another</u> confirmatory trial?

3. What do we do from here?

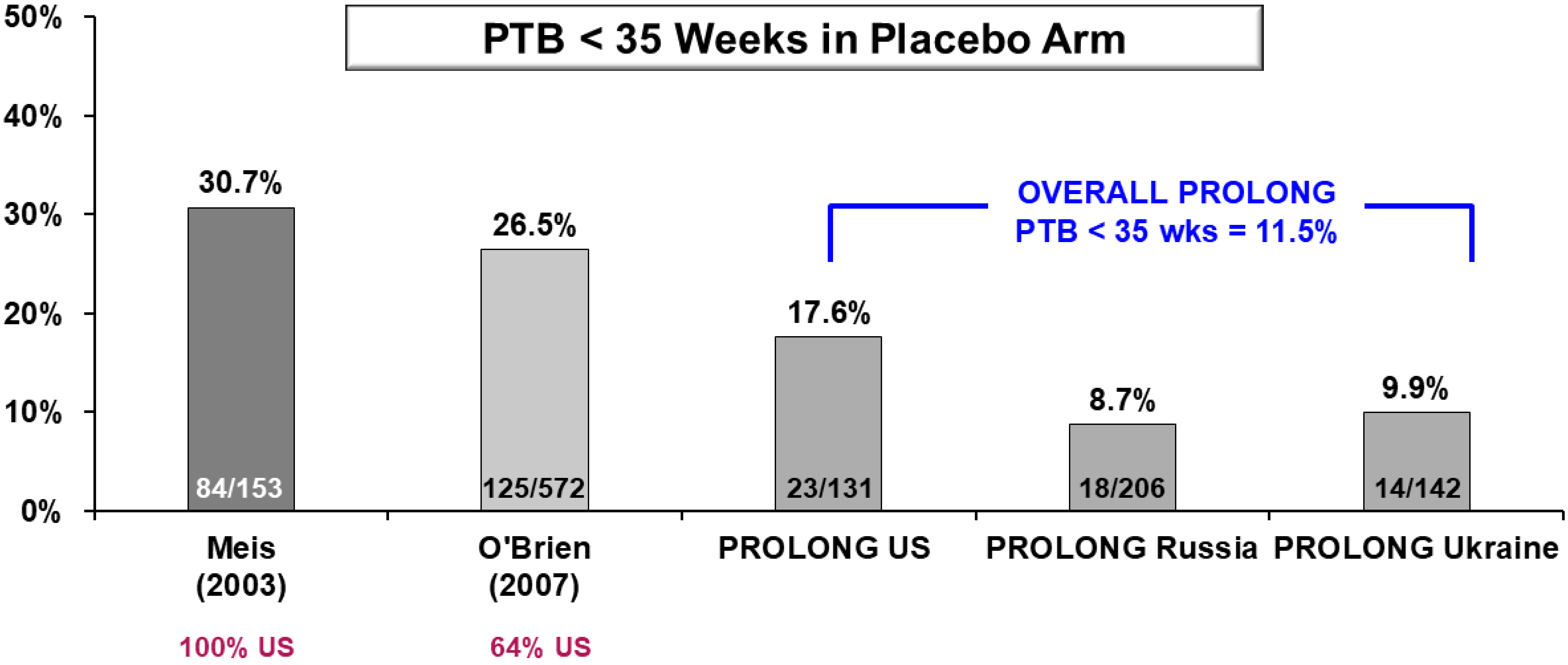
Question #1

Why did PROLONG efficacy results differ from Meis?

Differences in Clinical Characteristics Between Meis And PROLONG Study Populations

	Meis	PROLONG
Recruitment	100% US Academic Medical Centers	75% ex-US 60% Russia & Ukraine
Race	60% Black	7% Black
Surrogates of SES		
Unmarried with no partner	50%	10%
Smoking	22%	8%
≤ 12 years of education	71%	44%
> 1 prior PTB	27%	14%
PTB in placebo groups		
< 32 wks	19.6%	5.2%
< 35 wks	30.7%	11.5%
< 37 wks	54.9%	21.9%

Placebo Arm PTB Rates Across Different Clinical Trial Populations



PROLONG US: Recruitment Challenges

2003
ACOG committee opinion supports use of progesterone

2006
2/3 board certified MFMs already using progesterone

2009
PROLONG Trial enrollment initiated

- Many MFMs unwilling to participate
- No MFMU centers
- Few academic medical centers
- US sites generally where limited access to 17P

Ness, AJOG, 2006

PROLONG US: Enrollment Challenges

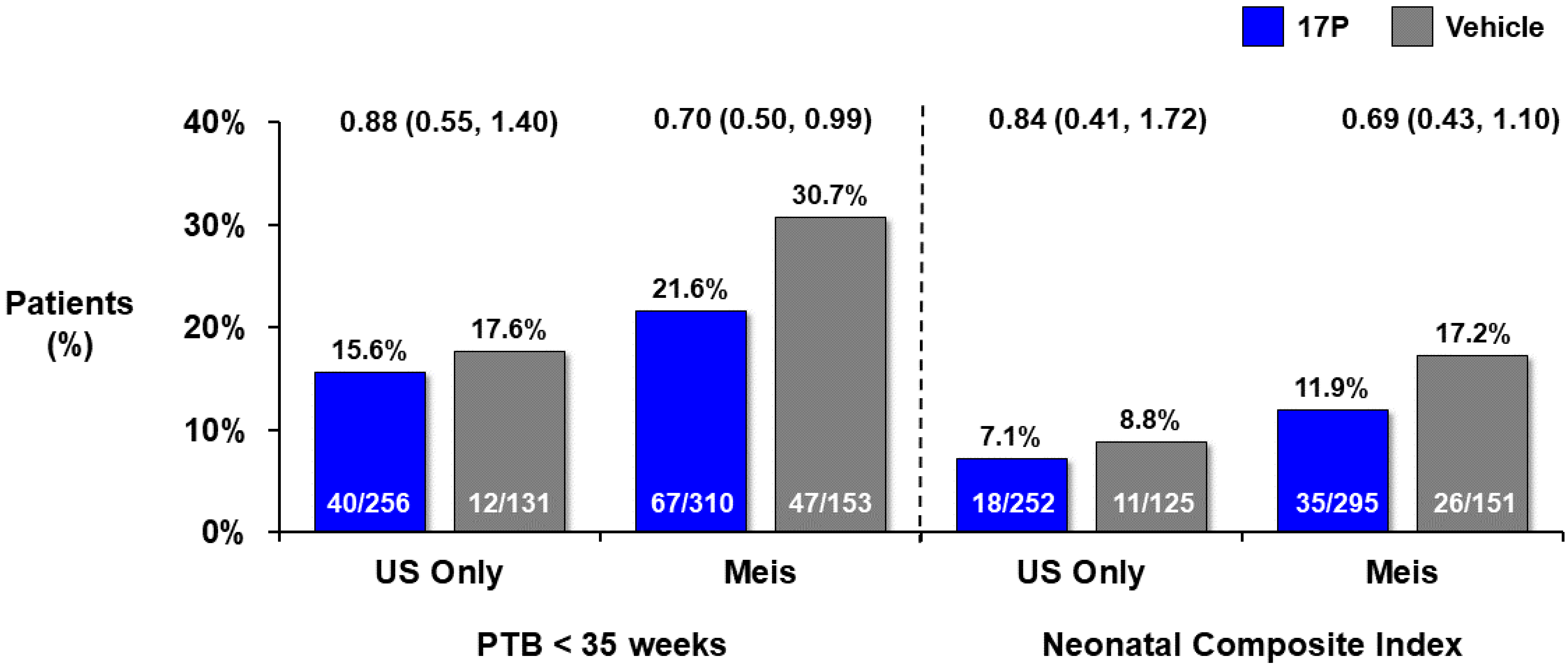
- Patients potentially steered from RCT to get open-label therapy (compounded 17P, vaginal progesterone, other)

- PROLONG
  - Low rate PTB > 1
  - Very low rate short cervix (< 2%)

PROLONG: Low Event Rates

- Sample size and expected event rate based on Meis trial
- 50% lower rates in PROLONG than Meis
- To design a trial today based on these low rates
  - 90% power would require
    - 3,600 women for PTB < 35 weeks
    - 6,000 for neonatal composite morbidity
- Population differences and low event rates make PROLONG results inconclusive

PROLONG: Treatment Effect Trends in US Only



96.5% CI to adjust for the interim analyses and number of prior preterm birth for PTB<35
95%CI adjusted for number of prior preterm birth for NCI

Question #2

Is it feasible to do another confirmatory trial?

Another Confirmatory Trial is Not Feasible

- US physicians won't accept placebo controlled RCT
- Where could we do another placebo controlled RCT?
  - Difficulty finding combination of
    - High-risk women
    - No access to 17P
    - Research infrastructure to conduct major trial

Feasibility of Another Confirmatory Trial: Trial of Two Therapies?

- No evidence-based therapies vs. 17P
- Vaginal progesterone: no benefit in 3 large RCTs
- Cervical cerclage and pessary also no proven benefit

	N	Endpoint	Vaginal progesterone	Placebo	95% CI
O'Brien	659	PTB ≤ 32 weeks	10%	11.3%	OR 0.9 (0.52 to 1.56)
OPPTIMUM*	1,053	PTB < 34 weeks or fetal death	15.9%	18.8%	OR 0.82 (0.58 to 1.16)
PROGRESS*	787	PTB < 37 weeks	36.5%	37.2%	aRR 0.97 (0.81 to 1.17)

*Included 12 women with twin pregnancies

1.O'Brien et al., 2007. 2. Norman et al., The Lancet. 2016. 3. Crowther et al., 2017

Question #3

What should we do from here?

SMFM Statement (October 25, 2019)

"Based on the evidence of effectiveness in the Meis study, which is the trial with the largest number of US patients, and given the lack of demonstrated safety concerns, SMFM believes that it is reasonable for providers to use 17-OHPC in women with a profile more representative of the very high-risk population reported in the Meis trial."

ACOG Practice Advisory (October 25, 2019)

"ACOG is not changing our clinical recommendations at this time and continues to recommend offering hydroxyprogesterone caproate as outlined in Practice Bulletin # 130, Prediction and Prevention of Preterm Birth."

What Will Happen if FDA-Approved 17P is Not Available?

- Many clinicians will use compounded 17P
  - Lack of GMP
  - Potential variance/sterility issues
  - No labeling
- Most physicians will not tolerate NO TREATMENT
  - Other off-label therapies (non-evidence based)
  - Many will choose cerclage (surgical therapy)

What Will I Do?

- Meis and PROLONG not contradictory
  - Meis showed efficacy in population similar to my patients
  - PROLONG reaffirms safety
  - Overall positive benefit/risk ratio
- Essential to be able to offer FDA-approved 17P

AMAG Actions Following PROLONG

Julie Krop, MD
Chief Medical Officer
EVP Clinical Development and Regulatory Affairs
AMAG Pharmaceuticals, Inc

Totality of Evidence Support Continued 17P Access

- Meis study demonstrated substantial evidence of efficacy
  - Basis of medical societies recommending 17P as standard of care
- PROLONG results inconclusive given differences in patient populations

What Have We Learned from PROLONG?

- Impossible to conduct confirmatory trial once 17P was recommended by medical societies as standard of care
  - Lead to bias towards lower risk population
- PROLONG confirmed favorable safety profile
  - Supported by 8 years of post-marketing surveillance

Does Meis Trial Alone Meet Criteria for Single Trial as Basis for Approval?

- FDA guidance for single trial approval
  - Second trial not feasible or ethical
  - Statistically persuasive findings
  - Clinically relevant endpoint
  - Robust, consistent results across multiple subgroups
- PTB at <37, < 35 and < 32 weeks increases risk to neonate
  - Should no longer require a confirmatory trial
- Orphan disease with NO alternative treatment options

FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998

17P is an Important Treatment Option for Pregnant Women With History of Preterm Birth

- Physicians and patients can make informed decisions together
- PROLONG results recently published in American Journal of Perinatology
- Label update with PROLONG safety and efficacy data

Considerations for Another Confirmatory Study

- Randomized placebo-controlled trial
  - Not feasible given current clinical practice guidelines
- Observational study
  - Challenging to control for known and unknown PTB risk factors

Positive Benefit-Risk Profile of 17P Supports Continued Access for Physicians and Patients

- Preterm birth remains major US public health concern
- Critical to keep 17P available to patients who need it most

17 α-Hydroxyprogesterone Caproate (Makena®) for Women with Singleton Pregnancy and Prior Singleton Spontaneous Birth

FDA Advisory Committee Meeting

Division of Bone, Reproductive and Urologic Products

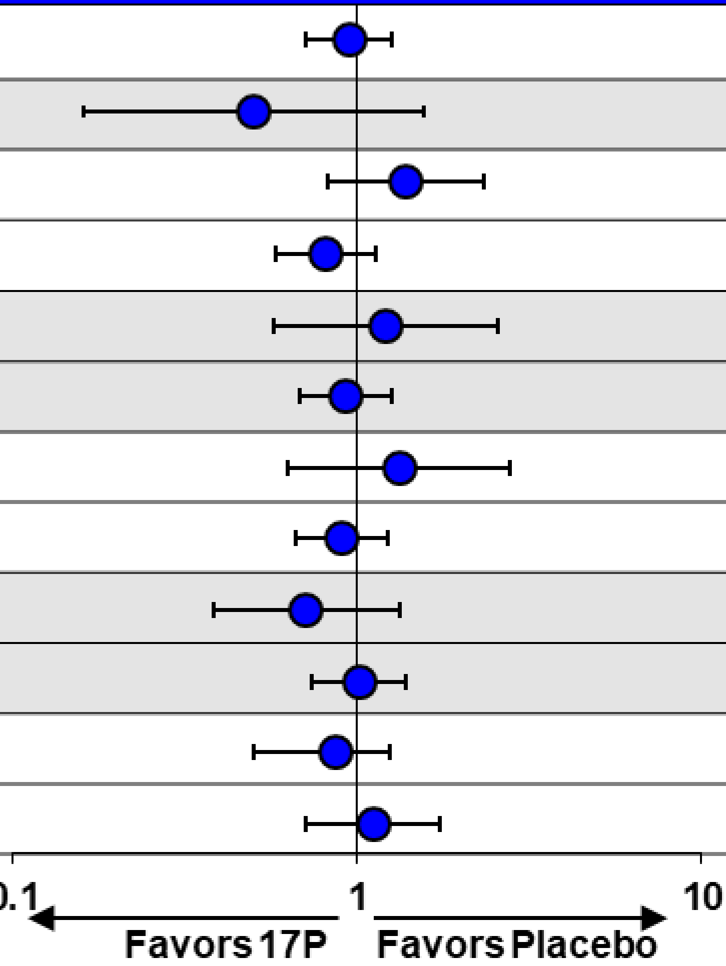
AMAG Pharmaceuticals, Inc.

October 29, 2019

Back-up Slides Shown

PROLONG Study: PTB < 35 Weeks with 17P Across Multiple Subgroups

Subgroup	17P (n/N)	Vehicle (n/N)	Relative Risk (95% CI)
All patients	122/1113	66/574	0.95 (0.71, 1.26)
Cervical Length < 25 mm	4/18	4/9	0.50 (0.16, 1.55)
> 1 Prior SPTB	42/164	15/81	1.38 (0.82, 2.34)
Only 1 Prior SPTB	80/949	51/491	0.81 (0.58, 1.13)
Black	17/72	8/41	1.21 (0.57, 2.56)
Non-Black	105/1041	58/533	0.93 (0.68, 1.26)
Unmarried	22/117	8/56	1.32 (0.63, 2.77)
Married	100/996	58/518	0.90 (0.66, 1.22)
Smoke or substance use	19/105	13/51	0.71 (0.38, 1.32)
No smoke or substance use	103/1008	53/523	1.01 (0.74, 1.38)
Education ≤ 12 years	64/474	40/256	0.86 (0.50, 1.24)
Education > 12 years	58/638	26/318	1.11 (0.71, 1.73)



Stillbirth: PROLONG and Meis MFM Review

Stillbirth affects 1 in 160 pregnancies each year in general population
Several underlying fetal/maternal causes[1]

- **PROLONG**:
  - 17P: 12/1128 (1.1%)
    - 11 underlying factors; 1 unknown
  - Vehicle: 3/578 (0.5%)
    - All had underlying factors

- **Meis**:
  - 17P: 6/306 (2.0%)
    - 5 underlying factors; 1 unknown
  - Vehicle: 2/153 (1.3%)
    - 1 underlying factor; 1 unknown

1. Silver JAMA 2011

Makena (hydroxyprogesterone caproate injection)
New Drug Application 021945/Supplement 023

Opening Remarks

Bone, Reproductive and Urologic Drugs Advisory Committee Meeting

October 29, 2019

Christine P. Nguyen, M.D.
Deputy Director for Safety
Division of Bone, Reproductive and Urologic Products
Office of New Drugs, Center for Drug Evaluation and Research
Food and Drug Administration

Clinical Background

- Neonatal mortality and morbidity from preterm birth (PTB) is a significant public health concern
- No therapies approved to reduce the risk of neonatal mortality and morbidity from prematurity
- Progestogens (intravaginal or intramuscular) used to reduce the risk of PTB
  - Only Makena (hydroxyprogesterone caproate injection) approved for reducing the risk of recurrent PTB

Regulatory History

- Makena approved in 2011 under accelerated approval to reduce the risk of PTB in women with a singleton pregnancy and a prior spontaneous PTB
- Approval: a single trial conducted 1999-2002 in the U.S., based on surrogate endpoint of gestational age (GA) of delivery <37 weeks
- As required under accelerated approval regulations, the Applicant conducted a postapproval confirmatory trial to verify clinical benefit for the neonate

Confirmatory Trial - 003

- International, randomized, double-blind, placebo-controlled trial in 1708 pregnant women
  - Russia, Ukraine, and U.S. enrolled 36%, 25%, and 23% subjects
- Design, eligibility criteria similar to Trial 002, except for primary endpoints
  - Trial 002: GA at delivery <37 weeks
  - Trial 003: GA at delivery <35 weeks, neonatal morbidity/mortality index
- Conducted 2009-2018

Trial 003 Results:
No Treatment Effect

Efficacy Endpoints* (% of patients)	Makena (N=1130)	Placebo (N=578)	Difference (95% CI)	P-value
Coprimary: Neonatal composite index (%)	5.4	5.2	0.2 (-2.0, 2.5)	0.84
Coprimary: PTB <35^0 weeks (%)	11.0	11.5	-0.6 (-3.8, 2.6)	0.72
PTB <32^0 weeks (%)	4.8	5.2	-0.4 (-2.8, 1.7)	
PTB <37^0 weeks (%)	23.1	21.9	1.3 (-3.0, 5.4)	

*FDA's Analysis

Trial 003 Exploratory Subgroup Analyses

- No statistically significant treatment difference or interaction between treatment effect and these factors:
  - Region (U.S. vs. non-U.S.)
  - Race (Black vs. Non-Black)
  - Elements that may increase PTB risk:
    - 1 vs. >1 prior PTB, substance use in pregnancy, ≤12 years of education, single/no partner

❖ These factors may be prognostic, but they do not appear to be effect modifiers

- There was no consistent, convincing evidence of a treatment effect within any particular subpopulation across Trials 002 and 003.

Totality of Evidence: Trial 002 and Trial 003

- Trial 002 - efficacy on gestational age of delivery (*surrogate endpoint*)
  - Conducted 1999-2002 in the U.S.
  - Issues regarding generalizability: ~60% self-identified black, all from academic centers, 27% from a single center, high recurrent preterm birth rate <37 weeks in placebo arm (55%)
- Trial 003 – no efficacy on neonatal outcomes (*clinical endpoint*) or gestational age at delivery (*surrogate endpoint*)
  - Conducted 2009-2018, powered to detect treatment effect in Trial 002
  - International (23% from the U.S.), lower risk population, lower recurrent preterm birth rate in placebo arm than in Trial 002

Totality of Evidence

Endpoint	Efficacy on Endpoint	Approval Efficacy Requirement Issues
<u>Surrogate endpoint</u>: GA at delivery	Yes (Trial 002) No (Trial 003) ❖ **Conflicting efficacy findings**	**<u>Issue 1:</u>** Substantial Evidence of Effectiveness
<u>Clinical endpoint</u>: Neonatal composite index	No (Trial 003) ❖ **No verification of clinical benefit**	**<u>Issue 2:</u>** Accelerated Approval

Issue 1: Substantial Evidence of Effectiveness

- Statutory standard of establishing efficacy for FDA drug approval*, including accelerated approval
  - Traditionally, significant findings from ≥ 2 adequate and well-controlled trials, each convincing on its own (independent substantiation) on the efficacy endpoint(s), reduces risk false positive from chance or bias

- When appropriate, a single adequate, well-controlled trial with persuasive findings may be accepted as substantial evidence

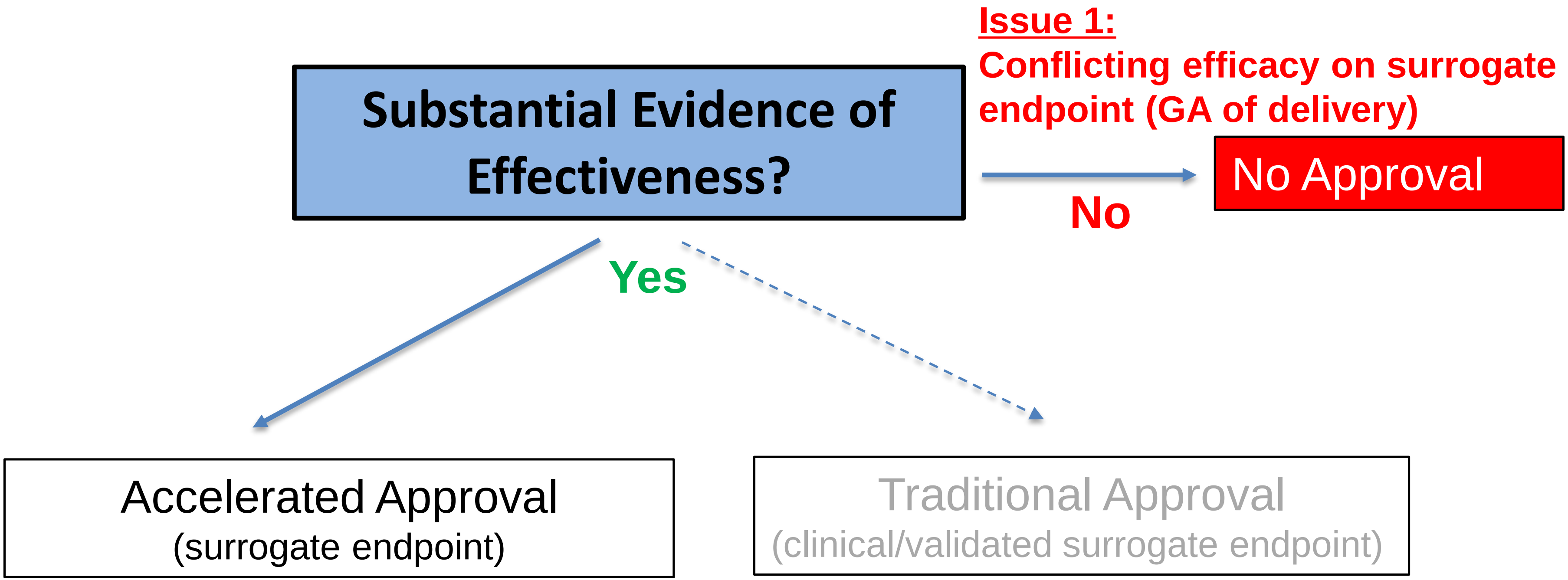
*Substantial evidence defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations.."

Issue 1: Substantial Evidence of Effectiveness

- 2011 accelerated approval of Makena based on a single trial
- If there were additional adequate and well-controlled trials in 2011, FDA would have considered those data when deciding about substantial evidence of effectiveness
- Now there are 2 adequate and well-controlled trials (Trials 002 and 003)

Issue 1: Trial 003 did not substantiate Makena's treatment effect on GA of delivery: Is there still substantial evidence of the drug's effect on reducing the risk of preterm birth?

Issue 1: Substantial Evidence of Effectiveness



Issue 2: Accelerated Approval

- Traditional approval: based on *clinical endpoint* (directly measures how patients feel, function, or survive) or *validated surrogate endpoint*
- Accelerated approval: based on a *surrogate endpoint* reasonably likely to predict clinical benefit
  - Expedited drug development pathway
  - Reserved for certain drugs treating serious/life-threatening conditions with unmet medical need
  - Must meet same statutory effectiveness standards as those for traditional approval

Issue 2: Accelerated Approval

- Makena accelerated approval based on treatment effect on *surrogate endpoint (GA of delivery)*
  - GA of delivery is not a direct measure of how neonates feel, function, or survive
  - Spontaneous PTB poorly understood syndrome with potential for multiple pathophysiologic pathways
  - Prolonging GA of delivery may not consistently translate into improved neonatal outcomes

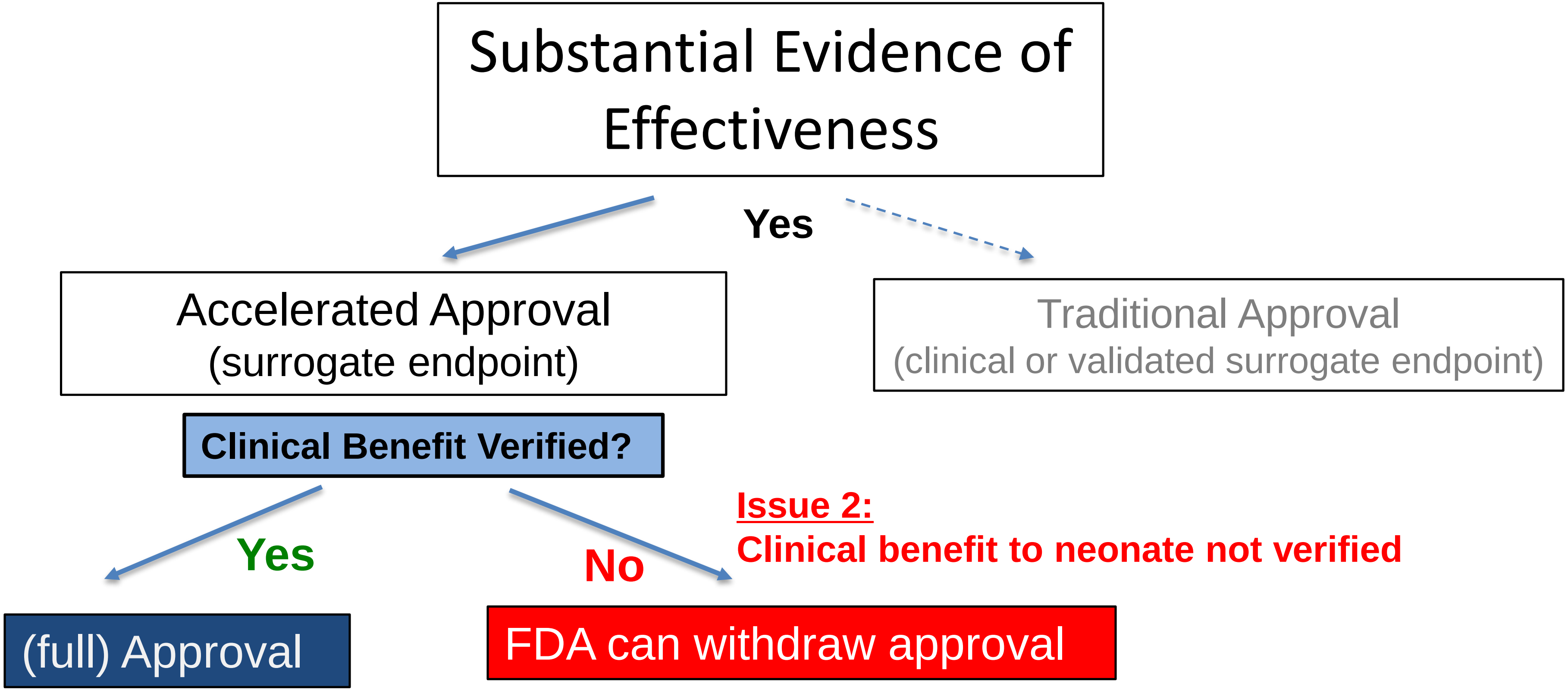
Issue 2: Accelerated Approval

- More uncertainty at the time of approval that the treatment effect on surrogate endpoint (GA at delivery) will translate into clinical benefit (neonatal outcomes)
  - Therefore, must undergo a postapproval confirmatory trial to verify clinical benefit

- FDA can withdraw approval of the drug or indication if the Applicant does not conduct the required trial(s) with due diligence or the trial(s) fail to verify clinical benefit

Issue 2: Trial 003 did not verify Makena's clinical benefit to the neonate

Issue 2: Accelerated Approval



Discussion and Voting Questions

Discussion Question 1

- Discuss the effectiveness of Makena on recurrent preterm birth and neonatal morbidity and mortality.

Discussion Question 2

- If a new confirmatory trial were to be conducted, discuss the study design, including control, dose(s) of study medication, efficacy endpoints and the feasibility of completing such a trial.

Discussion Question 3

- Discuss the potential consequences of withdrawing Makena on patients and clinical practice.

Voting Question 4

- Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal outcomes?
  - Provide rationale for your vote.

Voting Question 5

- Based on the findings from Trial 002 and Trial 003, is there substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth?
  – Provide rationale for your vote.

Voting Question 6

FDA approval, including accelerated approval, of a drug requires *substantial evidence of effectiveness (Issue 1).*

For drugs approved under the accelerated approval pathway based on a surrogate endpoint, the Applicant is required to conduct confirmatory trial(s) to *verify clinical benefit (Issue 2)*. If the Applicant fails to conduct such a trial(s) or if such trial(s) does not verify clinical benefit, FDA may, following an opportunity for a hearing, withdraw approval.

Voting Question 6 Continued

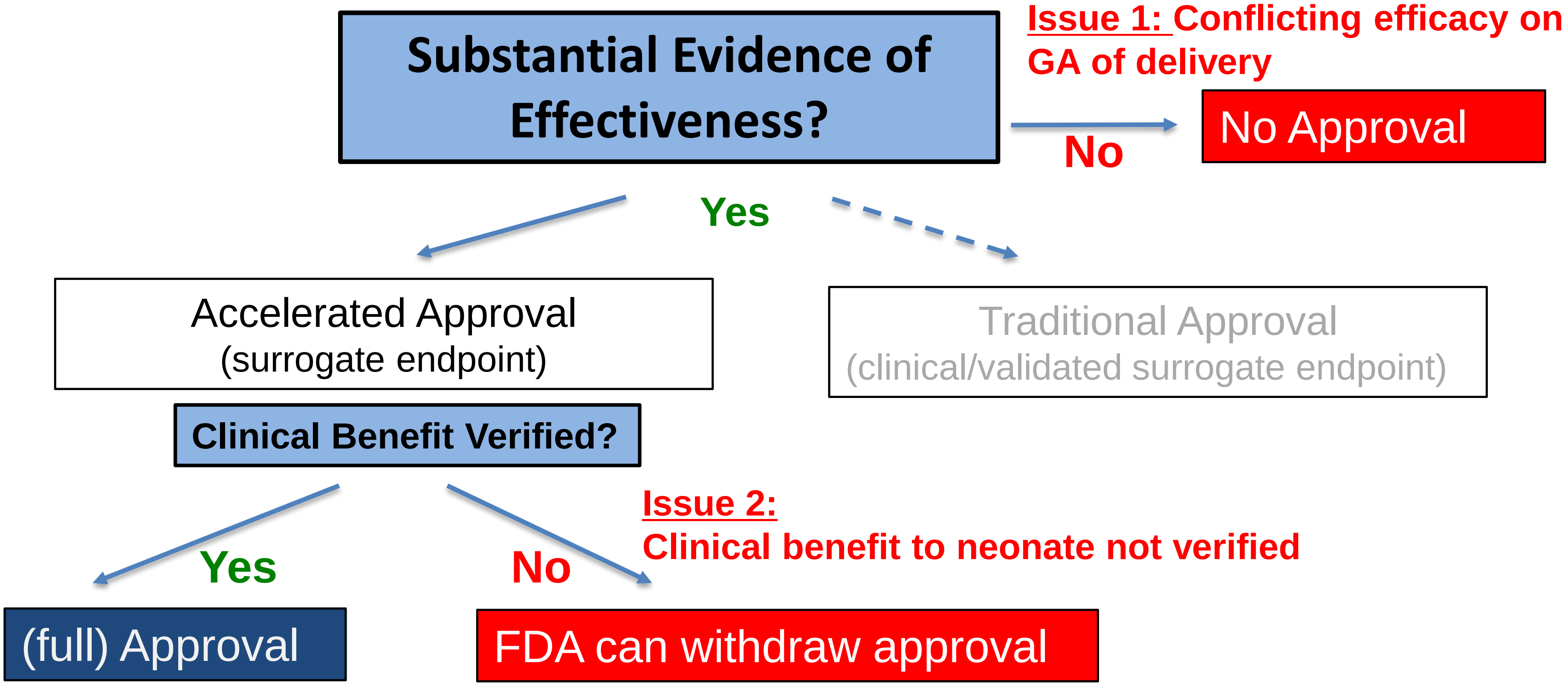
- Should FDA:

  (A) Pursue withdrawal of approval for Makena

  (B) Leave Makena on the market under accelerated approval and require a new confirmatory trial

  (C) Leave Makena on the market without requiring a new confirmatory trial

Approval: Efficacy Requirement Issues



Voting Question 6 Continued

- **Vote A** (withdraw approval) may be appropriate if you believe the totality of evidence does not support Makena's effectiveness for its intended use.
  - Discuss the consequences of Makena removal

Voting Question 6 Continued

- **Vote B** (require a new confirmatory trial) may be appropriate if you believe the totality of evidence supports Makena's effectiveness in reducing the risk of recurrent PTB, but that there is no substantial evidence of effectiveness on neonatal outcomes AND you believe that a new confirmatory trial is necessary and feasible.
  - Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent PTB, based on the surrogate endpoint of gestational age at delivery.
  - Also discuss key study elements, including study population, control, dose(s), and efficacy endpoints of the new confirmatory trial (if not previously discussed in Discussion point 2) and approaches to ensure successful completion of such a trial.

Voting Question 6 Continued

- **Vote C** (leave Makena on the market without a new confirmatory trial) may be appropriate if you believe Makena is effective for reducing the risk of recurrent PTB and that it is not necessary to verify Makena's clinical benefit to neonates.
  – Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent PTB and why it is not necessary to verify Makena's clinical benefit to neonates.

FDA U.S. FOOD & DRUG ADMINISTRATION

Makena (hydroxyprogesterone caproate injection)
New Drug Application 021945/Supplement 023

Clinical Overview

Bone, Reproductive and Urologic Drugs Advisory Committee Meeting

October 29, 2019

Barbara Wesley, M.D., M.P.H.
Medical Officer
Division of Bone, Reproductive and Urologic Products
Office of New Drugs, Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Trial 002 and its history (1999-2011)
  - Findings, areas of controversy
- 2006 Advisory Committee
- FDA Actions (2006, 2009, 2011)
- Accelerated approval postmarketing requirement - Confirmatory Trial 003

Background of Trial 002

- 1999-2002: Funded by National Institute of Child Health and Human Development NICHD; conducted by Maternal-Fetal Medicine Units Network (MFMU).
- 2003: Positive findings of hydroxyprogesterone caproate (HPC) reducing the risk of preterm birth <37 weeks published in the New England Journal of Medicine*
- 2006: Submission of new drug application (NDA) for HPC 250 mg/mL

*Meis PJ, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;348(24):2379-85.

Makena

Indication

- To reduce the risk of preterm birth in women with a singleton pregnancy and a history of spontaneous preterm birth

Dosage & Administration

- 250 mg once a week beginning between 16^0 weeks and 20^6 weeks gestation to week 37 of gestation or birth

Trial 002 Design

Study Medications

- HPC in castor oil
- Placebo

Primary Efficacy Endpoint

- Birth <37^0 weeks

Additional Efficacy Endpoints (post hoc)

- <35^0 weeks and <32^0 weeks
- Composite index of neonatal morbidity
  - Death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), Grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis, necrotizing enterocolitis (NEC)

Trial 002: Preterm Births
<37^0 Weeks Gestation

Primary Efficacy Endpoint P= 0.001

HPC N = 310	Placebo N = 153	% Difference [Adjusted 95% Confidence Interval]
Number (%) Preterm Births		
115 (37%)	84 (55%)	-18% [-28%, -7%]

- PTB rate of **55%** in placebo arm considerably greater than rate in other MFMU Network studies (~36%)
- PTB rate of **37%** in HPC arm similar to PTB rate in placebo arms in other MFMU Network study

PTB Rate in Placebo Arm by Race in Trial 002

Race	Placebo - n/N (%)
Black	47/90 **(52%)**
Non-black	37/63 **(59%)**

Percent of Preterm Births at Various Gestational Age Thresholds (Trial 002)

Age at Delivery (Weeks)	HPC N=310	Placebo N=153	% Difference [Adjusted 95% Confidence Interval]
	Percent Delivered		
<37^0	37	55	-18.0% [-28%, -7.4%]
<35^0	21	31	-9.4% [-19.0%, -0.4%]
<32^0	12	20	-7.7% [-16.1%, -0.3%]

Makena prescribing information, Drugs@FDA

Confidence intervals **adjusted for the interim analyses and the final analysis**. To preserve overall Type I error rate of 0.05, p-value boundary of 0.035 used for the adjustment (equivalent to a 96.5% confidence interval).

Composite Neonatal Morbidity (Trial 002)

Morbidity	HPC N=295 n (%)	Placebo N=151 n (%)
Death (live births only)	8 (2.6)	9 (5.9)
Respiratory distress syndrome	29 (9.9)	23 (15.3)
Bronchopulmonary dysplasia	4 (1.4)	5 (3.3)
Gr. 3/4 intraventricular hemorrhage	2 (0.7)	0 (0.0)
Proven sepsis	9 (3.1)	4 (2.6)
Necrotizing enterocolitis	0 (0.0)	4 (2.7)
Composite Index of Morbidity*	**35 (12%)**	**26 (17%)**
*** No. subjects with one or more of the listed morbidities**		

Summary of Effectiveness Issues

- Applicant sought approval for HPC based on
  - Findings from a single clinical trial
  - A surrogate endpoint for infant mortality/morbidity (preterm birth <37 weeks)

- Concern about generalizability to general U.S. population
  - Notably high preterm birth rate in placebo arm (55%)
  - Approximately 60% Black or African American
  - Enrollment from academic centers only; 27% from one academic center

2006 Advisory Committee Meeting

Which gestational age at birth is an adequate surrogate? (21 members voting)

- PTB <37 weeks – yes = 5
- PTB <35 weeks – yes = 13
- PTB <32 weeks – yes = 20

2006 FDA Action: Not Approved

- Major deficiency: New trial to provide substantial evidence of efficacy - direct benefit on neonatal morbidity and mortality or the surrogate PTB <35 and <32 weeks of gestation

- Address the concern regarding early pregnancy loss

Between 2009 and 2011 FDA Actions: Effect of Late-Preterm Birth

- **Late-Preterm Infants** – defined as infants born between 34 $^{0/7}$ and 36 $^{6/7}$ weeks of gestation: "are often mistakenly believed to be as physiologically and metabolically as mature as term infants"
- Higher rates of infant mortality and morbidity than term infants.

Engle, WA, et al. "Late-preterm" infants: a population at risk. Pediatrics 2007;120:1390-1401.
ACOG Obstetrics Practice Committee Opinion, Number 404, April 2008

2011 FDA Action: Accelerated Approval

- Recent data on effect of FDA to reconsider gestational age at delivery
- FDA concluded that delivering at <37 weeks of gestation was an adequate surrogate endpoint
- Findings of Trial 002 now deemed sufficient to support accelerated approval
- Trial 003 was ongoing and Applicant demonstrated that it could be successfully completed

Applicant's Obligation

As a condition of accelerated approval, the Applicant was required to complete the confirmatory clinical trial of Makena (Trial 003) to verify the clinical benefit to neonates from the reduction in the risk of PTB.

FDA U.S. FOOD & DRUG ADMINISTRATION

Makena (hydroxyprogesterone caproate injection)
New Drug Application 021945/Supplement 023

Efficacy in Confirmatory Trial 003

Bone, Reproductive and Urologic Drugs Advisory Committee Meeting

October 29, 2019

Jia Guo, Ph.D.
Statistical Reviewer
Division of Biometrics 3
Office of Biostatistics, Center for Drug Evaluation and Research
Food and Drug Administration

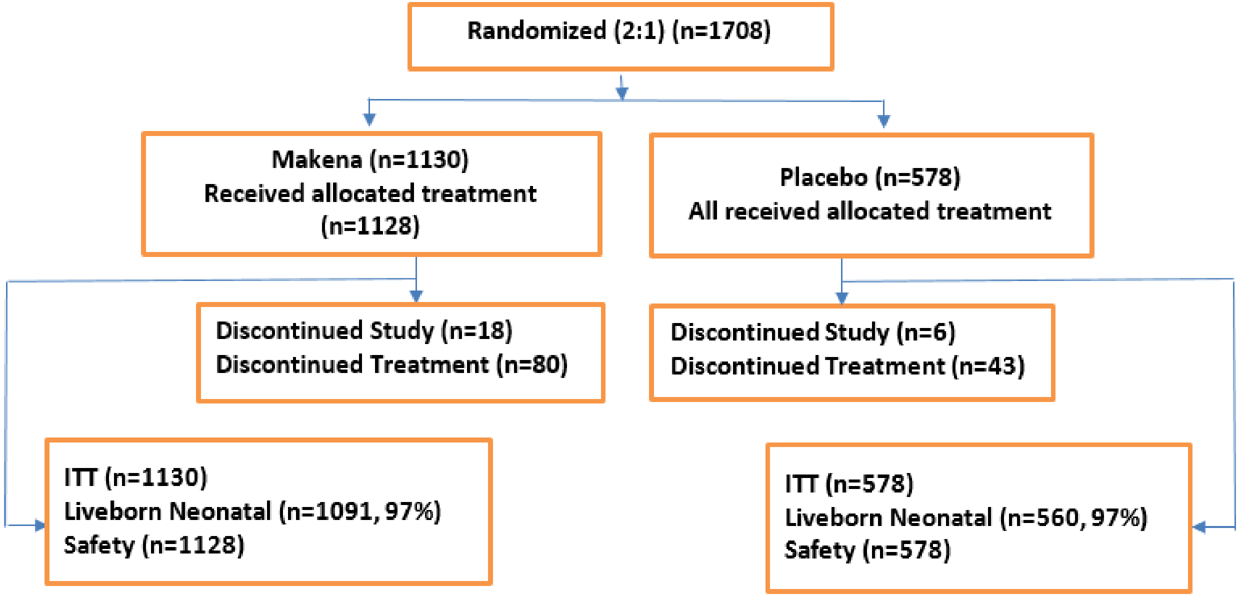
Outline

- Overview of Trial 003
  - Trial Design
  - Subject Disposition
  - Demographics and Baseline Characteristics
  - Efficacy Results
- FDA's Exploratory Analyses
- Concluding Remarks

Trial 003 Study Design

- **Study Design**
  - Multicenter, randomized, double-blind, placebo-controlled
  - Makena or placebo (2:1) stratified by study site and gestational age at randomization (16^0-17^6 weeks, 18^0-20^6 weeks)
- **Power**
  - 90% to detect a 35% reduction (from 17% to 11%) in the rate of the neonatal composite index
  - 98% to detect a 30% reduction (from 30% to 21%) in the rate of preterm birth <35^0 weeks of gestation
- **Key Inclusion Criteria**
  - Aged ≥18 years
  - With a previous singleton spontaneous preterm delivery
  - Gestational age between 16^0 to 20^6 weeks
- **Key Exclusion Criteria**
  - Had significant medical disorder
  - Multifetal gestation
  - Known major fetal anomaly or fetal demise

Trial 003 Subject Disposition



- Intent-to-treat (ITT) population: all randomized subjects
- Liveborn neonatal population: all neonates of randomized subjects who were liveborn and had morbidity/mortality data available

Trial 003 Demographics and Baseline Characteristics

Makena and placebo groups were comparable across all demographics and baseline characteristics.

Variable	Makena (N=1130) n (%)	Placebo (N=578) n (%)	All (N=1708) n (%)
Race			
White	1004 (89)	504 (87)	1508 (88)
Black	73 (6)	41 (7)	124 (7)
Other	53 (5)	33 (6)	86 (5)
Single or without a partner	117(10)	56 (10)	173 (10)
≤12 years	488 (43)	259 (45)	747 (44)
Any substance use during pregnancy	106 (9)	52 (9)	158 (9)
>1 previous SPTB	166 (15)	82 (14)	248 (15)
Region, United States	258 (23)	133 (23)	391 (23)

SPTB = spontaneous preterm birth

Trial 003 Efficacy Endpoints

- **Coprimary Endpoints**
  - Preterm birth (PTB) prior to 35^0 weeks of gestation (Yes/No)
  - Neonatal composite morbidity and mortality index: Yes, if the liveborn neonate had any of
    - RDS
    - BPD
    - Grade 3 or 4 IVH
    - NEC
    - Proven Sepsis
    - Death

- **Secondary Endpoints**
  - PTB prior to 32^0 Weeks
  - PTB prior to 37^0 Weeks

Trial 003 Efficacy Results

Efficacy Endpoint	Makena (N=1130)	Placebo (N=578)	Difference* (95% CI)	P value*
Neonatal Composite Index (%)	**5.4**	**5.2**	**0.2 (-2.0, 2.5)**	**0.84**
PTB <35^0 weeks (%)	**11.0**	**11.5**	**-0.6 (-3.8, 2.6)**	**0.72**
PTB <32^0 weeks (%)	4.8	5.2	-0.4 (-2.8, 1.7)	
PTB <37^0 weeks (%)	23.1	21.9	1.3 (-3.0, 5.4)	

N: number of randomized subjects
* CMH method stratified by gestational age at randomization
FDA analysis

No statistically significant benefit of Makena (vs. placebo) was demonstrated in either coprimary and secondary efficacy endpoints.

FDA's Position

- Generally FDA does not support subgroup analyses for inference of efficacy when the primary analysis result does not demonstrate efficacy (FDA 1998, FDA 2017b)
  - Inflation of type I error
  - FDA considers such analyses for hypothesis-generating

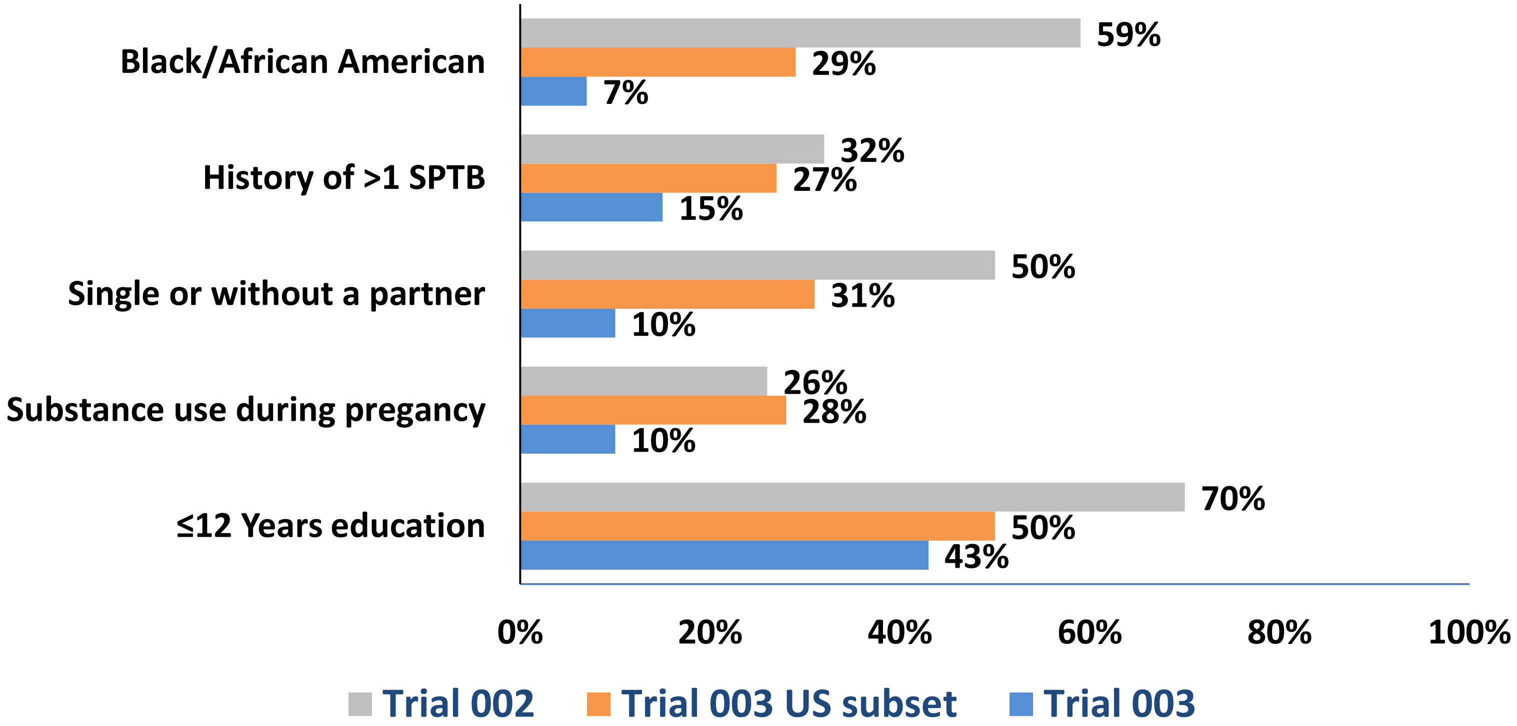
Guidance for Industry *E9 Statistical Principles for Clinical Trials* (September 1998) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9-statistical-principles-clinical-trials

Draft Guidance for Industry *Multiple Endpoints in Clinical Trials* (January 2017) https://www.fda.gov/media/102657/download

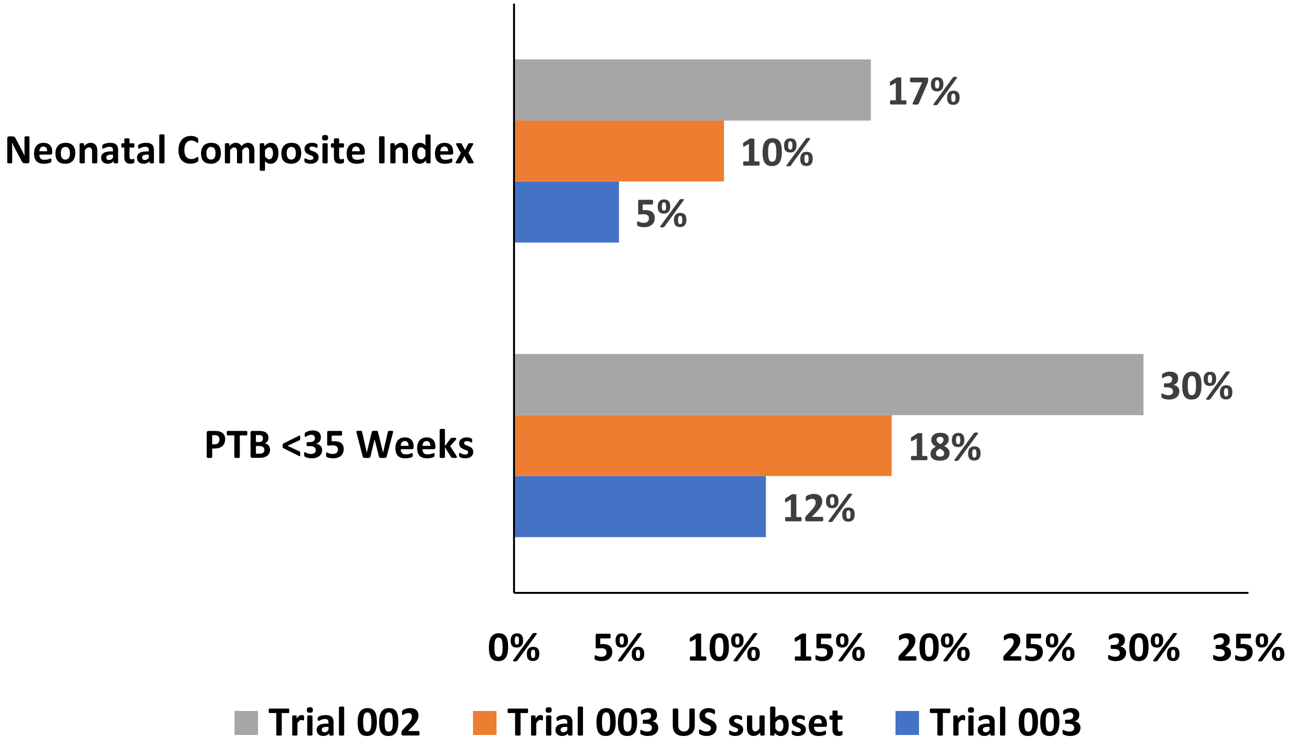
FDA Exploratory Analyses

- FDA reviewed the Applicant's post hoc subgroup analyses results to explore if differences in key aspects of Trials 003 and 002 might clarify the divergent results
  - Comparison between Trial 002 and Trial 003
  - Subgroup analyses

Comparison Between Trials 003 and 002 – Study Population

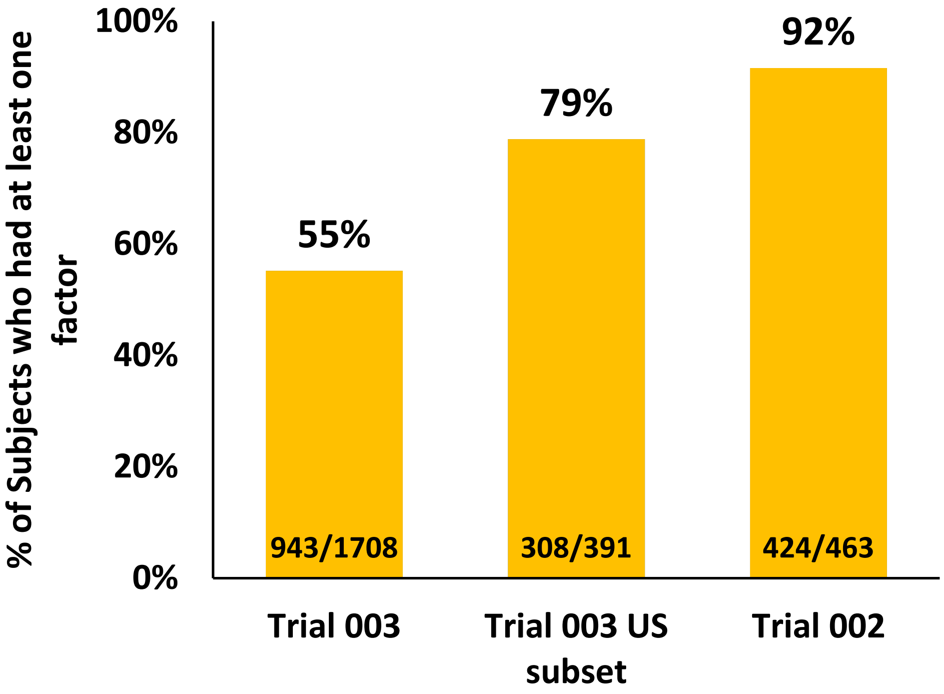


Comparison Between Trials 003 and 002 – Placebo Group



Comparison Between Trials 003 and 002 – "Composite" Risk at Baseline

- **"Composite" Risk Profile:**
  - Black
  - History of >1 prior SPTB
  - Single or without a partner
  - Substance use during pregnancy
  - ≤12 years of education



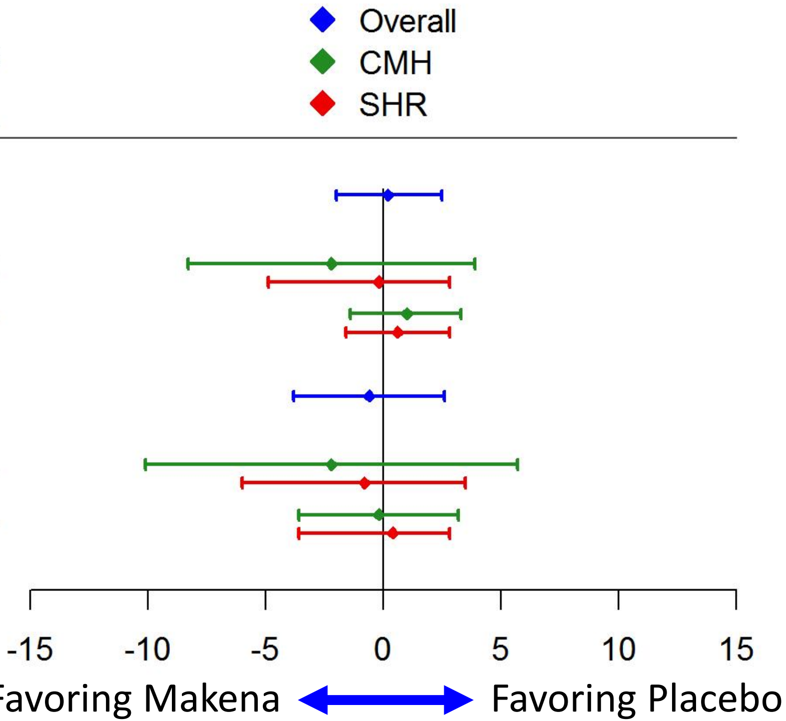
FDA Subgroup Analyses

- By single factor (stratified Cochran–Mantel–Haenszel (CMH) and shrinkage estimation)
  - Region (U.S., non-U.S.)
  - Race (Black, non-black)
  - History of SPTB (1 previous SPTB, >1 previous SPTB)
- By "composite" risk at baseline (no factor, ≥1 factor, ≥2 factors)

FDA Subgroup Analysis – by Region (003)

- No evidence of treatment effect on coprimary endpoints in either regional subgroup

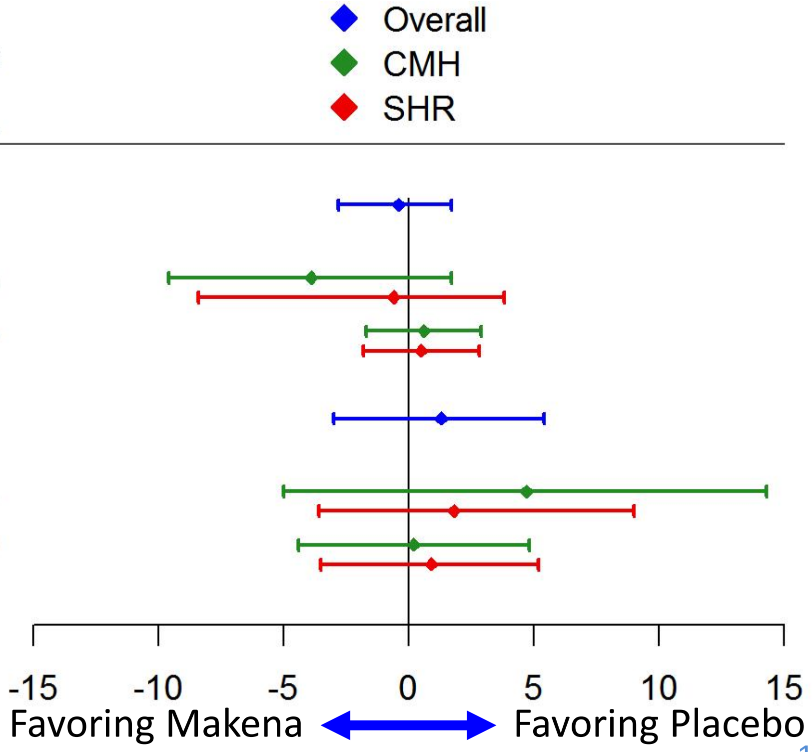
Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
Neonatal Index (%)	5.4	5.2	0.2	
US (252, 126)	7.1	9.5	-2.2	-0.2
Non_US (839, 434)	4.9	3.9	1.0	0.6
PTB<35 Weeks (%)	11.0	11.5	-0.6	
US (256, 131)	15.6	17.6	-2.2	-0.8
Non_US (857, 443)	9.6	9.7	-0.2	0.4



FDA Subgroup Analysis – by Region (003)

- No evidence of treatment effect on secondary efficacy endpoints in either regional subgroup

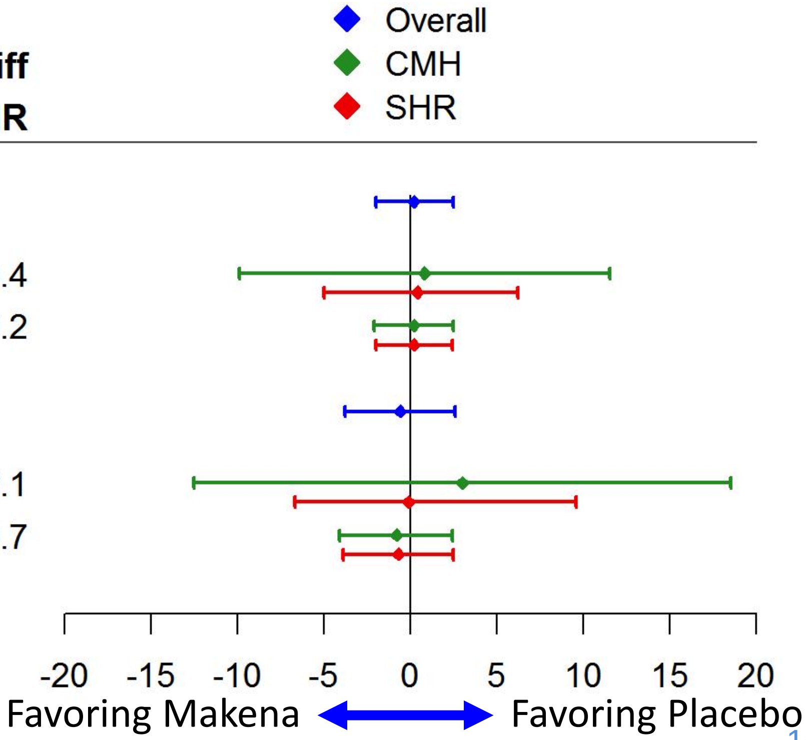
Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
PTB<32 Weeks (%)	4.8	5.2	-0.4	
US (256, 131)	5.5	9.2	-3.9	-0.6
Non_US (860, 443)	4.7	4.1	0.6	0.5
PTB<37 Weeks (%)	23.1	21.9	1.3	
US (256, 131)	33.2	28.2	4.7	1.8
Non_US (856, 441)	20.1	20.0	0.2	0.9



FDA Subgroup Analysis – by Race (003)

- No evidence of treatment effect on coprimary endpoints in Black or non-Black subgroups

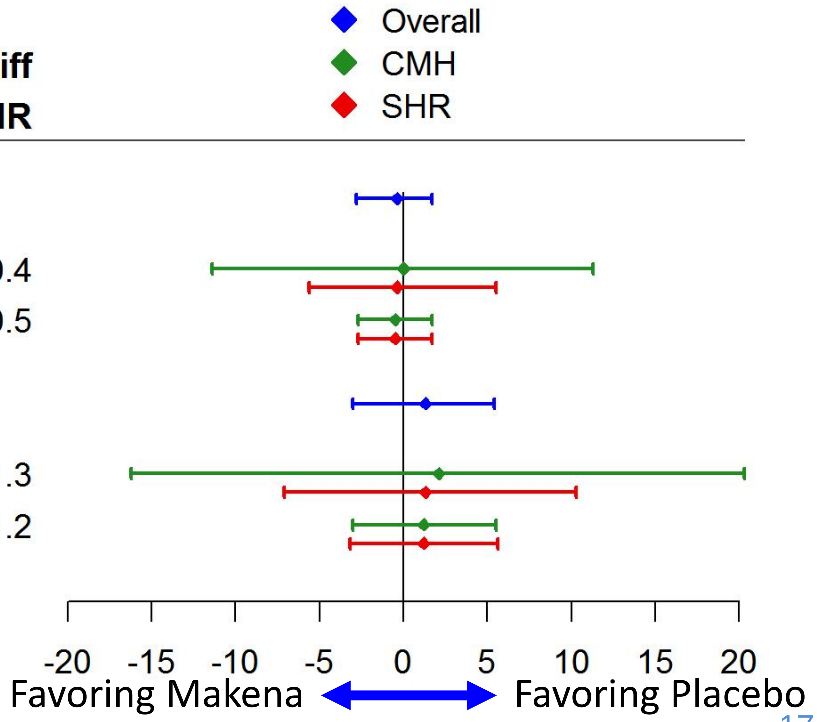
Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
Neonatal Index (%)	5.4	5.2	0.2	
Black (69, 40)	8.7	7.5	0.8	0.4
Non-Black (1022, 520)	5.2	5.0	0.2	0.2
PTB<35 Weeks (%)	11.0	11.5	-0.6	
Black (72, 41)	23.6	19.5	3.0	-0.1
Non-Black (1041, 533)	10.1	10.9	-0.8	-0.7



FDA Subgroup Analysis – by Race (003)

- No evidence of treatment effect on secondary endpoints in Black or non-Black subgroups

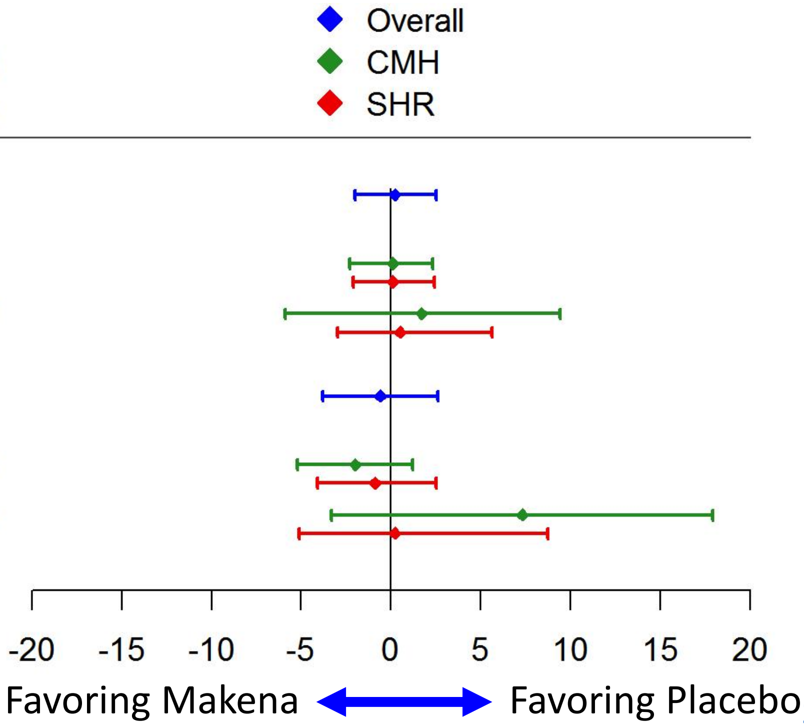
Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
PTB<32 Weeks (%)	4.8	5.2	-0.4	
Black (72, 41)	11.1	9.8	0	-0.4
Non-Black (1044, 533)	4.4	4.9	-0.5	-0.5
PTB<37 Weeks (%)	23.1	21.9	1.3	
Black (72, 41)	37.4	34.2	2.1	1.3
Non-Black (1041, 533)	22.1	20.9	1.2	1.2



FDA Subgroup Analysis – by History of SPTB (003)

- No evidence of treatment effect on coprimary endpoints in either subgroup defined by history of SPTB

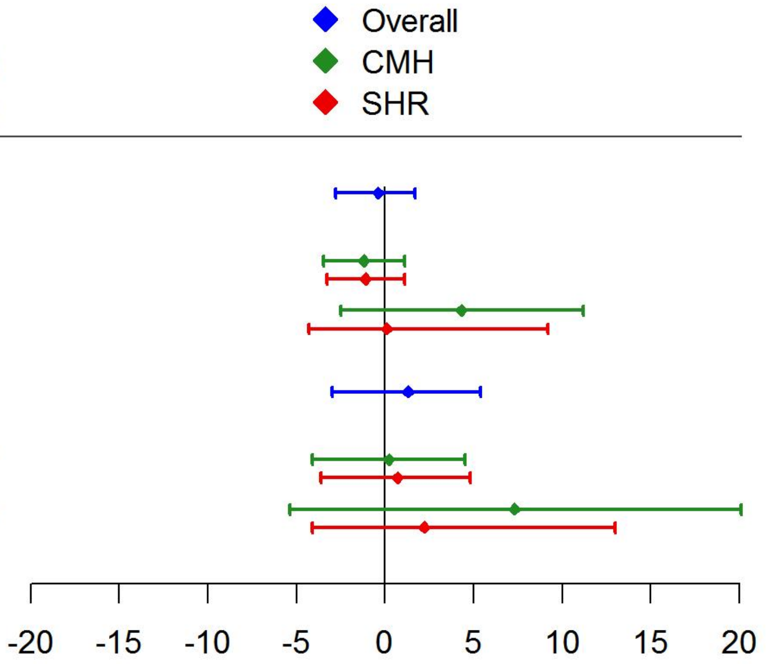
Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
Neonatal Index (%)	5.4	5.2	0.2	
1 (933, 478)	4.6	4.6	0	0.1
>1 (158, 80)	10.1	8.8	1.7	0.5
PTB<35 Weeks (%)	11.0	11.5	-0.6	
1 (949, 491)	8.4	10.4	-2.0	-0.9
>1 (164, 81)	25.6	18.5	7.3	0.2



FDA Subgroup Analysis – by History of SPTB (003)

- No evidence of treatment effect on the secondary efficacy endpoints in either subgroup with history of SPTB

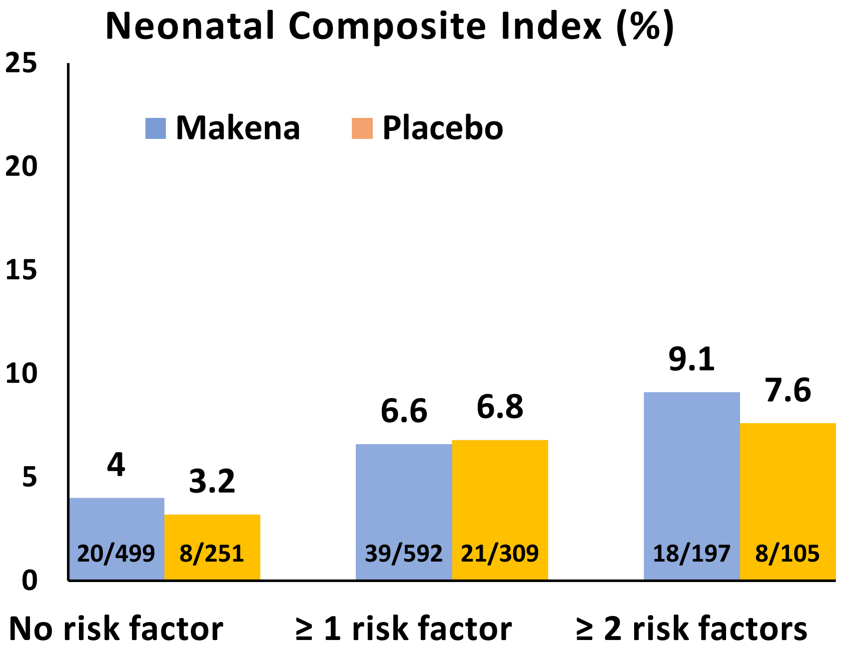
Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
PTB<32 Weeks (%)	4.8	5.2	-0.4	
1 (951, 491)	3.9	5.1	-1.2	-1.1
>1 (165, 81)	10.3	6.2	4.3	0.1
PTB<37 Weeks (%)	23.1	21.9	1.3	
1 (948, 489)	19.8	19.6	0.2	0.7
>1 (164, 81)	42.1	35.8	7.3	2.2

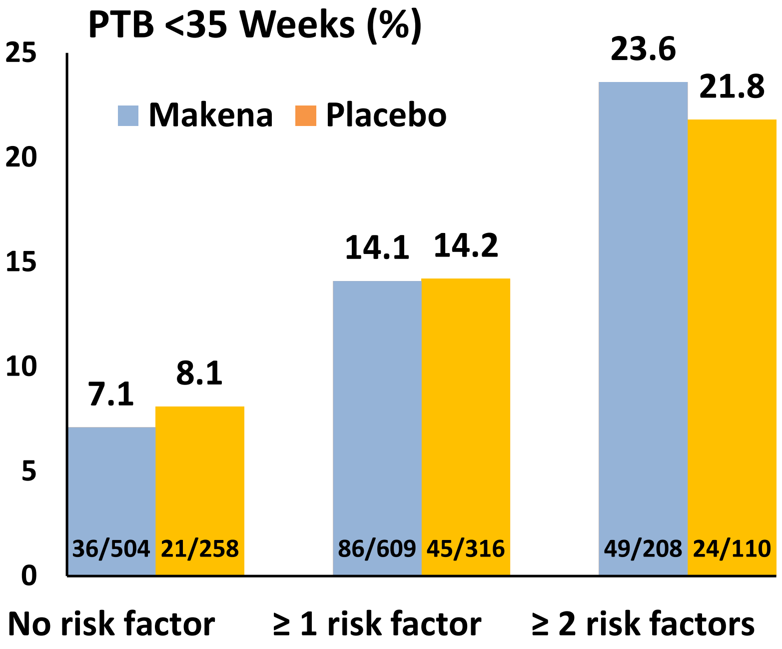


Favoring Makena ⟷ Favoring Placebo

FDA Analysis
by "Composite" Risk Level (003)

- No evidence of treatment effect in any risk groups defined using the 5 selected factors.





Concluding Remarks

- **Primary Analysis**
  - Makena did not demonstrate statistically significant treatment benefit vs. placebo on either gestational age at delivery or the neonatal composite index in Trial 003
- **Exploratory Analyses**
  - No evidence that Makena had a treatment effect on the efficacy endpoints vs. placebo in the subgroups
  - Although baseline risk factors can impact the overall probability of a PTB or the neonatal composite index, there is no evidence that they are effect modifiers to Makena's treatment effect

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA U.S. FOOD & DRUG ADMINISTRATION

Makena (hydroxyprogesterone caproate injection)
New Drug Application 021945

Hydroxyprogesterone caproate (HPC) Utilization in the United States

Bone, Reproductive and Urologic Drugs Advisory Committee Meeting

October 29, 2019

Huei-Ting Tsai, Ph.D.
Epidemiologist
Division of Epidemiology II
Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research
Food and Drug Administration

Outline

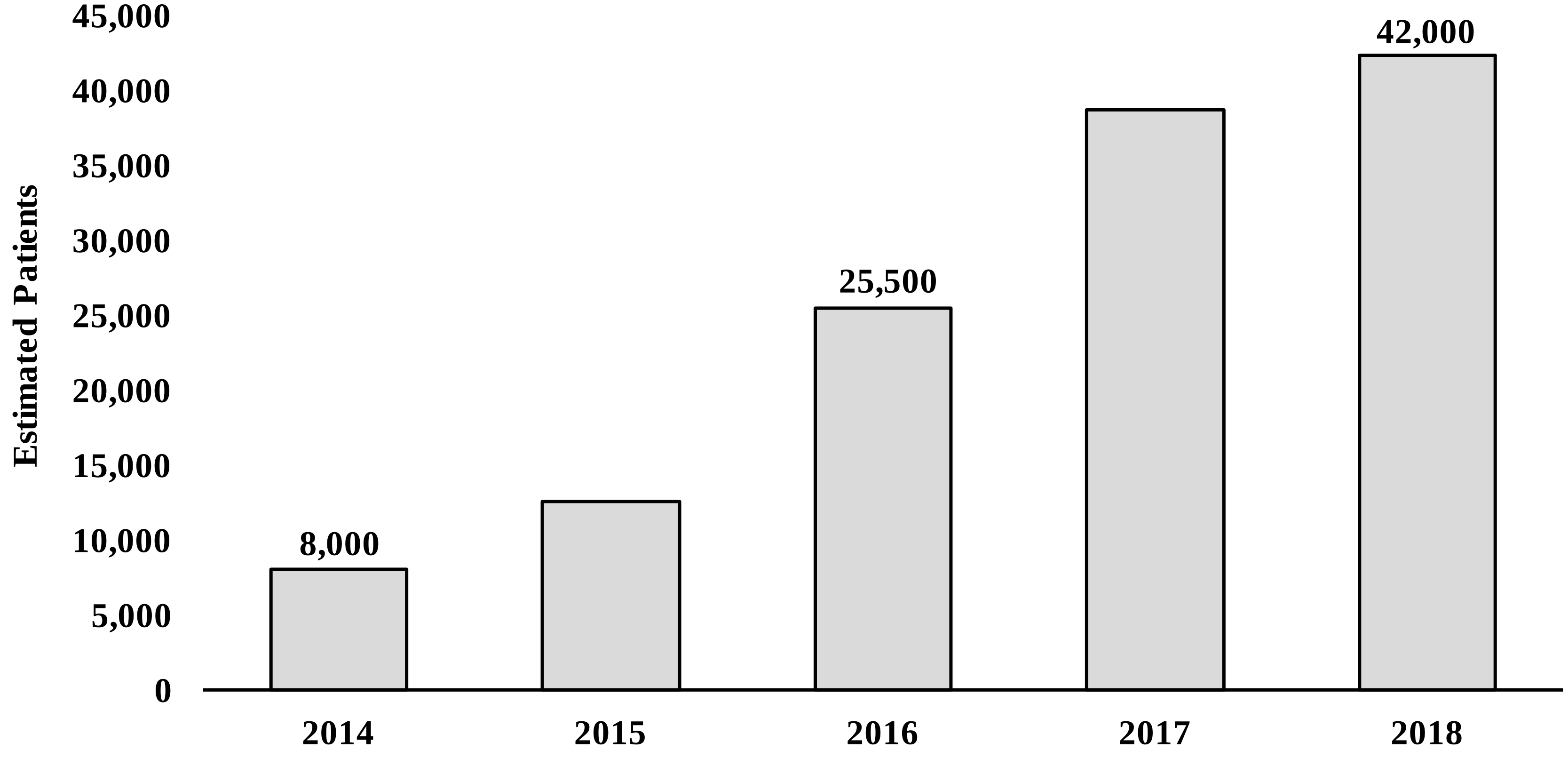
We evaluated 1) HPC utilization and 2) possible reasons for HPC use in each of two separate analyses below:

1. In U.S outpatient settings
   - Patients, pregnant and non-pregnant
   - National estimates

2. During 2nd or 3rd trimesters in live-birth pregnancies
   - In Sentinel Distributed Database
   - Not national estimates

HPC Utilization in U.S. Outpatient Settings

Increased Number of Patients With HPC Prescriptions (2014-2018)



Estimated annual number of 15- to 44-year-old patients with dispensed prescriptions for injectable hydroxyprogesterone, from U.S. retail and mail order/specialty pharmacies, 2014 through 2018

Source: Symphony Health IDV® Integrated Dataverse. Data years 2014-2018. Extracted August 2019. Unique patient counts should not be added across time periods due to the possibility of double counting those patients who received multiple products within the same calendar year or over multiple periods in the study. Prescriptions for bulk powder forms of hydroxyprogesterone were not included.

Physician Survey for Diagnoses Associated With Injectable HPC Use Among 15- to 44-Year-Old Women

- Injectable HPC
  - Supervision of high risk pregnancy (50%)
    - Of which 78% for supervision of pregnancy with history of preterm labor
  - History of preterm labor (20%)
  - Supervision of normal pregnancy (13%)
  - Preterm labor in current pregnancy (10%)

- Progesterone Products
  - Supervision of high risk pregnancy (14%); female infertility (40%)

Source: Syneos Health Research and Insights, TreatmentAnswers™ with Pain Panel. Data years 2013-2018. Extracted July 2019. Diagnosis data are not directly linked to dispensed prescriptions but obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity one day a month.

Limitations and Summary

- Limitations
  - Patient estimates obtained for retail and mail-order pharmacy settings, not hospital or clinics
  - Diagnoses related to HPC use were obtained from physician survey data
    - Do not directly link to dispensed prescriptions
    - Do not necessarily result in dispensed prescriptions
- Summary
  - Outpatient injectable HPC use increased from 2014 to 2018; use was low
  - HPC use was largely associated with history of preterm labor diagnosis

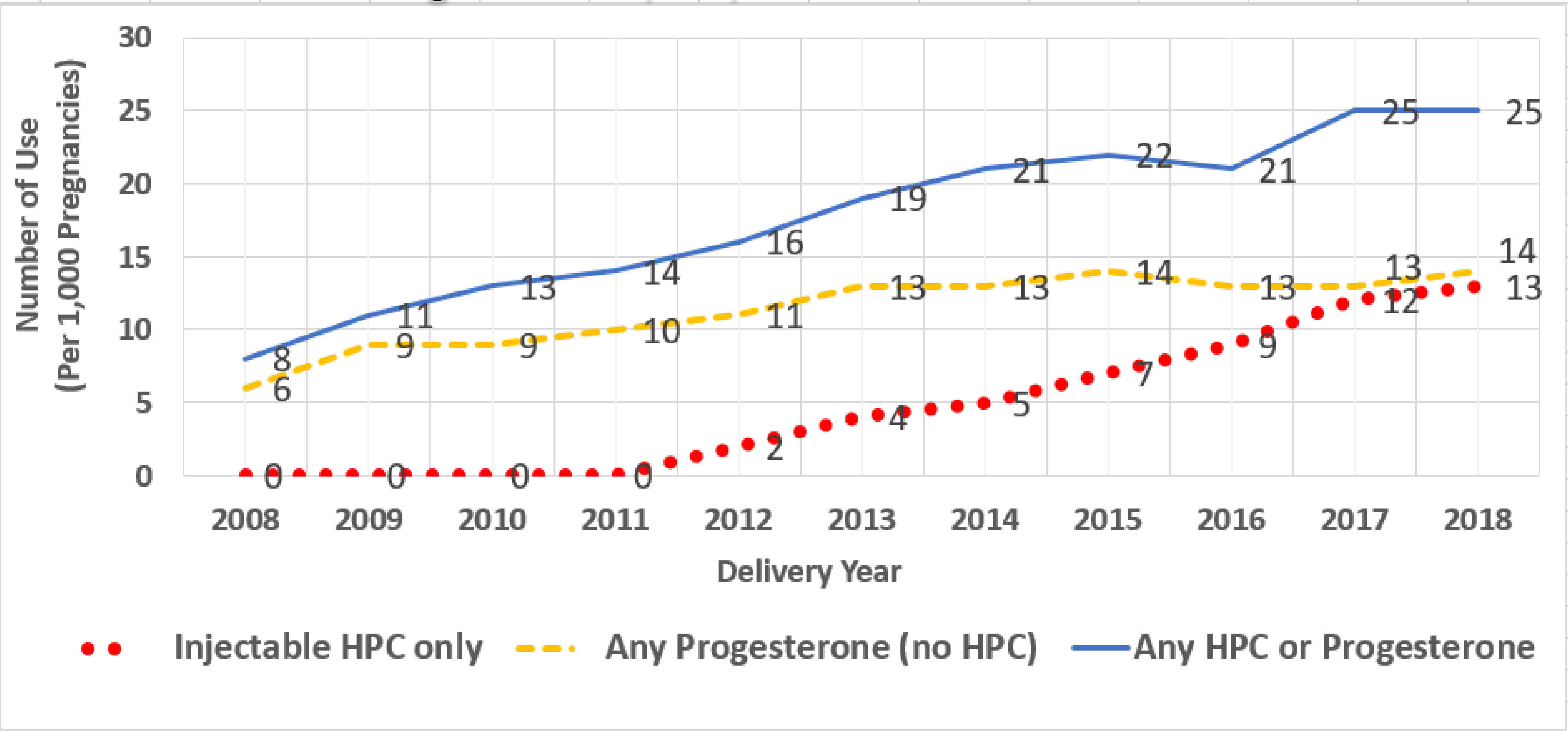
Utilization During 2nd or 3rd Trimesters in Pregnancy in Sentinel Distributed Database

Methods: Utilization in 2nd or 3rd Trimesters of Pregnancy

- Database: Sentinel Distributed Database
- Population: Live-birth pregnancies delivered Jan 2008-Apr 2019
- Medications of interest: HPC or progesterone
- Related obstetrical conditions (possible reasons for use):
  - Narrow definition:
    - Preterm delivery in a <u>prior</u> pregnancy
    - Preterm labor in a <u>current</u> pregnancy
    - Cervical shortening in a <u>current</u> pregnancy
  - Broad definition:
    - Same three obstetrical conditions above recorded in a <u>prior or current</u> pregnancy

Temporal Trend on Number of Pregnancies With HPC Use Per 1,000 Pregnancies

- Total Live-Birth Pregnancies: 3,451,121



[1] Data from 2019 was incomplete and excluded from the figure

Injectable HPC Users:
Most Had a Related Obstetrical Diagnosis Code

Related Obstetrical Conditions	Injectable HPC (N=16,535)	Progesterone (N= 40,144)	Any HPC or Progesterone (N= 61,615)
Narrow Definition			
1. Preterm delivery in a prior pregancy	39%	11%	20%
2. Preterm labor in a current pregnancy	49%	45%	47%
3. Cervical shortening in a current pregnancy	20%	32%	27%
Any of the conditions above	73%	61%	65%
Broad Definition			
1. Preterm labor or delivery in a prior pregnancy	95%	37%	56%
2. Preterm labor or delivery in a current pregnancy	54%	55%	56%
3. Cervical shortening in a past or current pregnancy	24%	33%	29%
Any of the conditions above	98%	75%	83%

Limitations and Summary of Sentinel Analysis

- Limitations
  - May not be generalizable to women without a commercial health plan
  - Unspecified timing between related obstetrical conditions and injectable HPC use
  - Inability to capture out of pocket payment

- Summary
  - Overall modest use of injectable HPC during 2nd or 3rd trimesters among pregnancies with a live birth
  - A high percentage (at least 73%) of pregnancies using injectable HPC had a related obstetrical condition recorded before or during the current pregnancy.

FDA U.S. FOOD & DRUG ADMINISTRATION

Makena (hydroxyprogesterone caproate injection)
New Drug Application 021945/Supplement 023

Summary Remarks

Bone, Reproductive and Urologic Drugs Advisory Committee Meeting

October 29, 2019

Christina Chang, M.D., M.P.H.
Clinical Team Leader
Division of Bone, Reproductive and Urologic Products
Office of New Drugs, Center for Drug Evaluation and Research
Food and Drug Administration

Background

- Neonatal morbidity and mortality from preterm birth (PTB) is a significant public health concern
- No drugs are approved to reduce the risk of neonatal mortality and morbidity due to prematurity
- Progestogens have been used to reduce the risk of preterm birth*

*American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin (2012, reaffirmed 2018) and Society for Maternal-Fetal Medicine Statement (March 2017)

NDA 021945 Makena

- Received accelerated approval 2011 based on a single clinical trial
- Indication
  - To reduce the risk of preterm birth in pregnant women with a singleton pregnancy who have a history of spontaneous preterm birth
- Dosage & Administration
  - Administered at a dose of 250 mg once a week beginning between 16^0 weeks and 20^6 weeks gestation to week 37 of gestation or birth

Pre-Approval Data (Trial 002)

- Completed in 2002
- Double blind, randomized, placebo-controlled
- 463 U.S. women randomized to receive either HPC (n=310) or placebo (n= 153)
- Efficacy evaluated using a surrogate endpoint
  - Delivery at <37 weeks gestation
  - "Reasonably likely to predict a clinical benefit" in reducing adverse clinical outcomes, such as infant mortality/morbidity
- Makena reduced proportion of women who delivered prior to 37 weeks by 18% (37% Makena vs. 55% placebo)
- Possible safety signal of fetal loss

Design: Confirmatory Trial (Trial 003)

- Completed in 2018
- Double-blind, randomized, placebo-controlled, international trial
- Virtually identical design as Trial 002 except:
  - Gestational age surrogate endpoint
  - Adding clinical outcome
- Efficacy evaluated with two coprimary endpoints:
  - Delivery prior to 35 weeks gestation
  - Neonatal morbidity/mortality composite index*

*The neonatal morbidity/mortality composite index includes neonatal death, Grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and proven sepsis.

Results: Confirmatory Trial (Trial 003)

- Total number of subjects randomized = 1708
  - Makena (n=1130) vs. placebo (n=578)
  - Total U.S. subjects randomized (n=391, 23%)

- No statistically significant treatment effect for either coprimary endpoints:
  - Proportion of women delivering <35 weeks (11% Makena vs. 12% placebo-vehicle, p=0.72)
  - Neonatal composite index (5.4% Makena vs. 5.2% placebo-vehicle, p = 0.84)

- Proportions of women delivering <32 weeks and <37 weeks were also not different between the Makena and placebo groups.

Results: Confirmatory Trial (Trial 003)

- No relevant differences in the treatment effect when analyzed by region (U.S. vs. non-U.S.) or subgroups (e.g., race, previous # of spontaneous PTB)

- In the U.S. subgroup:
  - Makena did not improve the neonatal outcome
  - Makena did not reduce the risk of delivery <35 weeks (16% Makena vs. 18% placebo)

- Safety findings:
  - Number of fetal/neonatal deaths were low but were similar between groups
  - The study met the prespecified endpoint of excluding a doubling of the risk of fetal/early infant deaths for Makena

Effectiveness Standard for Drug Approval

FDA

- All approved drugs, including those approved under accelerated approval, must meet the statutory standard of "substantial evidence" of effectiveness

Evidence consisting of adequate and well-controlled investigations, including clinical investigations… to evaluate the effectiveness of the drug involved…*

*21 U.S.C. § 355(d), FD&C Act Section 505(d)

Trial 002 vs. Trial 003

Trial 002

- Assessed efficacy based on gestational age at delivery (surrogate)
- U.S. academic centers only
- ~60% blacks
- Unusually high PTB rate (55%) in placebo group
- Makena reduced proportion of PTB <37 weeks by 18%

Trial 003

- Assessed efficacy based on neonatal outcomes (clinical benefit) and gestational age at delivery (surrogate)
- International trial (but 23% from United States)
- Makena had no treatment effect for proportion of delivery <35 weeks, <32, or <37 weeks
- No difference in neonatal outcomes

Substantial Evidence of Effectiveness

Accelerated Approval

(surrogate endpoint)

Allows for earlier access to therapy

Less certainty that observed treatment effect translates into clinical benefit

Requires verification of clinical benefit

Traditional Approval

(clinical endpoint or validated surrogate endpoint)

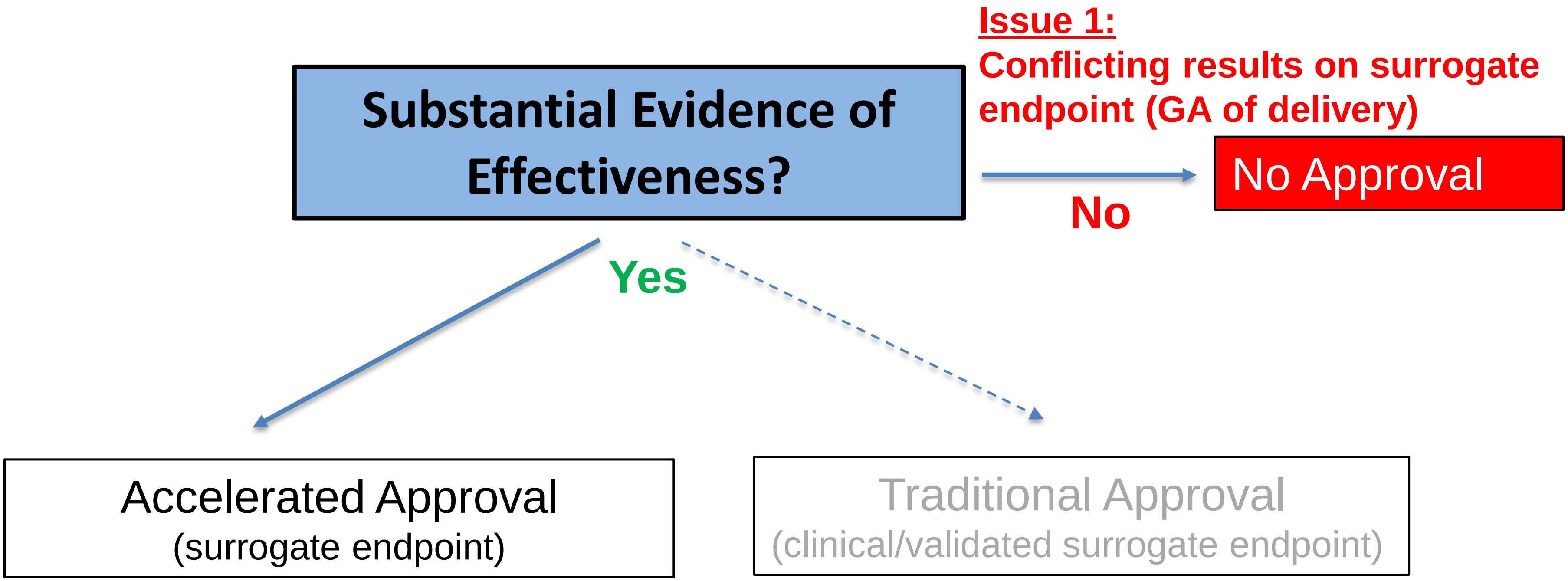
Directly measuring how a patient feels, functions, or survives (the outcome of interest)

FDA Approval

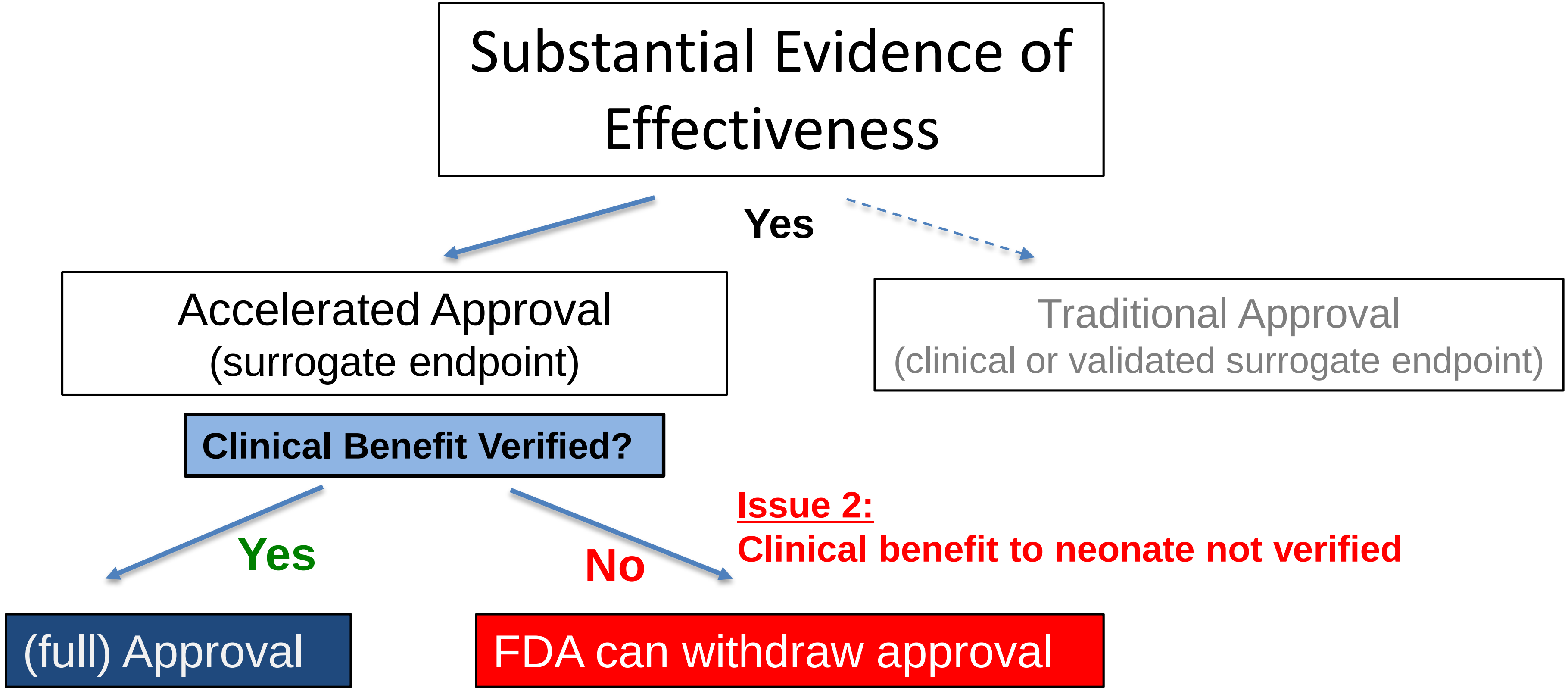
Why the Discrepant Results?

- Trial 002 (with the surrogate endpoint only) falsely positive?
- Trial 003 falsely negative?
- Discrepant results between Trials 002 and 003 due to unknown factors?

Issue 1: Substantial Evidence of Effectiveness



Issue 2: Accelerated Approval



FDA U.S. FOOD & DRUG ADMINISTRATION

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

BONE, REPRODUCTIVE. AND UROLOGIC DRUGS

ADVISORY COMMITTEE

(BRUDAC)

Tuesday, October 29, 2019

8:15 a.m. to 4:26 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Kalyani Bhatt, BS, MS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

BONE, REPRODUCTIVE AND UROLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

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Professor of Medicine and Epidemiology & Biostatistics

University of California, San Francisco

San Francisco, California

Matthew T. Drake, MD, PhD

Associate Professor of Medicine

Chair, Metabolic Bone Disease Core Group

Division of Endocrinology

Mayo Clinic College of Medicine

Rochester, Minnesota

Vivian Lewis, MD
(Chairperson)
Vice Provost for Faculty Development & Diversity
Professor, Obstetrics and Gynecology
University of Rochester
Rochester, New York

Pamela Shaw, PhD
Associate Professor
Department of Biostatistics and Epidemiology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

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Vice-Chair of Pediatrics
Chief of Newborn Medicine
The Floating Hospital for Children at Tufts
Medical Center
Professor of Pediatrics
Tufts University School of Medicine
Boston, Massachusetts

Ahizechukwu Eke, MD, MPH
Assistant Professor
Division of Maternal Fetal Medicine
Department of Gynecology & Obstetrics
Johns Hopkins University School of Medicine
Baltimore, Maryland

Annie Ellis
(Patient Representative)
White Plains, New York

Daniel Gillen, PhD
Professor and Chair, Statistics
University of California, Irvine
Irvine, California

Kimberly Hickey, MD

Colonel, Medical Corps, US Army

Chief, Maternal Fetal Medicine

Walter Reed National Military Medical Center

Deputy Director, National Capital Consortium

Uniformed Services University of the Health Sciences

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P R O C E E D I N G S

(8:15 a.m.)

Call to Order

Introduction of Committee

DR. LEWIS: Good morning. I would first like to remind everyone to please silence your cell phones and any other devices if you haven't already done so. I would also like to identify the FDA press contact, Amanda Turney. She's standing there in the back. We're going to get started with the meeting.

My name is Vivian Lewis, and I'm the chair of the Bone, Reproductive, and Urologic Drugs Advisory Committee, and I'll be chairing this meeting. I will now call upon today's Bone, Reproductive, and Urologic Drugs Advisory Committee members to introduce themselves. The meeting's now call to order. We'll start with the FDA on my left, and we'll go around the table for everyone to say their name.

DR. NGUYEN: Thank you, Dr. Lewis. Good morning. I'm Christine Nguyen, and I am the deputy director for safety in the Division of Bone, Reproductive, and Urologic Products; otherwise known as

DBRUP.

DR. CHANG: Good morning, everyone. My name is Christina Chang. I am a clinical team leader in the division.

DR. WESLEY: Good morning. I'm Barbara Wesley. I'm the primary medical reviewer and have been since the beginning of this drug.

DR. GUO: Good morning. My name is Jia Guo. I'm the statistical reviewer from the Office of Biostatistics.

DR. EKE: Good morning, everyone. My name is Ahizechukwu Eke. I am a maternal fetal medicine physician at Johns Hopkins.

DR. HICKEY: Good morning. I'm Kimberly Hickey. I'm one of the maternal fetal medicine physicians at Walter Reed.

DR. LINDSAY: Good morning. I'm Michael Lindsay. I'm a maternal fetal medicine specialist at Emory University.

DR. REDDY: Hi. I'm Uma Reddy, maternal fetal medicine division director at Yale.

DR. WING: Good morning. I'm Deborah Wing. I am the senior client partner at Korn Ferry. I'm a former professor of OB/GYN and division director of maternal fetal medicine at the University of California Irvine.

DR. DRAKE: Good morning. My name is Matthew Drake. I'm an adult endocrinologist at the Mayo Clinic in Rochester, Minnesota.

MS. BHATT: Good morning. I'm Kalyani Bhatt. I'm the designated federal officer for this advisory committee.

DR. BAUER: Good morning. My name is Doug Bauer. I'm from the departments of medicine, epidemiology, and biostatistics from UCSF in San Francisco.

DR. SHAW: Good morning. I'm Pam Shaw. I'm at the Department of Biostatistics, Epidemiology, and Informatics at University of Pennsylvania.

MS. ELLIS: Good morning. I'm Annie Ellis, and I'm a patient representative.

DR. ORZA: Good morning. I'm Michele Orza. I'm the chief of staff at the Patient-Centered Outcomes Research Institute, and I'm the acting consumer representative today.

DR. GILLEN: Good morning. Daniel Gillen, professor and chair of statistics at UC Irvine.

DR. HUNSBERGER: Good morning. I'm Sally Hunsberger at the biostatistics research branch at NIAID, at NIH.

DR. SMITH: Good morning. I'm Brian Smith. I'm a neonatologist at Duke.

DR. WADE: Good morning. I'm Kelly Wade. I'm a neonatologist for Children's Hospital of Philadelphia and the chair of the Pediatric Advisory Committee.

DR. DAVIS: Good morning. I'm Jon Davis, chief of neonatology at Tufts Medical Center in Boston and chair of the Neonatal Advisory Committee at FDA.

DR. LEWIS: Thank you. We'll have one other panel member, and that will be Dr. Jarugula. He's stuck in traffic. He'll introduce himself once he gets here.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of the issues and that individuals can express those views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to refrain from discussing the meeting topic during breaks or during lunch. Thank you.

I'd now like to pass it to Kalyani Bhatt, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

MS. BHATT: The Food and Drug Administration is convening today's meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal -- [inaudible - audio gap].

(Pause.)

MS. BHATT: -- statistically significant difference between the treatment and placebo arms for the co-primary endpoints of reducing the risk of recurrent preterm birth or improving neonatal mortality and morbidity. The committee will consider the trial's findings and the supplement NDA in the context of AMAG Pharmaceutical's confirmatory study application.

This is a particular matters meeting during which specific matters related to AMAG and the supplemental NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we'd like to disclose that Dr. Jarugula is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Jarugula's role at this meeting is to represent industry in general and not any particular company. Dr. Jarugula is employed by Novartis Institutes for Biomedical Research.

We'd like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationship that they may have with the firm at issue. Thank you.

DR. LEWIS: Thank you.

Before we go to the FDA opening remarks, I'd like the one last panel member who just got here to please introduce himself.

DR. JARUGULA: Good morning, everybody. Sorry. I got stuck in heavy traffic. I didn't anticipate this heavy D.C. traffic. My name is Venkat Jarugula. I'm representing the industry here. I am from Novartis Pharmaceuticals. Thank you.

DR. LEWIS: Thank you. We will now proceed with the FDA opening remarks from Dr. Nguyen.

FDA Opening Remarks - Christine Nguyen

DR. NGUYEN: Good morning, everyone. I want to thank each one of you for sacrificing a beautiful holiday to be here with us. We are convening this advisory committee meeting to discuss the evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth and improving neonatal outcomes. In my introductory remarks, I will be covering the key issues that you will hear about and discuss throughout the day.

We appreciate that neonatal mortality and morbidity from preterm birth is a significant public health concern. Currently, there are no therapies approved to reduce the risk of these adverse neonatal outcomes from prematurity. Progestogens, which include progesterone and progestins, have been used in clinical practice over the years to reduce the risk of preterm birth. However, only Makena has been approved to reduce the risk of recurrent preterm birth.

In 2011, we approved Makena under accelerated approval to reduce the risk of preterm birth in women with a singleton pregnancy and a prior spontaneous singleton preterm birth. This approval was based on a single trial conducted between 1999 and 2002 in approximately 460 women in the U.S., and this trial showed persuasive efficacy findings on the surrogate endpoint of gestational age of delivery of less than 37 weeks.

I will refer to this trial as Trial 002. As required under accelerated approval regulations, the applicant conducted a post-approval confirmatory trial to verify the clinical benefit for the neonates, and I'll be expanding on these key concepts that are underlined later in my presentation.

The confirmatory trial was an international, randomized, double-blind, placebo trial that enrolled approximately 1700 pregnant women. The top three enrolling countries were Russia, Ukraine, and the U.S., with the U.S. enrolling 23 percent of total subjects. I would note that the number enrolled in Trial 003 from the U.S., which was about 390, was not substantially less than the number that was enrolled in Trial 002, which is 460.

The design eligibility criteria were similar to Trial 002, except for the primary endpoints. Trial 002's primary efficacy endpoint was gestational age of delivery less than 37 weeks, and for child Trial 003, it was gestational age of delivery less 35 weeks and the clinical endpoint of neonatal morbidity and mortality Index. This trial was conducted between 2009 and 2018.

As you can see here, there are no treatment effects between Makena and placebo for the co-primary endpoints, and there also no treatment effects for the two key secondary endpoints, which were preterm birth of less than 32 weeks and less than 37 weeks. I remind you that the endpoint of preterm birth of less than 37 weeks was the primary efficacy endpoint for Trial 002.

Because of the contradictory results for the gestational age of delivery endpoint, we conducted multiple exploratory subgroup analyses for factors that were dissimilar between the two trials. The subgroup analyses included that for region, race, and certain elements that the applicant identified that may increase the risk of preterm birth. These included the number of previous preterm birth, substance use in pregnancy, number of years of formal education, and partner status.

There were no statistically significant

treatment difference for any of these subgroup analyses. In addition, there was no statistically significant interaction between treatment effect and these factors, meaning that these factors may be prognostic for preterm birth, but they do not appear to be effect modifiers; meaning that if a woman has these factors, she may be at increased of having preterm birth, but these factors do not render her having more favorable response to Makena.

Also, there are no consistent convincing evidence of a treatment effect within any particular subpopulation across the two trials.

This is the totality of the evidence in front of us today. Trial 002 shows efficacy on gestational age of delivery, which is a surrogate endpoint. However, this trial was conducted almost 20 years ago, but it was conducted in the United States. There were issues regarding generalizability to the general U.S. population that I've listed in my slide.

Trial 003, on the other hand, did not show any efficacy on neonatal outcomes or gestational age at delivery. It was conducted more recently, and it was adequately powered to the treatment effect that was observed in Trial 002. However, it was an international trial, but I'll remind you, approximately 1 in 4 women enrolled in 003 was from the U.S., and it evaluated a low-risk population who showed a low recurrent preterm birthrate in placebo arm than 002.

The efficacy in Makena was evaluated by two different types of endpoints. The first endpoint is a surrogate endpoint of gestational age of delivery. Both Trials 002 and 003 evaluate this endpoint. While 002 show efficacy, 003 did not. So we concluded there's conflicting efficacy findings for this endpoint, and this raises the first issue regarding the approval requirement of substantial evidence of effectiveness.

The second type of endpoint evaluated was a clinical endpoint of neonatal composite index. This endpoint was only appropriately evaluated in 003, and as you can see, Trial 003 did not show a treatment effect in this endpoint, so we conclude that there's not been verification of the clinical benefit of Makena to the neonates, so this raises the second approval issue concerning accelerated approval.

Going back to issue 1, substantial evidence of effectiveness, this is the statutory standard for establishing efficacy for FDA drug approval, including accelerated approval. Traditionally, we look for significant findings from at least two adequate and well-controlled trials, each convincing on its own to provide independent substantiation on the efficacy endpoint. This approach also reduces the risk of false positive from chance or bias, which may remain undetected from a single trial.

The concept of independent substantiation is the scientific principle that underlies the legal standard of substantial evidence of effectiveness. That said, when appropriate, a single adequate and well-controlled trial with persuasive findings may be accepted as substantial evidence, and this is what happened for Makena in 2011 when we approved it based on Trial 002.

Note that if there were additional adequate and well-controlled trials at the time of approval, we would have considered those data when deciding about substantial evidence. In 2019, we now have two adequate and well-controlled trials, and the first issue is that Trial 003 did not substantiate Makena's treatment effect on gestational age of delivery. So is there still substantial evidence of a drug's effect on reducing the risk of recurrent preterm birth?

Here in this diagram, I wanted to lay out where this first issue lies. To gain approval, any approval, a drug must demonstrate substantial evidence of effectiveness. Whether or not it receives accelerated approval or traditional approval depends on the efficacy endpoint that was evaluated. For accelerated approval, it will be the surrogate endpoint, which is what happened for Makena. If there lacks substantial evidence of effectiveness, then there will be no approval.

At this point, we have contradictory efficacy findings on the gestational age of delivery. So that puts in question whether or not there is still substantial evidence of a drug's effectiveness for that endpoint.

The second issue relates to accelerated approval. As I've shown in this earlier slide, traditional approval is granted when there is substantial evidence of the drug's effect on a clinical endpoint, and that is one that directly measures how patients feel, function, or survive, or a validated surrogate endpoint, which is one that is known to predict clinical benefit.

We grant accelerated approval when there's a drug's effect on the surrogate endpoint, which is one that reasonably likely predicts clinical benefit. Accelerated approval is an expedited drug development pathway, and we reserve it only for certain drugs treating serious or life-threatening conditions with unmet medical need. As I mentioned, it must meet the same statutory effectiveness standards, that is substantial evidence of effectiveness, as those for traditional approval.

I will take a second here to explain why gestational age of delivery is not a clinical endpoint, and we do not consider at this time a validated surrogate endpoint. Gestational delivery is not a clinical endpoint because it doesn't directly measure how neonates feel, function, or survive. When we're talking about treatment for prematurity, it is the improved outcomes to a neonate that is most meaningful.

It's not considered a validated surrogate endpoint because spontaneous preterm birth is a poorly understood syndrome with potential for multiple pathophysiologic pathways. So prolonging gestation may not consistently translate into improved neonatal outcomes.

Let's take a hypothetical example of a woman going to preterm labor at 35 weeks due to some subclinical, undiagnosed, low inflammatory process. We now iatrogenically prolong that pregnancy for another week, and the baby is delivered at 36 weeks. However, the fetus has been exposed for an additional week in a relatively unhealthy in utero environment, so it's unclear whether or not that fetus, when born, will have improved neonatal outcomes.

As you can see, there's more uncertainty, at the time of accelerated approval, that the treatment effect on the surrogate endpoint will translate into clinical benefit. Therefore, the drug must undergo a post-approval confirmatory trial to verify its clinical benefit.

FDA can withdraw approval of the drug or the indication if the applicant does not conduct such required trial, or if the trial fails to verify the clinical benefit. That's the second issue that we face, which is that Trial 003 did not verify Makena's clinical benefit to the neonates.

Back to this diagram, let's assume we don't have a problem with substantial evidence of effectiveness. Makena now still sits under accelerated approval. Its clinical benefit must still be verified. If the clinical benefit is not verified, FDA can withdraw approval.

I'll wrap up my presentation by walking you through 3 three discussion questions and 3 voting questions, or 6 questions total that you'll be seeing later on today. The first discussion question, discuss the effectiveness of Makena on recurrent preterm birth and neonatal morbidity and mortality.

Discussion question 2. If a new confirmatory trial were to be conducted, discuss the study design, including control, dose(s) of study medication, efficacy endpoints, and importantly, the feasibility of completing such a trial.

Discussion question 3. Discuss the potential consequences of withdrawing Makena on patients and clinical practice.

Voting question 4. Do the findings from Trial 003 verify clinical benefit of Makena on neonatal outcomes? Provide your rationale.

Voting questions 5. Based on the findings from Trial 002 and 003, is there substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth based on the surrogate endpoint of gestational age of delivery? Provide your rationale.

Voting question 6 requires a preamble. FDA approval, including accelerated approval of a drug, requires that there is a demonstration of substantial evidence of effectiveness of the drug on the efficacy endpoint. This is the first approval issue that I discussed earlier.

For drugs approved under accelerated approval, the applicant is required to conduct a confirmatory trial to verify the clinical benefit. That is the second approval issue that I discussed earlier. If the applicant fails to conduct such a trial, or if such a trial does not verify the clinical benefit, FDA may, following an opportunity for a hearing, withdraw approval.

There are three voting options for this question. Should FDA, A, pursue withdrawal of approval from Makena; B, leave Makena on the market under accelerated approval and require a new confirmatory trial; or C, leave Makena on the market without requiring a new trial?

Back to this diagram, I wanted to remind you, again, the approval steps and how one could take these two issues into consideration within the context of the three voting options. As I mentioned, at the very top, to gain approval, a drug must demonstrate substantial evidence of effectiveness; and if it doesn't, then there will be no approval.

So that's where our first issue lies. There are contradictory efficacy findings on gestational age of delivery. Assuming that substantial evidence of effectiveness is not an issue, Makena is still sitting in the accelerated approval box, which means that its clinical benefit must be verified. And if the clinical benefit has not been verified, FDA can withdraw approval.

I remind you that either issue in and of itself can impact approval so that you not have to have problems with both issues to impact approval. Let's go back to option A, which is to remove the approval of Makena. That will be appropriate if you find that issue 1, or issue 2, or both, is such that Makena's approval should be removed.

Option B, which is, to leave Makena on the market under accelerated approval -- so again, it will be sitting in the accelerated approval box but require a new confirmatory trial -- would be appropriate if you believe that issue 1 has been adequately resolved so that accelerated approval is still appropriate, but that there is no substantial evidence of effectiveness on the neonatal outcomes and that a new trial is necessary and feasible.

Option C, which is to leave Makena on the market without a new trial, would be appropriate if you believe issue 1 has been adequately resolved and that the clinical benefit of Makena to the neonate does not need to be verified, so that issue 2 is moot.

I'll walk you through this. Vote A, may be appropriate if you believe that the totality of the evidence does not support Makena is effective for its intended use. If you vote A, please discuss the consequences of Makena's removal.

B, which is to leave Makena on the market under accelerated approval but to require a new confirmatory trial, may be appropriate if you believe that the totality of the evidence supports Makena's effectiveness in reducing the risk of recurrent preterm birth, but that there is no substantial evidence on neonatal outcomes; and you believe that a new confirmatory trial is necessary and feasible.

Let me just comment on this new confirmatory trial being necessary. This will be appropriate if you find that Trial 003, which is a large, adequate and well-controlled trial, is significantly flawed in some way such that its results are not usable or could be discounted.

If you vote B, please discuss how the existing data provides substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth, and also discuss the key study elements of this new trial and approaches to ensure its successful completion.

Lastly, vote C, which is the leave Makena on the market without doing anything else, without requiring a new trial, may be appropriate if you believe Makena is affective for reducing the risk of recurrent preterm birth and that is not necessary to verify Makena's clinical benefit to neonates. If you vote C, discuss how the existing data provide substantial evidence of Makena in reducing the risk of recurrent preterm birth and why it is not necessary to verify its clinical benefit to neonates.

Thank you for your attention, and I now turn the meeting back to Dr. Lewis.

DR. LEWIS: Thank you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency of the advisory committee meeting, FDA believes that it is important to understand the context of every individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests in those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationship. If you choose not to address the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now have presentations from AMAG Pharmaceuticals.

Applicant Presentation - Julie Krop

DR. KROP: Good morning, Dr. Lewis, members of the committee, FDA colleagues. My name is Julie Krop, and I'm the chief medical officer at AMAG Pharmaceuticals. Thank you for this opportunity to share the results from the PROLONG study and review them in the context of prior clinical trials evaluating 17P.

17P, including our product Makena and recently approved generic formulation, is the only FDA-approved therapy to reduce the risk of recurrent preterm birth. 17P is a synthetic progestin. It contains the active pharmaceutical ingredient 17 alpha hydroxyprogesterone caproate. It is not the same as progesterone or vaginal progesterone.

While its exact mechanism of action is unknown, it is thought to support gestation by decreasing inflammation and inhibiting uterine muscular activity. It's important to note that unlike progesterone, 17P is not metabolized into androgens, estrogens, or corticosteroids. For the rest of the presentation. to be clear, we'll refer to the product we're talking about today as 17P since the discussion is about the entire class, including both Makena and the recently approved generics.

17P is approved to treat women with a singleton pregnancy who've had a prior singleton spontaneous preterm birth. This population represents a subset of all pregnant women, affecting about 3 percent. That's 130,000 pregnancies every year, and that is why Makena qualifies as a orphan drug.

17P has a prolonged half-life and is administered weekly. Treatment is initiated between 16 and 20 weeks of pregnancy and continues until 37 weeks or delivery, whichever comes first. Prior to the FDA approval of Makena, 17P was available only through pharmacy compounding, which is not held to good manufacturing standards, and that creates the potential for safety and efficacy concerns.

FDA approved 17P under the Subpart H accelerated pathway in 2011. Subpart H approvals are reserved for therapies that treat serious or life-threatening conditions with an important unmet medical need, where efficacy is demonstrated on a surrogate endpoint that is considered reasonably likely to predict clinical benefit.

As FDA pointed out in its briefing book, by the time of 17P's approval, multiple clinical studies evaluating the consequences of late preterm birth had established that preterm infants are less physiologically and metabolically mature than term infants, and therefore at a higher risk of morbidity and mortality. Based on these studies, FDA accepted preterm birth less than 37 weeks as a surrogate endpoint that was reasonably likely to predict clinical benefit.

A condition of accelerated approval was to conduct a confirmatory trial with clinically relevant endpoints. 17P received approval based on the compelling results of study 002, which from this point on we'll refer to as the Meis study. This landmark study was conducted by the National Institute of Child Health and Human Development's maternal fetal medicine units. It was enrolled entirely within the United States.

The Meis study established substantial evidence of efficacy, demonstrating that 17P significantly reduced the rate of preterm birth compared to placebo. The highly statistically significant results demonstrated the superiority of 17P compared to placebo at the primary endpoint of less than 37 weeks, but also at less than 35 weeks and less than 32 weeks, which have the highest incidence of neonatal complications.

I'd like to highlight some key events in 17P's approval pathway, starting in 2003 when the Meis trial results were published in the New England Journal of Medicine. The Meis results were hailed as a significant advance in obstetrics and ultimately led medical societies to recommend its use to prevent recurrent preterm birth.

After the completion of the study, Adeza Biomedical was granted full access to the data to pursue FDA approval for 17P and submitted an NDA in 2006. Later that year, an FDA advisory committee concluded that the Meis data provided substantial evidence of 17P's safety and efficacy. Most panelists agreed that an effect on early preterm birth at less than 35 weeks and particularly at less than 32 weeks were clinically meaningful, and could therefore serve as adequate surrogates for reducing neonatal morbidity and mortality. The advisory committee recommended a confirmatory study to verify and describe 17P's clinical benefit.

With increasing adoption of 17P as the standard of care, clinical experts and investigators raised concerns about the feasibility of conducting a placebo-controlled trial in the U.S. In November of 2009, the first patient was enrolled in study 003, from this point on we'll refer to as the PROLONG study.

In 2011, 17P was approved with two required post-approval studies, the confirmatory efficacy and safety study and the associated incident follow-up study, which is still ongoing. Not surprisingly, given the rarity of the condition and the fact that 17P became quickly adopted as the standard of care, recruitment for the PROLONG study was challenging.

Enrolling the requisite 1700 patients required going to sites outside of the United States. In 2014, AMAG became the sponsor, inheriting the study with approximately 50 percent of the patients enrolled. In total, recruitment took 9 years. Enrollment was finally completed in 2018.

Preterm birth is a major public health concern in the United States, particularly in the most vulnerable patients. It is one of the leading causes of infant morbidity and mortality and can lead to serious long-term health consequences. It's important to remember that recurrent preterm birth represents only a small proportion of all preterm births. While the impact on the total preterm birth rate is minimal, the impact on these women is substantial.

Today, based on the Meis data, clinicians rely on 17P. In fact, based on the sample of nearly a thousand patient charts published in 2018, about 75 percent of patients with a prior spontaneous preterm birth were treated with 17P. 17P is the only FDA-approved therapy to reduce recurrence of preterm birth, supported since 2008 by the American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine, as the standard of care to prevent recurrent preterm birth.

Today, we face a unique challenge. How do we make sense of the PROLONG study in the context of the prior positive Meis study, which demonstrated consistent and statistically significant efficacy across multiple clinically important endpoints. In the presentations that follow, we'll highlight key differences in study population and background rates of preterm birth that we believe account for the inability of the PROLONG study to demonstrate significant reductions in preterm birth.

The Meis study enrolled patients exclusively in the United States at inner city academic medical centers with high rates of preterm birth. The background or placebo rate of preterm birth at less than 35 weeks was high, around 30 percent. In contrast, the PROLONG study enrolled patients with much lower rates of preterm birth, particularly in Russia and Ukraine.

Background rates of preterm birth at less than 35 weeks were approximately 11 percent, far lower than the rates seen in the Meis study, highlighting the difference in the patient populations, which likely contributed to the different results between the two studies. That said, the strong consistent efficacy demonstrated in the Meis study, along with previous supporting clinical trial data, and most important, a favorable and reassuring safety profile, all support the continued availability of 17P.

Now let's review the agenda. Next, Dr. Michelle Owens will discuss the clinical background and continued need for 17P; then Dr. Baha Sibai will present the clinical design and the key results from the Meis study. Dr. Laura Williams will present the PROLONG study efficacy and safety data, followed by Dr. Sean Blackwell, who will provide his clinical perspective on the PROLONG data and the overall benefit-risk of 17P.

Finally, I will conclude by summarizing AMAG's action following PROLONG and then moderate the question and answer session. We also have additional experts with us today to help answer your questions. All external experts or their institutions have been compensated for their time and travel with the exception of Dr. Blackwell, who has been reimbursed only for travel.

Thank you, and I will now turn the

presentation over to Dr. Owens.

Applicant Presentation - Michelle Owens

DR. OWENS: Good morning, everyone. I'm Michelle Owens, a maternal fetal medicine physician and professor at the University of Mississippi. I appreciate the opportunity to discuss preterm birth, a significant problem in the United States. One in 10 babies, nearly 400,000, are born prematurely in the United States each year. The rate is even higher for a subset of pregnant women who are disadvantaged socioeconomically, educationally, or by limited access to health care and healthy lifestyle choices. It puts their unborn children at substantial risk, both in the short term and long term.

Fortunately, we have an FDA-approved therapy, 17P, to prevent this in that small subset of women with a prior spontaneous preterm birth, and it's critical that doctors and pregnant women have continued access to it. The stakes are high. We're talking about the health of infants in the short term and throughout their life. I see babies like this one far too often. They can spend weeks or months in the neonatal intensive care unit.

These babies are often on ventilators because their lungs are immature. They're at high risk for infections. They're also more likely to suffer brain damage or a brain bleed. And even if they get to leave the NICU, many of them don't get a chance to see their first birthday. And for those who do survive, they often face a lifetime of complications.

Let's use 39 weeks as the reference point for the risk of infant mortality with a relative risk of 1. Babies born at 34 weeks are nearly 10 times more likely to die than those who go full term, and babies who make it to 36 weeks are nearly 4 times more likely to die.

Preterm birth and its complications are the number one cause of death of babies in the United States. I've mentioned just a few of the short term risks, and even when we deal with those, the risks don't just go away by getting these infants out of the NICU. While the long-term complications are rare, they are profound and can affect these infants throughout their lives. These babies are at increased risk of learning difficulties, hearing and vision impairments, and chronic respiratory problems, including asthma.

Babies born at lower gestational ages have higher rates of neonatal morbidity and mortality. An analysis from Manuck, published in the American Journal of Obstetrics and Gynecology in 2016, including more than 100,000 women and their babies, demonstrated a higher rate of death and major morbidities in babies born earlier than 32 and 35 weeks. Approximately 14 percent, that's 1 in 7 babies, born at less than 32 weeks either die or have a major morbidity. At less than 35 weeks, it's 1 in 10 babies.

For context. Let's discuss some background on preterm birth. One in six of all preterm birth occur earlier than 32 weeks gestation, a critical timepoint because of the high prevalence of serious neonatal complications. Our goal is to prolong pregnancy so that we can decrease the chance of these serious complications.

Across the United States, preterm birth rates vary substantially by geography. The March of Dimes assigned the grades of A to F to individual states based on preterm birth rates. The highest rates are found predominantly in the southeast. My state, Mississippi, has consistently received an F despite our best efforts, though recently we have seen improvements in preterm birth rates.

In addition to where a woman lives, there are many other risk factors for singleton preterm birth, including a multitude of social determinants that, quite frankly, are often overlooked in research. But I can tell you as a clinician practicing in a poor state, these make a difference in overall health, particularly as it pertains to pregnancy. Lower socioeconomic status, higher psychosocial stress, and less access to healthcare all contribute to prematurity.

17P is an effective and integral part of how I help women at risk avoid a subsequent preterm birth. Like most OB/GYNs, I follow the guidelines set forth by SMFM in 2012. For women with no prior history of preterm birth and a short cervix, SMFM recommends vaginal progesterone. For the subset of women with a prior spontaneous preterm birth, SMFM recommends 17P.

Now, it's important to note that this is not a treatment for preterm birth, but the one tool we have to prevent it. We don't always know which specific patients will benefit, similar to a flu shot or other preventive therapies. In patients with both a prior preterm birth and a short cervix, we continue 17P and place a cervical suture known as cerclage.

In summary, preterm birth remains a major public health concern, particularly in this country. Too many infants are spending weeks or months in the NICU, and too many women with a history of preterm delivery have to watch their babies fight for life. They are afraid to live through that again. As a maternal fetal medicine specialist, my vision is that every child receives the best possible start in life by reducing the preterm birth rate and preventing its complication.

For the small subset of women with a prior preterm birth, 17P provides more than just preventive therapy. It actually provides hope for mothers who are traumatized by the experience of preterm birth, and taking it away would deprive the patients who need it most. Thank you, and I'll now turn the presentation over to Dr. Sibai.

Applicant Presentation - Baha Sibai

DR. SIBAI: Thank you, Dr. Owens.

Good morning. My name is Baha Sibai. I am a maternal fetal medicine physician and professor at UT Health in Houston. I have been in practice for more than 40 years, and I was one of the study investigators. I am here today to describe and summarize the study design and the results that led to 17P's approval, but before jumping into study details, let me explain the premise of studying 17P for recurrent preterm birth.

In 1986, the National Institute of Child Health and Human Development established the Maternal Fetal Medicine Units Network, known as the MFMU. The network's primary aim is to reduce preterm birth by conducting rigorous clinical trials. I was one of the original investigators with the MFMU. I continue to be active in numerous studies.

The MFMU has a rigorous process for selecting both network centers and determining which randomized trials to conduct, given the limited resources. Network centers are selected, in part, based upon the adequate obstetric populations being at least 40 percent high risk. Additionally, the network has a diverse patient population available for conducting research. The hospitals that are part of the MFMU serve patients at the highest risk due to their social circumstances, and they are often considered safety net hospitals.

Let's review some of the earlier studies of preterm birth. There have been a number of meta-analyses of progestogen. In 1990, Keirse restricted the meta-analysis to only 17P, as this was the most well studied progestational agent. Although these five studies are small and not definitive on their own, they come together. There is a statistically significant relative risk of 0.58, which translates to a 42 percent reduction in recurrent preterm birth with 17P compared to a placebo. Of note, the only study that did not favor 17P was in twin pregnancies for which 17P is not recommended.

This meta-analysis served as the basis for evaluating 17P in a large multicenter trial, which was a research proposal championed by Dr. Paul Meis for the

Maternal Fetal Medicine Network. The Meis study involved women with a history of singleton spontaneous preterm births at less than 37 weeks. Women were randomized in a 2 to 1 ratio to 17P or a matching vehicle placebo.

Women began receiving weekly intramuscular injections between 16 weeks and 20 weeks and 6 days. The Meis population was very high risk for recurrent preterm births given the populations served by centers and the Maternal Fetal Medicine Units Network. There was an imbalance in the proportion of women with more than one previous preterm birth, with 28 percent in the 17P group and 41 percent in the vehicle group. However, this was subsequently and appropriately adjusted for in the statistical analysis.

The other demographics and baseline characteristics were well balanced between treatment groups. The majority were black. The gestational age of the qualifying delivery was about 31 week and approximately 25 percent used substances such as smoking, alcohol, illicit drugs during pregnancy.

The primary outcome was preterm delivery at less than 37 weeks. We estimated that the sample size of 500 women was needed, expecting a recurrence rate of 37 percent in the placebo group and a reduction of recurrent preterm births with 17P by one third. The Meis study had a very high rate of completion and treatment compliance. The main number of injections was about 40 in both groups. Compliance was defined as not missing 10 days or more between doses. More than 90 percent were compliant in each group.

We began the study in 1999, and it was stopped early due to 17P's clear benefit. In 2002, at a second planned interim analysis, the prespecified stopping criteria for efficacy had been met. The MFMU and the Data Safety Monitoring Board determined that if 17P demonstrated efficacy with a p-value of 0.015, recruitment would be halted. This decision was made so that once 17P's efficacy was established, women at risk for recurrent preterm birth would not receive a placebo.

Outcome data were available for 463 out of the total 500 patients. This represented 93 percent of the planned study population. The data you see here are from our New England Journal of medicine publication. We found a significant reduction in preterm birth rates with 17P compared to vehicle at 37 weeks, at 35 weeks, and at 32 weeks. These women who are at very high risk for preterm birth, 17P significantly reduced recurrent preterm birth compared to vehicle.

When we certified the results by these factors for preterm birth, we saw consistent reduction across all subgroups. Importantly, regardless of the number of prior preterm births, the relative risks were similar. However, these are just some of the no-risk factors for preterm birth. There are many more unknown factors as described by Dr. Owens, but across the board, these results demonstrate the robust and consistent efficacy of 17P.

Turning now to neonatal complications, the reductions I just showed you in preterm birth rates translated to direct clinical benefit for the neonates. Although the Meis trial was not adequately powered to evaluate neonatal complications, there were consistent reductions with 17P. With the exception of neonatal sepsis, all point estimates of relative risk favors 17P with some significance.

These neonatal complications, particularly some of those listed at the top, have important clinical implications for long-term outcomes. We clearly see the benefits of 17P by looking at neonatal intensive care unit admissions. Mothers receiving 17P were less likely to have their infant admitted to an ICU; and if their infant was admitted the mean days in the NICU were shortened.

Let's look closer at perinatal death. The overall perinatal deaths were similar between groups. The rate of neonatal deaths with 17P was half that of the vehicle. There was a small and non-significant increase in the rate of miscarriage and stillbirth in the 17P group. This was evaluated further in the PROLONG study, which you will hear about shortly from Dr. Williams.

When we give medications in pregnancy, long-term safety of the babies and healthy development is always a concern. The MFMU conducted a follow-up of babies enrolled in the Meis study and confirmed the long-term safety of 17P exposure in utero. Nearly

80 percent of eligible children completed development assessment, including the Ages and Stages Questionnaire shown here. That includes five domains.

The median age at follow-up was 4 years. There were no differences between 17P and vehicle. Caretakers also administered the preschool activities inventory, which showed no gender-specific differences. Also, this follow-up study reassured long-term safety and development of babies exposed to 17P.

When we published our findings in the New England Journal of Medicine in 2003, the results were considered a significant advance in obstetrics. Overall, 17P reduced preterm birth by about one-third, which was highly statistically and clinically significant, with a absolute difference in preterm delivery of nearly 19 percent.

Numbers needed to treat are often used to convey efficacy of medications. A number needed to treat of hundred is typically considered an appropriate threshold for a clinical value. Remarkably, based on these data, we need to treat with 17P only 5 to 6 women who have had a prior singleton spontaneous preterm to prevent one recurrent preterm birth.

In summary, the Meis study established substantial evidence of 17P's efficacy and formed the foundation of today's standard of care for high-risk pregnant patients where a history of spontaneous preterm delivery. Since 2003, clinicians have relied on 17P. I have seen 17P reduce recurrent preterm birth in my patients with a history of spontaneous preterm birth, and I continue to routinely prescribe it for these patients.

Without FDA-approved 17P, there will be no acceptable alternative to prevent recurrent preterm birth in this patient population. Moreover, our obstetric community has extensive clinical experience with 17P and supports its use in this subset of patients who are at high risk for preterm birth. Thank you. I now would ask Dr. Williams to come.

Applicant Presentation - Laura Williams

DR. WILLIAMS: Good morning, and thank you Dr. Sibai.

I'm Laura Williams, senior vice president at AMAG and head of clinical development and biostatistics. Today I'll be reviewing the efficacy and safety results from the PROLONG study.

PROLONG was designed to mirror the Meis trial, and as you've heard, it did not meet its co-primary endpoints. Despite similar entry criteria, background preterm birth rate in the placebo group were much lower in PROLONG compared to Meis, which likely played a significant role.

Let me first take you through the PROLONG study design. PROLONG was a double-blind, vehicle-controlled, multicenter, randomized study in women with a singleton pregnancy and a history of a previous singleton spontaneous preterm birth. The key objective was to further demonstrate the safety and efficacy of 17P in this study population. Eligible women could be randomized between 16 weeks 0 days and 20 weeks 6 days of pregnancy.

In total, 1708 were randomized in a 2 to 1 ratio to receive either 17P or vehicle, respectively. Women received weekly intramuscular injections of study drug until 36 weeks 6 days of pregnancy or delivery, whichever occurred first.

In addition to routine follow-up for the mom following study completion, a prospective, non-interventional, infant follow-up study, similar to what was done in Meis, is also being conducted for PROLONG. This study remains blinded to complete the follow-up with database lock anticipated in late 2020.

The co-primary outcomes for PROLONG were preterm birth at less than 35 weeks gestation and a neonatal composite index that highlights the significant morbidity and mortality often associated with preterm birth, which Dr. Owens previously highlighted. The index included respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 3 intraventricular hemorrhage, necrotizing enterocolitis, sepsis, or death.

Key secondary outcomes were the reduction in preterm birth by gestational age at delivery. The primary safety outcome was to exclude a doubling in the risk of perinatal deaths. This was included to address concerns from the original review. The sample size and powers assumptions for the PROLONG study were based on results from the Meis trial.

Based on preterm birth rates in the vehicle group in Meis, a sample size of 1707 patients provided 98 percent power to detect a 30 percent reduction in preterm birth at less than 35 weeks gestation and a 90 percent power to detect a 35 percent reduction in the neonatal composite index. Assuming a 4 percent fetal or early infant death rate in both treatment arms, the sample size provided 83 percent power to exclude a doubling in risk of perinatal death.

Let's look at the patient disposition. Impressively, 99 percent of patients completed the study; 1113 in the 17P arm and 574 in the vehicle arm had data for the preterm birth endpoint and were included in the intent-to-treat or ITT population to evaluate efficacy. The most common reasons for treatment discontinuation were withdrawal of consent or lost to follow-up. All patients who received at least one dose of study drug were included in the safety evaluation.

Now, let's take a look at enrollment by geographic region. As you heard earlier, since 17P was recommended in treatment guidelines and had rapid uptake in clinical practice, enrollment in the U.S. was extremely challenging. The first patient was enrolled in November of 2009, and as expected, enrollment in the U.S. became increasingly difficult. For that reason, approximately 75 percent of patients in PROLONG were enrolled outside of the U.S. Notably, 61 percent were from Russia and Ukraine.

Let's take a closer look at enrollment over time. The study enrolled from 2009 to 2018, and nearly all U.S. patients enrolled by 2014. In the last four years of the study, only 49 additional U.S. patients were enrolled. With enrollment rates plateauing in the U.S. it was clear that in order to complete the study, ex-U.S. sites would be needed. And beginning in 2014, enrollment increased in Russia and Ukraine, allowing for study completion.

Turning now to demographics and baseline characteristics, demographics and other baseline characteristics thought to be associated with preterm birth were similar across treatment groups. The mean age was 30, most women were white, non-Hispanic or Latino, and married or living with a partner during this study. The mean prepregnancy BMI was around 24 with a small percentage of patients having a short cervix, that is less than 25 millimeters at the less than or equal to 20 weeks gestational age.

Less than 10 percent in both treatment arms reported any substance used during pregnancy at baseline. Prior pregnancy history was also similar across treatment groups. A prior spontaneous preterm birth was an entry criteria such that the median was 1. Only 12 to 13 percent of women had more than one prior spontaneous preterm birth, and the mean and median age of the prior qualifying delivery was around 32 and 33 weeks, respectively.

Let's move now to study drug compliance. The number of study drug injections were comparable across treatment groups, injections were administered at the investigator site, and more than 90 percent of patients were fully compliant with their scheduled appointment to receive weekly injections.

Now let's review the study results. Here we show the preterm birth endpoint on the left and the neonatal composite index on the right. The relative risk with 95 percent confidence intervals are provided above the bar graphs for each endpoint. As you can see, the results were not statistically significant between treatment groups for either endpoint. Preterm birth rates at less than 35 weeks were around 11 percent and neonatal composite index rates were around 5 percent.

In addition to the preterm birth rates at less than 35 weeks, there were similar results for preterm birth rate at less than 32 and less than 37 weeks gestation. Recognizing that most patients were enrolled outside the U.S., we also looked at efficacy by geographic region, which was a prespecified analysis, and we found no statistically significant difference between treatment groups by region. However, the preterm birth rates were notably higher in the U.S. compared to ex-U.S.

In fact, they were one and a half to 2 times higher, at nearly 18 percent in the U.S. compared to almost 10 percent ex-U.S. The neonatal composite index rate was around 9 percent in the U.S. compared to only 4 percent ex-U.S.

Given the lower background preterm birth rates seen here in PROLONG compared to Meis, we conducted various exploratory analyses in an effort to better understand the efficacy results from the two registrational studies, Meis and PROLONG. We first examined baseline characteristics between these two study populations, and differences in PROLONG compared to Meis were noteworthy.

Patients in PROLONG were nearly 4 years older. They were 50 percent less likely to have had more than one prior spontaneous preterm birth. Only 7 percent were black and 9 percent were Hispanic. Only 10 percent were unmarried and only 9 percent reported substance use during pregnancy. But interestingly, and perhaps not entirely unexpected, those differences were far less prominent when looking at the U.S. PROLONG population, which was clearly more similar to Meis. That said, it's also important to reiterate differences in background preterm birth rates in the placebo group in Meis at 31 percent versus U.S. PROLONG at nearly 18 percent.

As FDA has noted, the cause of preterm birth, or causes of preterm birth, are multifactorial, and the uncertainty around the relative contribution of any given risks makes finding markers of response very challenging. We thought a lot about how best to interrogate the data to provide additional insights and have conducted various additional analyses, some of which were post hoc, exploratory, and hypothesis generating.

Although the U.S. PROLONG subset population was not identical to Meis, given the more similar demographics and background characteristics, we were compelled to look at the subset population in much more detail. And here you see the aforementioned results for preterm birth rates at less than 35 weeks for PROLONG on the far left, Meis in the middle, and U.S. PROLONG to the far right.

In the U.S. PROLONG subset population, there are trends and relative risk reductions indicating benefit favoring 17P, and the relative risk of 0.88 is directionally aligned to that seen in Meis at 0.70. We also saw similar findings for preterm birth rate at less than 32 weeks, with relative risk reductions in preterm birth at less than 32 weeks, again, indicating benefit favoring 17P, and the relative risk of 0.58 is even lower than that seen in Meis at 0.64.

Importantly, those trends in reductions in preterm birth rates also translated to relative risk reductions in the neonatal composite index in the U.S. PROLONG subset, similar to what was seen in Meis. So while analyses of efficacy by geographic region were prespecified, we fully acknowledged that these analyses are exploratory and in no way change the overall efficacy findings. However, these trends that favor 17P in a smaller subset U.S. population that was not powered to show these differences are promising and directionally aligned with results from Meis.

So how do we summarize these efficacy data? PROLONG did not meet its primary efficacy outcomes, but these findings do not refute the efficacy results seen in the Meis trial. Key differences in background rates of preterm birth across different study populations are the most plausible reason, and as you evaluate subset populations like U.S. PROLONG, which had higher background preterm birth rates than PROLONG overall, there were trends for benefit favoring 17P in a much smaller subset population that was not powered to demonstrate efficacy. Nevertheless, these findings are promising as they directionally align to those from the Meis trial.

Now then, let's take a look at the safety data. The key safety outcome was to exclude a doubling in risk of perinatal death in the 17P group compared to vehicle. If the upper bound of the confidence interval is less than or equal to 2, a doubling in risk of perinatal or neonatal death would be excluded. Fetal and early infant death, or neonatal death, was defined as a spontaneous abortion or miscarriage occurring from 16 weeks to 20 weeks gestation, a stillbirth occurring at greater or equal to 20 weeks gestation, or an early infant death, which is a liveborn death at less than or equal to 24 weeks gestation with death occurring from minutes after birth until 28 days of life.

With anticipated low rates for this outcome, sample size considerations to exclude a lower risk level were taken into account for this orphan population when the FDA defined and added this specific endpoint. However, I think we all agree that the most important outcome is the overall rate of all perinatal deaths.

As shown here, the prespecified primary safety outcome, total fetal or early infant deaths had low and similar rates across both treatment groups. Rates of miscarriage were numerically lower in the 17P group compared to vehicle, while rates of stillbirth were numerically higher. Most importantly, the rates of all perinatal deaths were low and similar across treatment groups.

Overall, the incidence of adverse events and maternal pregnancy complications were comparable between treatment groups. Rates of adverse events leading to study drug withdrawal and serious adverse events were also low and similar, and there were no maternal deaths occurring during the study.

This table shows adverse events and maternal pregnancy complications occurring in at least 3 percent of patients in the 17P arm. Maternal pregnancy complications are denoted by an asterisk. As shown, the rates were low and comparable between the two treatment groups. Only 15 patients in the entire study discontinued study medication due to an adverse event or a maternal pregnancy complication, again with low and similar rates across treatment groups.

This table captures serious adverse events in maternal pregnancy complications that occurred in two or more patients, and, again, the rates were low and comparable across treatment groups. As is usually done with similar design registration studies, a pooled safety data analysis combining Meis and PROLONG was also conducted as a post hoc analysis. Additional details of those pooled safety data are included in the briefing package, but they are similar to what I've shown for PROLONG.

Finally, we will review postmarketing safety findings. Among the estimated cumulative U.S. Makena exposure of nearly 300,000 patients, safety data obtained from postmarketing surveillance remains very consistent with both Meis and PROLONG. The most frequent adverse event reports were consistent with the registration studies with injection site reactions leading the list. The overall postmarketing safety data in general and around perinatal deaths in particular had very low reporting rates and are, again, also consistent with what was seen in the registration studies.

So how do we summarize the safety data? PROLONG reaffirmed the safety of 17P that was demonstrated in the Meis study. We saw no new or unexpected findings and no clinically meaningful difference in safety between treatment arms. Overall, across both studies and in clinical practice, 17P has consistently demonstrated favorable maternal and fetal safety.

Thank you. I'll now turn the presentation over to Dr. Blackwell.

Applicant Presentation - Sean Blackwell

DR. BLACKWELL: Thank you, Dr. Williams.

Good morning. I'm grateful for the opportunity to provide my perspectives on the role of 17P in this high-risk patient population. I was the lead author of the PROLONG publication, and I have thought a lot about why the findings were different from the Meis trial. I am also a maternal fetal medicine physician and departmental chair at McGovern Medical School at the University of Texas in Houston. I lead a physician team, which includes 25 maternal fetal medicine physicians, 50 obstetricians, 12 maternal fetal medicine fellows, and 48 OB/GYN residents across 10 hospitals.

One of my jobs is to make sure that physicians are providing the best care for our patients, and as a high risk pregnancy specialist, this definitely includes trying to prevent recurrent preterm birth. So these discussions and decisions about 17P are not theoretical or abstract. They will affect what we do every day.

The goal of my presentation is to address three key questions? Why did the PROLONG efficacy results differ from the Meis trial; is it feasible to conduct another confirmatory trial; and what should we do from here; and how should I guide my team of physicians in the care of their patients?

To the first question, why did PROLONG efficacy results differ from the Meis trial? You have heard from Dr. Sibai as he described the Meis trial and

Dr. Williams explain PROLONG. It was perplexing at first. How could two studies with the same enrollment criteria in the same treatment protocol, that both performed with high methodologic rigor, have such different results?

The bottom line is that these two clinical trials ended up studying two very different groups of women. The Meis trial studied women from university based academic medical centers in the United States. This population included a very high percentage of African American women and women with lower socioeconomic status. These women enrolled in Meis had a very high background rate of preterm birth and were motivated to participate based on their obstetrical history.

PROLONG recruitment was 75 percent outside the United States, and the two countries with the largest recruitment were Ukraine and Russia. There were only 7 percent of women in PROLONG who were black, and their socioeconomic status in PROLONG appeared to be greater, on average, than women enrolled in the Meis trial. The percentage of women with greater than one prior preterm birth was half that of the Meis trial. These facts are manifest in the comparison of the rates of preterm birth in the placebo arm of these two trials. e can see marked differences in the preterm birth rates at 32 weeks, 35 weeks, and 37 weeks.

This slide illustrates these differences between three trials using preterm birth less than 35 weeks as a proxy for baseline risk of preterm birth. and I've chosen preterm birth less than 35 weeks since it was a co-primary outcome for the PROLONG trial. This slide not only highlights the differences in the baseline risk between me and PROLONG but also the differences between women recruited in the U.S. versus outside the U S for a PROLONG.

I have also included the O'Brien trial for additional context. This was an international, placebo-controlled trial of vaginal progesterone, which was also studied in women with a prior spontaneous preterm birth, and the vast majority of women were recruited from the United States. The importance of this slide is to emphasize the differences in the recurrent preterm birth rate in the U.S. versus non-

U.S. sites across various study populations.

Recruitment challenges in the United States were a second major factor for why PROLONG had such a lower risk patient population. The first patient recruited for PROLONG was in 2009, but in 2003, less than 5 months after publication of Meis, ACOG published a committee opinion supporting the use of progesterone for women with a prior spontaneous preterm birth.

In 2006, a survey published in the American Journal of Obstetrics and Gynecology indicated that two-thirds of board certified maternal fetal medicine physicians were already using progesterone for women with a prior spontaneous preterm birth. By the time prolonged started its recruitment in 2009, most maternal fetal medicine physicians in the United States were already using this treatment, and therefore most likely not willing to participate in a placebo-controlled trial.

As an example, no center in the Maternal Fetal Medicine Units Network and very few university academic medical centers in the United States were recruitment sites for PROLONG. Neither Dr. Sibai nor I, while at different institutions, felt it proper to refer our patients to PROLONG. In our minds, a placebo-controlled trial was only appropriate where 17P was not accessible.

These challenges resulted in enrollment bias in PROLONG favoring a lower risk patient population. Due to this bias, women at greater risk for preterm birth, such as those with a short cervix or more severe obstetrical history, were potentially steered away from participating in PROLONG in favor of some other open-label therapy. PROLONG had one-half the number of women with greater than one prior preterm births than Meis, and less than 2 percent of women in PROLONG had a short cervix, a percentage much lower than one would expect from prior trials.

The sample size estimates for PROLONG were based on the Meis trial, yet the rates in PROLONG were 50 percent lower than Meis. If we were to design a new trial today based on these lower event rates, 3,600 women would be required for a 90 percent power for preterm birth less than 35 weeks and 6,000 women would be needed for the neonatal composite index. Based on these population differences and low event rates in PROLONG compared to Meis, the results are inconclusive regarding efficacy.

In PROLONG, there was a preplanned subgroup analysis of 17P treatment effect by U.S. versus the non-U.S. population. These analyses by their nature are exploratory and hypothesis generating and not meant to be conclusive. In the U.S.-only subgroup, there are trends for benefit for both co-primary outcomes with relative risks 0.88 and 0.84, respectively. Although less robust, these are in a similar direction as Meis and would be clinically significant.

The second question, is it feasible to do another confirmatory trial? As a maternal fetal medicine physician who conducts clinical trials, my ears perk up when someone proposes we do another one. However, in this case, the answer is no. I do not think another interventional trial or a confirmatory trial is feasible. I do not believe physicians or patients will accept a placebo in this patient population, even with the lack of benefit noted in the PROLONG trial. At worst, the trial would be futile, and at best, the same enrollment bias would occur.

This is certainly true in the United States, but I also believe would occur outside the United States in any developed country. In order to conduct this trial, we would have to identify a population of women at sufficiently high risk who also have no access to 17P and be in a setting where there is research infrastructure to conduct a major trial. All this seems improbable.

Now, another option would be a comparison of two therapies, thus no one would receive a placebo. The problem is that there are no other evidence-based therapies that would be a good alternative to 17P. Vaginal progesterone has been studied in women with a prior spontaneous preterm birth. Three recent large placebo-controlled trials -- O'Brien, Norman, and Crowther -- included 2000 women with a high baseline risk of preterm birth. All reported no benefit for this population. Other potential therapies such as cervical cerclage or cervical pessary have also not shown benefit for women with a prior spontaneous preterm birth.

Finally, what should we do from here, given the robust findings from the Meis trial, and then a larger trial, PROLONG, that is inconclusive? Following the publication of PROLONG trial, both SMFM and ACOG have given updated guidance to physicians regarding the role of 17P. I am the past president and prior chair of the SMFM Publications Committee, but due to my involvement with PROLONG, I was not involved in the new SMFM guidelines statement.

SMFM states that based on the evidence of effectiveness in the Meis study, which is the trial with the largest number of U.S. patients, and given the lack of demonstrated safety concerns, SMFM believes that it is reasonable for providers to use 17P in women with a profile more representative of the very high-risk population reported in the Meis trial.

ACOG has not changed their clinical recommendation at this time and continues to recommend offering 17P as outlined in their practice bulletin. We also have to consider what will happen if an FDA-approved 17P would no longer be available. It is my belief that many experts and clinicians will still consider the risks and benefits of 17P in a positive balance that supports its use. If there is not a 17P FDA-approved version available, many will turn to a compounded 17P. Others will advise off-label, unproven medical therapies or choose a surgical option with cervical cerclage, which has not been proven to work and has a greater risk for patient harm.

Finally, last question, what will I do? How do I recommend we take care of our patients? First, I believe that the Meis and PROLONG studies do not contradict each other. Meis shows robust treatment effects for a high-risk U.S. population similar to my patients. PROLONG did not confirm treatment efficacy in a much lower risk population and was inconclusive due to its sample size. PROLONG does provide reassuring data regarding safety, miscarriage, pregnancy loss, and gestational diabetes.

Overall, the benefit to risk ratio is positive considering the totality of efficacy data and the low safety risk profile. That is why I will continue to offer and recommend 17P to my patients. It's my belief, after counseling many women with a prior preterm birth, especially those who deliver at a very early gestational age, or those whose child suffered from complications related to preterm birth, we'll choose 17P therapy based on the available data.

In order for my team of physicians to provide the best care for our patients, it's essential that we have the ability to offer an FDA-approved 17P, especially to those at the highest risk. Thank you.

Applicant Presentation - Julie Krop

DR. KROP: Thank you, Dr. Blackwell.

I'd like to conclude our presentation by summarizing what you heard today and sharing the actions AMAG is taking following the PROLONG study. We have just reviewed the totality of the evidence that supports continued access to 17P. The Meis study demonstrated robust and substantial evidence of efficacy and was the basis of ACOG and SMFM's recommendation of 17P.

Last week, after reviewing the PROLONG publication, ACOG and SMFM announced their continued support of 17P. Because the placebo birthright in the placebo arm of the PROLONG study was much lower than rates typically seen in the United States, the results are inconclusive and difficult to apply to the U.S. population. Despite these differences, it neither refutes nor invalidates the findings of the Meis study.

So what have we learned over the 10 years it took to complete the PROLONG study? We've learned that since 17P was recommended by medical societies as the standard of care, it was not possible to conduct a placebo-controlled trial to confirm the Meis results. Once efficacy was established, U.S. physicians would not withhold an efficacious treatment from their patients. Bias was introduced. This bias skewed enrollment towards a low-risk patient population. Despite this bias, the U.S. subset still demonstrated trends favoring 17P for the co-primary endpoint. However, the U.S. subset was not powered to evaluate efficacy.

The PROLONG study did confirm 17P's favorable safety profile. We also have eight years of postmarketing surveillance, which firmly supports its safety in this population. While we successfully conducted and completed the confirmatory trial, the results are inconclusive. This leaves us with a question. If the Meis study was being reviewed here today, would Meis alone have met the criteria for full approval?

According to FDA's guidance on establishing evidence of effectiveness, approval may be supported by a single trial if a second trial is not feasible or ethical. To qualify, that single trial should demonstrate statistically persuasive findings on a clinically relevant endpoint, as well as robust, consistent results across multiple subgroups in the study. If so, the results of a single trial are frequently sufficient to support approval in the context of a rare or orphan condition.

Today, almost a decade after 17P's approval, there is now compelling evidence delivery at less than 37 weeks, but especially at less than 35 weeks and less than 32 weeks, are associated with significant increases in neonatal morbidity and mortality. This newer data strongly suggests preterm birth endpoints evaluated in the Meis study should no longer be considered surrogate endpoints that require a confirmatory study.

It's important to note that this population of women with a prior preterm birth still qualify today as an orphan condition with no available treatment options. Given what we know today, we believe 17P's reduction in preterm birth rates at less than 32, less than 35, and less than 37 weeks in the Meis study, coupled with its consistent statistically significant efficacy across multiple endpoints and subgroups, and 17P's overall reassuring safety profile, strongly support its continued availability.

It is vital that we put the PROLONG study into the proper context so we make the right decisions for these high-risk patients. It's critical to remember that 17P is not a treatment for preterm birth; it's a treatment aimed at reducing risks. Like other preventive measures, we do not expect to see a benefit in a low-risk patient population. We trust physicians and their patients to weigh the potential benefits and risks of treatment together.

To better inform these decisions, the PROLONG results have recently been published in the American

Journal of Perinatology. In addition, we propose working closely with FDA to update all relevant sections of the label with the PROLONG study data in order to provide clinicians with a comprehensive understanding of all available safety and efficacy data.

A question you face today is whether or not another confirmatory trial needs to be done. We have grappled extensively with this question and if any study could serve as a confirmatory study of the Meis study. As you've heard from Dr. Blackwell, another randomized, placebo-controlled trial is simply not feasible. Worse, it might even be considered unethical given the current clinical practice guidelines that recommend 17P's use in this high-risk subset of preterm birth.

We've also carefully considered alternative study designs such as an observational study. The challenge, how do account for the myriad of known and unknown risk factors for preterm birth that would be difficult or impossible to control for in a non-randomized trial. That said, we look forward to hearing your thoughts today. We are committed to working with the FDA to look for other potential studies that might better inform providers on the appropriate use of 17P.

The totality of the data we share today and nearly a decade of routine clinical use, support 17P's positive benefit-risk profile and the importance of continuing to make it available to physicians and their patients. Preterm birth remains a major public health concern, particularly in the most underserved and most vulnerable patients. These patients have the highest preterm birth rates, and they are the very patient population who benefited the most in the Meis study.

We look forward to today's discussion and partnering closely with the FDA on next steps. Most important, as we complete this work, it is critical that we do not take this medication away from the patients who need it the most. Thank you.

Before we take your questions, I wanted to mention that the lead statistician for the Meis and the PROLONG study, Dr. Anita Das, is unable to be here due to an emergency. Dr. Das lives in the area impacted by the current wildfires in California, and her neighborhood is under mandatory evacuation. She left to be with her family, but she will be joining us by phone today, so we're happy to take your questions.

Clarifying Questions to Applicant

DR. LEWIS: Thank you.

Are there any clarifying questions for AMAG Pharmaceuticals? Please remember to state your name for the record before you speak, and please identify which presenter your question is for, or if it is a general question for all presenters. We'll start with Dr. Davis.

DR. DAVIS: Thank you very much for the presentation. There's a lot of work and effort that goes into that. I was curious about a few things. One is if your group could clarify how you chose the sites and in what order. Clearly, I think we all recognize there are tremendous regional disparities globally with things such as preterm birth, so I was curious how you ended up in Russia and the Ukraine with the majority of your patients, and then the European sites look like they came later and had a much smaller percentage.

That's my first question, and once you answer that, I'll follow up with one more short

DR. KROP: Yes. The sites were selected in the United States based on specific criteria to make sure that they have the adequate neonatal care, level 3/level 4 NICUs, and appropriate experience doing research. It was quite challenging because the majority of centers that qualify for that were already part of the network and would not participate.

We had 42 sites in the United States attempt to enroll, and when it became clear, because of the entrenched guidelines, it became impossible to recruit at those centers, we had other centers in Europe as well as Ukraine and Russia. But we saw that those recruitments were going much better than the United States, and we continued to add sites there in order to complete the study. It's very difficult in an orphan population to get, as you can imagine, 1700 patients. Those were the sites that were the highest recruiters. We had sites also in Italy. We had sites in Spain. Unfortunately, they were not strong recruiters.

DR. DAVIS: Just one more brief question. It involves this neonatal morbidity index. This is by far the healthiest group of babies I've ever seen in my lifetime, and using it as an outcome measure, when you have a 98 percent survival and you have more deaths than any intraventricular hemorrhage, something didn't make a lot of sense to me.

At least to me, it suggested that these were mostly older, very healthy babies. The ones we are really concerned about were the ones delivering less than 30 weeks, or 28 weeks I guess was some of the data, and that didn't seem to have much of an influence by progesterone.

DR. KROP: Again, I think we did have a much healthier patient population. Our event rates in the neonatal index were much lower than we anticipated. Unfortunately, that made it very difficult to show benefit, I think, compared to the Meis trial, where there were much higher incidences of adverse affects in the infants, a much higher background rate of preterm birth and higher number of risk factors.

DR. LEWIS: Thank you. Dr. Bauer?

DR. BAUER: Thank you. I have a question for

Dr. Sibai about the Meis trial. Again, through much of the presentation, it's been discussed how this was really a landmark study, and it certainly was. But it's interesting. I really was struck by the unexpectedly high event rate in the placebo group, almost 55 percent. In fact, that is much, much higher than even the meta-analysis numbers that you showed, where it looks like it was about 28 percent above the other trials.

I'm wondering if you can discuss that because it looked like, based on the power estimates, that actually they expected the event rate in the placebo group to be closer to 36 percent, I believe, and it was 55; and in fact the event rate in the active treatment group was close to the placebo group, or expected in the placebo group. I don't know if you can mention that.

Also, if you could also just then comment what particular risk factor profile you think accounted for that really astronomically high event rate.

DR. SIBAI: Thank you for your question. The rate that we estimated the sample size was, we expected the rate to be 37 percent. However, given the nature of the network and the patients in the network, and considering the fact when the trial was performed, there was no other drug available, it required a woman to receive 20 intramuscular injections. So it became obvious, people who agreed to enroll in the trial pre-selected themselves to be at highest risk. If you look at that population, very high-risk women had more than one prior preterm birth. In addition, we had a high percentage of women who their qualifying prior preterm birth was at very risk.

Given all of this information, the risk factors for recurrent preterm birth, not only having a prior spontaneous preterm birth, it depends on the gestational age, when you had the prior preterm birth, as well as the number of prior preterm births. Because we had this very high rate in the placebo, we expected it to be 37 percent based on a study we did, an observational study with collected data, prospectively, to know what will be the baseline, so we ended up having a much higher rate.

However, this was wasn't surprising because the network did another study, which was a randomized trial of women who were assigned to Omega 3 versus a placebo to prevent recurrent preterm birth. All of these women received 17P, and still we had a very high rate of recurrent -- Omega 3 didn't work, but the rate was still the same.

More importantly, when we did a study after the availability of 17P, the compounded form, earlier we looked at data collected by one of the home health agencies that enrolled more than 5400 women in 40 states in the United States, all of these women received 17P, and the rate of recurrent preterm birth, at less than 37 weeks and at 35 weeks, was similar. So it seems as if the patient populations receiving the 17P are really at a very high risk of preterm birth. It wasn't only unique to the network.

DR. KROP: And I would add, I think these patients are still quite prevalent. I would ask Dr. Owens also to comment in terms of her experience at her center.

DR. OWENS: Michelle Owens, Jackson, Mississippi. My patient population is probably more similar to the Meis population that was studied. I do practice in a state that has led the country for years with the highest rates of preterm birth. We have significantly higher rates of not only preterm birth, but also, subsequent to that, infant mortality.

My patients reflect very similar demographics. They are socioeconomically disadvantaged, in many cases, educationally disadvantaged, and we have a high percentage of African American patients as well. Many of the patients where I live in my state, while I am in a metropolitan area, the largest city in my state, many of my patients will travel 3 or 4 hours from many more rural areas in order to receive their care.

I've been using 17P for women with a history of spontaneous preterm birth, and I have actually seen the benefits. The greatest complaint that we have come to expect from the women, who have had a preterm birth and then turn around and subsequently come in for care, is that they end up being more pregnant than they've ever been, and typically much more uncomfortable because they're carrying their pregnancies to longer gestations, This particular day is really important because I feel like we know that we have some seemingly confusing information in a lower risk population, but we do have really compelling data that tells us that this works exceptionally well in a very unique subset of women, and it's so integral that they continue to have access to this medication.

DR. KROP: It's also important to remember that about 50 percent of our sales are to Medicaid patients, which is representative of the population. I think about 43 percent of pregnant women are on Medicaid, so it is a high-risk patient population.

DR. LEWIS: Thank you. I have a quick question, and I'm not sure who would best answer it. That is, what have been the trends in U.S. preterm delivery rates, by race, I guess.

DR. KROP: I'll answer the last part of that question. The rates of preterm birth in United States have been about 10 percent, and they've been fairly steady over the last several years. You have to remember this as a very small subset of patients that this affects, so therefore, we wouldn't really expect to see a difference in the preterm birth rate. In fact, there was a survey done based on the Meis -- not a survey, an analysis done based on the Meis trial, where if you assume all 10,000 births that would be affected, it would only improve -- I think it would only decrease the overall preterm birth rate by like 0.3 percent, so it would be very difficult to detect, based on that.

DR. LEWIS: Thank you. Dr. Gillen?

DR. GILLEN: Thank you. I'm trying to put the general logic together in my mind here. The preface here is that the two studies disagree. Meis and PROLONG disagree because they have different patient populations. The implication would be that there is a different point estimate in effective treatment in those two populations due to effect modification by subgroups.

If we can start with -- and there is a question coming here, but I need to set it up. If we can start with slide C-034, which is the Meis study, which very beautifully -- and I think the sponsor presented this in 2006 -- shows consistency of results across all subpopulations, and quite strikingly in that consistency of results. I'm starting with, are there any subpopulations that were found in the Meis study for which there was a differential effect; in other words, for which we would expect effect modification if we had oversampled those individuals?

That's the first. Then if we go to slide C-056, I think there's a very strong preface here that says that it's a U.S. issue, that we've oversampled individuals outside of the United States. And if we focus on those individuals within the United States, we can see that we now have a similar patient demographic to that that was observed in Meis.

Then if we go to slide C-058, and here will be my question, alas, when we stratify on the U.S. population in PROLONG, first of all, isn't that point estimate of 0.88 with a confidence interval ranging from 0.55 to 1.40 exactly consistent with what is seen as the point estimate and confidence interval that's seen in the overall PROLONG population? We've seem to have treat it differently, and I think that the words were, "It's in the right direction, so with adequate power, it would have been significant." That presumes that 0.88 is the true estimate. That's not what it is. The confidence interval ranges from 0.55 to 1.40 there.

So my question is, was there any effect modification that was tested and observed in PROLONG with respect to the U.S. population, or with respect to any other subpopulation inside of PROLONG, where you can simply say, yes, there is a differential effect of this therapy in this subgroup?

DR. KROP: We conducted a number of post hoc group analyses looking at race, ethnicity, many of the traditional factors that you would think of, composites, level of background. I think we have a forest plot of the various subgroups that we looked at in PROLONG that we can bring up in a second.

I think you have to keep in mind, the PROLONG U.S. subset is substantially underpowered. It was not powered, obviously, to look at those endpoint. And when we went back retrospectively and tried to calculate the power we would have had in the U.S. subset, it was less than 20 percent, so that's a challenge.

I think with the subgroup analysis up here, you can see there really isn't anything, based on what we can understand of traditional risk factors, but one has to remember that there are a whole hosts and a myriad of other risk factors, as FDA points out, that we don't fully understand. When you enroll a very different patient population with different social characteristics, it's hard to understand what those impacts would be.

As Dr. Owens stated, in her practice, there are huge impacts of social determinants of health in terms of disadvantage that are impossible to incorporate into a clinical study. They're just different patient populations. I Ukraine and Russia, there are preventive services that are far more significant than we have here in the United States. Women are counseled before they ever become pregnant. There's a universal health care system; I mean, just a host of different factors.

DR. GILLEN: I appreciate that, but what I am as a committee member am struggling with is -- and this is Dr. Owens' words, "This works well in a selected population," but who was that population? Who are we talking about? In other words, we can't have it both ways. We can say, "Oh no, no, no, the population was what we had seen in Meis, but it was the wrong population in PROLONG." But we can't find that subpopulation in PROLONG to justify what was seen in Meis.

So I'm asking, what is that selective population that you're asking me to consider here?

DR. KROP: I'm going to call up Dr. Sibai in a minute, but I think it's important to remember the bias element that was in play in the U.S. Trying to do a clinical trial in the presence of an existing standard of care does bias your population that you put in, so I don't think we're seeing a generalizable population.

Dr. Sibai, would you like to comment on the patients that would be the most appropriate?

DR. SIBAI: Baha Sibai, UT Houston. There is really no doubt you have got degrees of risk and degrees of benefit, based on using this medication. Unfortunately, I as an obstetrician have to use a group of women who have a risk called prior preterm birth, and I am using a prophylactic medication.

The number needed to treat in populations similar to what we see in Meis is about 5 to 6 in other women with prior spontaneous preterm birth. They might still have the benefit, however, the number needed to treat could be 25 or could be 50. However, considering the safety of the medication, as well as how bad it takes to have a baby born and go into a neonatal intensive care unit, it becomes extremely important for me to use all women with prior spontaneous preterm birth because at the present time, I do not have any person who responds.

To give you an example, we currently screen every woman for group B strep. At least 1 million women screened positive. We give all of these women antibiotics during labor, and only probably 100 or 200 will have group B strep. However, we don't know who is this person, so we give -- I think of this as 17P, having a baby with group B strep is catastrophic, but having a premature baby at 1 to 6 weeks is also catastrophic.

So really, we're talking about prophylaxis.

At the present time, I cannot tell you who will benefit or not. All I can tell you is there are women who will have a huge benefit, but at the end of the day, our risk factor has to be a prior spontaneous preterm birth.

DR. KROP: Dr. Miller, would you comment to -- Dr. Miller was an investigator actually in the PROLONG study.

DR. MILLER: Hugh Miller from Tucson, Arizona, maternal fetal medicine specialist who actually did participate in the PROLONG study. I accept your question. In my study site, we enrolled 22 patients; 15 of them got 17P, 7 got vehicle, and we had a 20 percent reduction.

So I think there were segments of the PROLONG population that did substantially benefit. We saw an over 20 percent reduction in preterm birth. But you do have to remember that the paradigm of treatment at the time that the PROLONG trial was being conducted was that this was the standard of care. There was no question about that among obstetricians, among maternal fetal medicine experts.

Our problem was that we didn't have an FDA-approved drug. as time advanced and with the accelerated approval in 2011, it became increasingly difficult to ask any patient to participate, both ethically for us, as Dr. Blackwell said. It became kind of unconscionable to subject patients to a 33 percent chance of not getting a drug that we all believed in. And as access improved, Medicaid patients -- again, my population represents 55 percent Medicaid. Once Medicaid had an FDA-approved drug to approve, all of my patients no longer would participate in this trial.

So I think the premise that this was a very skewed population has to be accepted, and it's why the study, in large part, was driven to another part of the world where the background risk of preterm birth is just completely different.

DR. LEWIS: Thank you. Dr. Orza?

DR. ORZA: I have two questions that go to the possibility, the feasibility of conducting an additional trial, and the first one is for Dr. Blackwell about slide CO-85 and CO-86, where you encapsulate the statements from the SMFM and the ACOG.

Generally, the recommendations that come from clinical societies are accompanied by some indication of the strength of the recommendation and also the level of the evidence. Do you have that for either of these or whether there was any opinion in these guidelines as to what it would take for either of these societies to be in a position of equipoise and to require additional evidence?

DR. KROP: Dr. Blackwell?

DR. ORZA: First question.

DR. BLACKWELL: Hi. Sean Blackwell from UT Houston. I read the statements when they came out to the press just like everyone else. The statements, it's my impression that they are meant for interim guidance while experts and the society gain additional information. There is no strength related to the level of recommendation. There was no grade that we often use in our SMFM guidelines.

My interpretation and my understanding is that there's still a lot of work to be done to take the PROLONG results, and then combine them with other trials, formally and statistically. and to potentially be able to take a deeper dive into looking at subgroups or other aspects.

With the PROLONG study just coming out within a week of this meeting, I think it probably takes our society some time to mull over the data, to have some vigorous debates, and to argue through it before I think our society could come up with a practice recommendation, in order to make sure we get it right and not have to go back after something is so essential that was in routine clinical practice.

DR. ORZA: My second question goes to the additional evidence and analysis that you referenced. The organization that I work for, PCORI, has funded an individual participant level data meta-analysis, which the protocol for it is published, but the results are currently undergoing peer review, and I'm not privy to those. But my question for your company is, have you contributed your data to that IPD meta-analysis?

DR. KROP: I can take that as the sponsor. We have not participated, and the reason being is that the study you're referring to was already completed by the time we got the PROLONG data, so it was already almost under publication or in review. So we didn't; we weren't able to get that data in then.

DR. LEWIS: Thank you. Dr. Reddy?

DR. REDDY: Thank you for the clear presentations; a couple of clarifying questions. In comparing the Meis trial and the U.S. PROLONG population, it looks like the gestational age of the qualifying delivery, there's a 1 and a half week difference. Is that correct? For the U.S. PROLONG qualifying delivery, it's 32.5 it looks like, and for Meis, it's 30.6.

DR. KROP: Yes.

DR. REDDY: Okay. I just want to make sure.

DR. KROP: Yes.

DR. REDDY: There were differences. One and a half weeks at that gestational age and the risk of recurrence, that's a big difference to point out.

Then, I just wanted to ask about the trial and the sites again. There was a DSMB for the study for PROLONG?

DR. KROP: Yes, there was a DSMB. The DSMB was charged with safety only, and they were looking at unblinded safety data, but they were not reviewing efficacy data.

DR. REDDY: So they didn't look at the rate of outcomes?

DR. KROP: No, they didn't. They add only the overall event rate in front of them. It was not unblinded. That was not the charge of the DSMB.

DR. REDDY: Okay. So until the end of the trial, there was no idea about the outcome rate.

DR. KROP: No, there was not.

DR. REDDY: Okay. And this is very basic. The vehicle was the same for both trials, right?

DR. KROP: The vehicle was exactly the same for both trials, and, yes, it was reviewed. When the approval originally of Makena was under review, there were comparability studies requested by FDA to assure that the product used in the Meis trial is similar to what we use now in the commercial product, which was used in PROLONG.

DR. REDDY: Thank you.

DR. LEWIS: Thank you. Dr. Jarugula?

DR. JARUGULA: Very nice and clear presentations from the sponsor. I just have a quick question, actually, to Dr. Sibai. I found the meta-analysis of 17P very interesting. It demonstrated 42n percent reduction with I think the analysis of five studies. I'm a clinical pharmacologist, so naturally inclined to know what is the dose used in these studies. I was wondering if you can share the doses used in these studies so we can reflect on the current dose being proposed or proposed for this 17P.

DR. KROP: I can have Dr. Sibai come up, but I would say that dose we used to select, I should say, for the PROLONG study was based on these studies, based on the LeVine, Johnson, and the Yemini study, as well as the Meis trial, all showing efficacy at the 250-milligram dose.

Dr. Sibai, do you have any additional --

DR. SIBAI: When we were designing the study, we had to rely on what's available. The 250-milligram dose was really used by several of these, and we relied on the study done by Johnson that was published in the New England Journal, which used the 250-milligram every week.

DR. REDDY: Thank you.

DR. LEWIS: Thank you. Dr. Wade will have the last question.

DR. WADE: Thank you --

DR. WING: Thank you. In follow-up -- I'm sorry.

DR. LEWIS: I said Wade.

DR. WADE: Thank you. As a neonatologist on the committee, I'm interested in how you chose the neonatal morbidity composite index. That seems to be an unusual neonatal outcome to use. I'm just wondering about its validity and how you chose it.

DR. KROP: This was really chosen based on discussions with FDA at the time and in concert with some of the maternal fetal medicine experts as to what would be the most relevant outcomes to include. We obviously looked at a whole host of other I should say complications, as well as secondary endpoints, but those were the ones that were chosen for the composite. There's nothing validated, if that's what you're asking.

DR. LEWIS: Thank you. Dr. Wing, and then break.

DR. WING: Thank you, Dr. Lewis. This is actually a follow-up to your question. Do we know -- and I think the answer's probably no, but since the widespread use of 17P, have we actually seen a drop in the frequency of recurrent spontaneous preterm births, or are the numbers just too small to be able to track?

DR. KROP: Yes. It's too small to be able to track based on the CDC -- the statistics they put out every year on preterm birth, it wouldn't be detected. It's a too small subset.

DR. WING: And then, perhaps, does Dr. Owens know? As somebody who monitors these morbidities in her state, do you have data from Mississippi that might help us understand whether or not there's been good clinical impact?

DR. KROP: Dr. Owens?

DR. OWENS: Michelle Owens from Jackson, Mississippi. So the information or the data that I do have is, unfortunately, not available. I can see if we might be able to get ahold of some of that data, but I can tell you that we have seen, with a concerted effort to expand within our 65 percent Medicaid-covered patient population -- to create, or eliminate, rather, all barriers to 17P. Subsequent to that initiative, we noticed an 18 percent decrease in overall preterm births within our state, and subsequent to that, received the Virginia Apgar Award from the March of Dimes as a result.

While there are clearly other things that we had also, other initiatives that were also underway during that time, it seemed very serendipitous that subsequent to increasing access for this large population of women who had historically had multiple barriers to receiving 17P, that once we were able to take that away, we saw this significant decrease that has been substantiated by our managed Medicaid plans, and that information has been made -- I know it's available publicly because it's been presented in public forums in the past. But I just don't know. We might be able to try to see if we can get ahold of that for you after the break, but I'm not sure that we'll be able to get ahold of that information.

DR. LEWIS: Thank you. We'll now take an approximately 10-minute break. Panel members, please remember no discussion of the meeting topic during the break, amongst yourselves or with any member of the audience. We will resume at 10:40.

(Whereupon, at 10:29 a.m., a recess was taken.)

DR. LEWIS: Thank you, everyone. Let's now proceed with the FDA presentations.

FDA Presentation - Barbara Wesley

DR. WESLEY: Advisory committee members, representatives from AMAG, representatives from the FDA, and guests, I am Barbara Wesley, the primary medical reviewer for this new drug application or NDA. I am also a maternal fetal medicine health specialist, and before coming to the FDA, I had 23 years of clinical practice at urban academic medical centers and also had a little over two years as director of maternal child health in the city of Philadelphia.

This presentation will review the FDA considerations and analysis of pivotal studies 002 regarding accelerated approval, Makena, FDA actions, and postmarketing requirements. More specifically, my presentation will focus on pivotal Trial 002 supporting approval, including the findings in areas of controversy; the 2006 advisory committee meeting; the three actions taken by the FDA; and the postmarketing requirement for the confirmatory trial.

Trial 002 was funded by the National Institute of Child Health and Development and conducted by the Maternal Fetal Medicine Units Network from 1999 to 2002. The positive findings of hydroxyprogesterone caproate, or HPC, to reduce the risk of preterm birth was published in the New England Journal of Medicine in 2003. This trial is also known as the Meis trial. Then in 2006, a new drug application was submitted to the FDA for HPC 250 milligrams weekly.

The indication for HPC or Makena is to reduce the risk of preterm birth in pregnant women with a history of at least one spontaneous preterm birth. Makena is administered at a dose of 250 milligrams once a week, beginning between 16 week 0 days and 20 weeks 6 days gestation until week 37 or birth, whichever occurs first. I would like to mention that this dose is the same dose that delalutin was approved for in 1956 for gynecologic indications.

The pivotal Trial 002 was a double-blind, placebo-controlled trial. They randomized subjects 2 to 1 to HPC or placebo. The primary efficacy endpoint was percent birth less than 37 weeks gestation. Additional endpoints requested by the FDA, after the trial's completion, and submission of the NDA, included percent birth less than 35 weeks and less than 32 weeks gestation, and a composite index of neonatal morbidities that was developed by the applicant.

The composite was based on the number of births of infants who experienced any one of the following: death, respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, proven sepsis, or necrotizing enterocolitis.

As stated previously, the primary efficacy endpoint was the percent of preterm births less than 37 weeks. Of the 310 subjects treated with HPC, 37 percent delivered prematurely and 55 percent in the placebo arm delivered prematurely. There was an 18 percent reduction in preterm births below 37 weeks. However, it is noteworthy that preterm birth rate of 55 percent in the placebo arm was considerably greater than the expected background rate of 36 percent in another Maternal Fetal Medicine Units Network study, the Home Activity Uterine Monitoring study, which was used to power this study.

Finally, I bring to your attention that the preterm birth rate of 37 percent in the HPC treatment arm was similar to the preterm birth rate of 36 percent in the placebo arm of that study. Sixty percent of the subjects in this study were black or African American. Therefore, data were broken down to black versus non-black. Although black Americans generally have a higher rate of preterm birth compared to other racial ethnic groups in the United States, there was no significant difference in the preterm birth rate by race in this trial.

In blacks, the placebo rate 52 percent. In non-blacks, the placebo rate was 59 percent. Therefore, this population with an overall placebo preterm birth rate of 55 percent was high risk regardless of race. However, despite the high placebo rate of preterm birth, the median gestational age in the HPC arm was 37.5 weeks and 36.5 weeks in the placebo arm. Also, in both arms -- and this is not on the slide; I have other slides that we'll show this in more detail -- in both arms, the median birth weight was 2500 grams or more, so the median was not low birth weight. Therefore, most of the preterm births were late preterm births.

We were particularly interested in the preterm birth rate at gestational ages less than 35 weeks since birth at these lower gestational ages at that time were thought to be a more robust predictor of infant mortality or morbidity.

This slide lists the percentages of preterm births at selected gestational ages. Based on the adjusted 95 percent confidence interval, the upper limits of the confidence intervals with delivery at less than 32 and less than 35 weeks were close to zero, indicating the treatment effect of Makena was not much different than placebo at these gestational ages.

Also, I want to note the adjustments that were made because of interim analysis.

The ultimate goal of reducing the rate of preterm birth is to prevent neonatal and long-term morbidity and mortality associated with prematurity. The individual morbidities listed in this slide were grouped to form a composite index of morbidity. All infants with one or more of the listed morbidities were counted in the index. We have not provided p-values because these comparisons were post hoc analyses, event rates were low, and no adjustments were made for the multiple endpoints.

It should be noted that HPC did not consistently decrease the incidence of individual components of the index. Also, the most common outcome respiratory distress syndrome, which appeared to drive the difference between Makena and placebo for the composite index, is highly correlated with gestational age of delivery, and is therefore not independent of the primary outcome.

Overall, the lower percentage of infants in the HPC arm, 12 percent, compared to 17 percent in the placebo arm, had one or more of the morbidities that comprise the composite index. However, the difference between the treatment arms was not statistically significant.

To summarize, the applicant sought approval for HPC based on findings from a single clinical trial and a surrogate endpoint less than 37 weeks gestation for infant mortality and morbidity. We were concerned that these findings may not be applicable to the general United States population. The recurrent preterm birth rate in the placebo arm was notably high, a majority of the subjects were black, and enrollment occurred from academic centers only, with one center recruiting 27 percent of the subjects, and that was the University of Alabama.

The main reason the FDA convened an advisory committee in 2006 for this application was to get their input on which gestational age at birth serves as a surrogate likely to reasonably predict infant mortality and morbidity from prematurity. Twenty-one members were present to vote, and the outcome of the vote was as follows: for preterm birth less than 37 weeks, 5 voted yes; for preterm birth less than 35 weeks, 13 voted yes; and for preterm birth less than 32 weeks, 20 voted yes.

In October 2006, the FDA determined that the NDA could not be approved. The primary deficiency was that evidence of efficacy based on a single trial that relied on a surrogate endpoint, deemed by most advisory committee members to be an inadequate surrogate, was not sufficiently robust evidence to support approval. The FDA determined that further evidence of efficacy in terms of direct benefit to the neonate or a surrogate, such as a preterm birth less than 35 weeks or less than 32 weeks, was needed.

The FDA also withheld approval in 2009 so the applicant could demonstrate they could conduct Trial 003. At this time, resulting from a publication in the Journal of Pediatrics, along with other publications, the American College of Obstetrics and Gynecology published committee opinion 404, which stated the following.

"Late preterm infants defined as infants born between 34 and 0-7ths and 36 and 6-7ths weeks are often mistakenly believed to be as physiologically and metabolically as mature as term infants. They have higher rates of infant mortality and morbidity than term infants, and this is the largest population of preterm births."

In 2011, the applicant resubmitted the application, which upon review FDA determined that they resolved previous deficiencies. The application was approved under the accelerated approval regulations to reduce the risk of preterm birth and women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

The effectiveness of Makena was based on a persuasive improvement on the proportion of women who delivered less than 37 weeks gestation, a surrogate endpoint that FDA now deemed acceptable in light of the new data indicating higher rates of neonatal mortality and morbidity in late preterm births.

Trial 003 three was ongoing, and the applicant demonstrated that it could successfully be completed. As a condition of accelerated approval, the applicant was required to complete the confirmatory clinical trial of HPC Trial 003 to verify the clinical benefit to neonates from the reduction in the risks of preterm birth.

I have now presented the complicated regulatory history of FDA's review, which culminated in 2011 in accelerated approval of Makena based on Trial 002. I will now turn our presentation over to my statistical colleague, Dr. Jia Guo, to discuss results from the confirmatory trial.

FDA Presentation - Jia Guo

DR. GUO: Good morning everyone. My name is Jia Guo. I'm the statistical reviewer from the Office of Biostatistics at CDER FDA. I'm going to present the efficacy results for Makena in confirmatory Trial 003. In my presentation, first I will provide an overview of Trial 003, including trial design, subject disposition, demographics, baseline characteristics, and efficacy results, followed by FDA's exploratory analysis and concluding remarks.

As you already heard from the applicant's presentation, Trial 003 was a multicenter, randomized, double-blind, placebo-controlled trial. Subjects were randomized to Makena or placebo with a 2 to 1 ratio. The randomization was stratified by study site and gestational age. The trial design and eligibility criteria were very similar to Trial 002.

Trial 003 enrolled women who are at least 18 years old with a singleton pregnancy, and the gestational age was between 16 to 20 weeks with a history of singleton spontaneous preterm birth. Subjects who had a significant medical disorder, or had multifetal gestation, or with no major fetal anomaly or fetal demise were excluded.

Based on Trial 002 efficacy results, Trial 003 was adequately powered to detect a 35 percent reduction, from 17 percent to 11 percent, in the percentage of neonates with at least one neonatal composite index event and a 30 percent reduction, from 30 percent to 21 percent in the percentage of preterm births prior to 35 weeks.

Approximately 1700 subjects were randomized to receive either Makena or placebo. Almost all subjects completed the study, and 93 percent of subjects completed treatment. The intent-to-treat population included all randomized subjects, and it was used for evaluation of preterm birth endpoints.

The liveborn neonatal population included all neonates of subjects in ITT population who were liveborn and have available morbidity and mortality data. There was a minor discrepancy on the sample size of liveborn population between the applicant's and FDA's analysis due to the mortality and the morbidity data change on 3 neonates. This discrepancy does not impact any conclusions in my presentation.

The Makena and the placebo groups were comparable across demographics and baseline characteristics. Overall, 88 percent of randomized subjects were white, 7 percent were self-identified black, and 5 percent of other races. Approximately 10 percent of randomized patients were single or without a partner.

Nine percent of subjects used substances, including alcohol, tobacco, and illicit drugs during pregnancy, and 15 percent of subjects had more than one previous spontaneous preterm birth; 391 subjects were enrolled from the U.S., which were about 23 percent of the overall study population. Please note the size of the U.S. subpopulation in Trial 003 was not substantially less than the size of Trial 002, which had 463 subjects.

Trial 003 was designed to demonstrate efficacy on co-primary endpoints, the surrogate endpoint preterm birth prior to 35 weeks and the clinical endpoint neonatal composite morbidity and mortality index, which is a yes/no variable defined as yes if the liveborn neonate had any of the events listed on the slide.

There are two secondary efficacy endpoints. Preterm births prior to 32 weeks and prior to 37 weeks were of clinical interest. This table summarizes the analysis results for the co-primary and the secondary efficacy endpoints. The percentage of neonates who had at least one neonatal composite index event and the percentage of preterm births prior to 35 weeks were much lower than expected. The neonatal composite index was scored as yes in 5.4 percent and the 5.2 percent in liveborn neonates in Makena and the placebo groups, respectively, with a difference of 0.2 percent.

The percent of preterm births prior to 35 weeks was 11 percent and 11.5 percent in Makena and placebo groups, with an estimated treatment difference of minus 0.6 percent. The p-values for testing the difference between Makena and placebo were much greater than 0.05, meaning treatment differences were not statistically significant, and the estimated differences between treatment groups were close to zero for both co-primary endpoints. With respect to the two secondary endpoints of preterm births prior to 32 weeks and prior to 37 weeks, no Makena benefit was noted either.

The applicant conducted post hoc analysis to understand the lack of correlation between efficacy results observed in Trial 002 and Trial 003. Generally, FDA does not support subgroup analysis for inference of efficacy when the primary analysis result does not demonstrate efficacy. There are multiple reasons to not consider subgroup analysis to support establishing efficacy when treatment benefit in the overall population is not significant.

The major statistical reason is the inflation of type 1 error probability. That is the heightened probability of incorrectly concluding treatment benefit. When such subgroup analyses are used to search for evidence of a benefit, there is the high probability that any observed favorable subgroup results are due to chance alone. Therefore, FDA considers such analysis for hypothesis-generating purpose only, generally.

Nevertheless, FDA reviewed the applicant's post hoc analysis results to explore whether differences in key design aspects of Trial 002 and Trial 003 might clarify the divergent efficacy results. FDA compared the two trials with respect to demographics, baseline characteristics, and the responses in the placebo groups, then conducted subgroup analysis.

Trial 002 and 003 were nearly identical in design. However, when comparing the demographics and the baseline characteristics, notable differences exist between the two trials with respect to five factors, including black race; history of more than one previous spontaneous preterm birth; single or without a partner; substance use during pregnancy; and less or equal

12 years of formal education.

This bar graph shows the percentage of each factor in Trial 002, Trial 003, and the U.S. subgroup in Trial 003, which are presented by the gray, blue, and orange bars. Compared to Trial 002, Trial 003 had a lower percentage of black subjects, as well as subjects who had more than one previous spontaneous preterm birth, who are single or without a partner, or who used substances during pregnancy, and also had a lower percentage of subjects who had lower education levels. The U.S. subgroup of Trial 003 falls in between Trial 002 and Trial 003.

Comparing the placebo group in the two trials, the percentage of neonates who had at least one neonatal composite index event and the percentage of preterm birth prior to 35 weeks were higher in 002 and lower in 003, with the percentage in U.S. subgroup of Trial 003 falling in between.

In the applicant's briefing document, the overall baseline risk of preterm birth was assessed across the two trials using a post hoc composite risk profile constructed by the applicant. The components of this composite risk of five selected baseline factors was presented on an earlier slide, and show, again, here. Please note, black race and a number of previous preterm births are associated with higher rates of preterm births, but the other factors have not been consistently associated with an elevated risk of preterm births.

This bar graph demonstrates the percentage of subjects who had at least one of these factors. Trial 002 had the highest percentage, Trial 003 had the lowest percentage, and the U.S. subgroup of Trial 003 was in between. Based on all the comparisons between Trial 002 and Trial 003, the overall study population of Trial 003 appeared to be at a lower risk of preterm birth and neonatal events compared to Trial 002, and the risk of U.S. subgroup of Trial 003 falls in between.

FDA conducted subgroup analysis by region, race, and history of spontaneous preterm birth. For each of this subgroup analysis, the difference between Makena and the placebo groups was computed using two methodologies, a stratified Cochrane-Mantel-Haenszel method and shrinkage estimation through Bayesian modeling.

The subgroup analysis using CMH method evaluates a particular subgroup category independently from other subgroup categories, and it relies only on the data from that category. The Bayesian shrinkage estimation analysis evaluates all subgroup categories jointly and borrows information across subgroup categories to reduce the variability of the estimates and to prevent random highs and random lows. Conclusions from these two subgroup analyses was similar, but we present results from both methods for completeness on the following slides.

Another analysis was conducted by the composite risk profile at baseline. This slide shows the subgroup analysis results by region for co-primary endpoints. The region was defined as U.S. and non-U.S. The upper part of the display is for the neonatal endpoint. The lower part is for the preterm birth prior to 35 weeks. The numbers in the parentheses after each region are the sample size of Makena and placebo groups in that region.

The second and third columns are for the percentage of subjects who had an event of each co-primary endpoint by treatment group, followed by the estimated percentage difference between Makena and the placebo using stratified CMH method and shrinkage estimation in the fourth and the fifth columns, respectively.

On the right is the plot of the point estimates with corresponding 95 percent confidence intervals. The X-axis is for the difference between Makena versus placebo. The middle vertical line is the reference line indicating no difference between treatment groups. The left side of the vertical line is favoring the Makena group and the right side is favoring placebo. The blue lines are for the overall population results. The green lines are for the subgroup results estimated using stratified CMH method, and the red lines are for the subgroup analysis results using shrinkage estimation.

As you can see, the confidence intervals for the treatment difference for both co-primary endpoints, in both the overall population and in the regional subgroups, include zero, indicating no evidence of Makena benefit versus placebo, based on both analysis methods. Furthermore, all estimated differences between treatment groups are small and close to zero, with some estimates favoring Makena and others favoring placebo, and with the magnitude of the differences slightly smaller based on the shrinkage estimation method. In addition, there was no treatment by region interaction for each co-primary endpoint.

In summary, the Trial 003 subgroup analysis did not show Makena had a favorable treatment effect compared to placebo for either co-primary endpoint in either the U.S. or non-U.S. region, and the results do not provide support for regional differences, explaining the differences in results between Trial 002 and 003.

This slide shows the subgroup analysis results by region for the two secondary endpoints. Similarly, no evidence of a treatment effect was seen for the endpoints of delivery prior to 32 weeks or prior to 37 weeks in either the U.S. or non-U.S. region.

This slide shows the results by race, black versus non-black. The estimates of the difference are close to zero with all confidence intervals including zero. This race subgroup analysis did not provide evidence that Makena had a treatment effect on either co-primary efficacy endpoint in the black or non=-black subgroups. Similarly, no evidence of treatment effect was seen for preterm birth prior to 32 weeks and prior to 37 weeks within race subgroups.

This slide presents the subgroup analysis results by the history of spontaneous preterm birth, which was categorized as had one or had more than one previous preterm births. This subgroup analysis did not provide evidence that Makena had a treatment effect on either co-primary efficacy endpoint in either subgroups.

This subgroup analysis did not provide evidence that Makena had a treatment effect on either of the secondary efficacy endpoints in either subgroups, defined based on history of spontaneous preterm births. We also conducted additional subgroup analysis by substance use during pregnancy, marital status, and education level.

The results show no evidence of a treatment effect for Makena versus placebo on all the four efficacy endpoints in this subgroup as well. In summary, Trial 003 does not provide any evidence that Makena had treatment benefit in a particular subgroup, based on the five factors that differentiate the study populations in the two trials.

We performed another analysis based on the applicant's post hoc composite risk profile as mentioned in a prior slide. Three groups were defined. The first group includes subjects who did not have any of the factors included in the composite; the second group includes the subjects who had at least one factor; and the third group includes subjects who had add these two factors.

The bar graph on the left is for the neonatal composite endpoint. The height of the bar represents the percentage of neonates in each treatment group for that race group. The difference between the blue bar and orange bar represents the treatment effect of Makena versus placebo for the neonatal composite endpoint in that risk group.

As we see from the bar graph, when the overall risk increases on the X-axis, the percentage of the neonates who had at least one neonatal composite index event in that treatment group, increases as well. However, the treatment effect of Makena versus placebo on this endpoint did not improve. In the group of subjects who had at least two factors, placebo was favored instead.

Similar results were seen for the preterm birth prior to 35 weeks, shown in a bar graph on the right. This analysis does not support the applicant's point that, overall, the lower risk of preterm birth or neonatal events in Trial 003 explains the lack of efficacy in Trial 003, given that no suggestion of efficacy was seen even in the groups with higher risk levels.

In summary, Makena did not demonstrate a statistically significant treatment effect versus placebo on the co-primary efficacy endpoints of gestational age at delivery and the neonatal composite index in Trial 003, and estimated differences versus placebo were close to zero. Furthermore, exploratory analysis did not show evidence that Makena has treatment benefit within any specific subgroup in Trial 002.

Although the selected risk factors may have an impact on the overall percentage of subjects who had preterm births or neonatal composite events, there's no evidence in Trial 003 that these factors may impact the treatment effect.

This concludes my presentation. Next, my colleague Dr. Huei-Ting Tsai, will present drug utilization in the U.S..

FDA Presentation - Huei-Ting Tsai

DR. TSAI: Good morning. I'm Huei-Ting Tsai. I'm an epidemiologist at the Office of Surveillance and Epidemiology. The objective of my presentation is to provide an overview of hydroxyprogesterone caproate use in the U.S. to evaluate its public health impact. I will refer to hydroxyprogesterone caproate as HPC throughout my talk.

My presentation includes the result from two separate analyses. In each analysis, we estimated a number of patients with injectable HPC use and the possible reason for the use. The first analysis estimated utilization of injectable HPC in U.S. outpatient setting. This analysis provides national estimates of HPC use among pregnant and non-pregnant patients using proprietary database available to FDA.

The second analysis evaluated injectable HPC use during the second or third trimester in pregnancies with live births, using a distributed Sentinel database. We conducted this analysis in Sentinel distributed database because it gives us information specific to these two trimesters of pregnancy, whereas the result of the first analysis does not.

I will first present the results of our analysis, the estimated injectable HPC use in U.S. the outpatient setting. This figure shows the estimated number of 15- to 44-year-old patients, regardless of pregnancy status, with a dispensed prescription of injectable HPC from U.S. outpatient pharmacies.

Our results show an estimated 8,000 patients received a dispensed prescription for injectable HPC in 2014, and then increasing to 42,000 in 2018. Of note, these results do not include bulk powder forms of HPC typically used for compounding in pharmacy or clinics.

We also obtained diagnosis associated with injectable HPC use in 15- to 44-year-old women, using a database that captured monthly surveys from a sample of 3200 office-based physicians reporting on patient activity during one day a month. This dataset provides prescriber intended reason for drug use and our national estimates.

For HPC, an estimated of 50 percent of the reported diagnosis was for supervision for high risk of pregnancy of which 78 percent was specifically for supervision of pregnancy with a history of preterm labor. Of note, this diagnosis data do not provide information about history of preterm delivery, specifically; only a history of preterm labor.

Because progesterone has also been used for preventing preterm births, we also look at the possible reason for progesterone use. The data has showed that 14 percent of the reported diagnosis call for supervision of high risk of pregnancy, while female infertility was the most common diagnosis related to progesterone use.

The analyses have some limitations, but the estimated number of patients using injectable HPC came from retail and mail-order pharmacy setting and did not include estimates from hospital or clinical settings where this product may also have been used. We obtained diagnosis related to HPC from an office-based physicians survey. The survey data do not necessarily result in dispensed prescriptions.

In summary, while outpatient injectable HPC use increased over the extended time frame of 2014 to 2018, utilization of HPC was low. Further, the use of injectable HPC was largely associated with a diagnosis or history of preterm labor.

For the next action, I will present the results of our analysis, focusing on utilization of HPC during the second or third trimester of pregnancy only. We conducted this analysis using the FDA Sentinel distributed database. The Sentinel distributed database contains administrative claim data for most of the commercially insured patients. We included pregnancy with live births delivered during January 2008 through April 2019. We evaluated all product forms of HPC and progesterone.

To understand possible reasons for injectable HPC use, we searched for the presence of three related obstetrical conditions to HPC use. The narrow definition includes any of the three conditions here: a preterm delivery but only in a prior pregnancy; a preterm labor but only in a current pregnancy; or cervical shortening only in a current pregnancy. In contrast, the broad definition includes the same three conditions as a narrow definition, but each condition was not restricted to either prior or current pregnancy.

We identify a total of 3.4 million live birth pregnancies in the Sentinel distributed database. This figures shows the number of pregnancies using HPC or any progesterone during the second or third trimester per thousand pregnancies over the time frame of 2008 to 2018.

The red line demonstrate that in 2018, injectable HPC was used in about 13 per 1,000 pregnancies. The number of pregnancies using injectable HPC increased over the study time frame, although the use was low compared to the total number of pregnancies. The blue line represents the use of either HPC or progesterone during their second or third trimester, approximately 25 per 1,000 pregnancies, or less than 3 percent of live birth pregnancies in the Sentinel database.

This table shows the majority of pregnancies using injectable HPC had a related obstetrical condition. This data on the left column are our narrow and broad definition of a related or obstetrical condition. The next column over shows of pregnancies using injectable HPC, 73 percent and 98 percent had at least one related obstetrical condition by narrow and broad definitions, respectively.

This analysis has the following limitations. First, it's conducted among live birth pregnancies in the Sentinel distributed database, so it does not project nationwide use and may not be generalizable to women without a commercial insurance plan. Second, we did not examine the timing of a related obstetrical condition relative to injectable HPC use, so the presence of a related obstetrical condition may not necessarily be the indication for injectable HPC use. Lastly, our data did not capture medications that are out of pocket, which may underestimate the use of injectable HPC.

In summary, we found modest use of injectable HPC during the second or third trimester of live birth pregnancies and a high percentage of pregnancies using injectable HPC during their second or third trimester, and at least one related obstetrical diagnosis recorded before or during the pregnancy.

Now, I would like to turn my presentation to my colleague, Dr. Christina Chang, to give a summary presentation from FDA's perspective. Thank you.

FDA Presentation - Christina Chang

DR. CHANG: Good morning. My name is Christina Chang, and, again, I am a clinical team leader in the Division of Bone, Reproductive, and Neurologic Products, and I will be giving the summary remarks on behalf of the FDA review team. Because both the applicant and my FDA colleagues have already presented quite a bit of information, I will stay with the key concepts that we think will be the most germane to the panel's deliberation.

As a reminder of why the topic of today's meeting is of tremendous importance, we know that neonatal mortality and morbidity from preterm birth remains a significant public health concern. Preterm birth, defined as the delivery prior to 37 weeks of gestation, currently affects approximately 10 percent of all births in the United States.

To date, we do not have any drug products specifically approved by the FDA to reduce neonatal mortality and morbidity due to prematurity, and in clinical practice, progestogen, whether in synthetic forms or natural progesterone, have been used to reduce the risk of preterm birth. For women with a singleton pregnancy and who already have a prior spontaneous preterm delivery, current professional practice guidelines recommend starting progesterone treatment in the second trimester of pregnancy to reduce the risk of return preterm birth.

At this time, Makena is the only pharmacotherapy approved to reduce the risk of recurrent preterm birth. Based on its accelerated approval, Makena's indication states that it is approved to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton, spontaneous preterm birth.

The data that supported the accelerated approval for Makena came primarily from a single clinical trial sponsored by the NICHD, Trial 002, which the applicant and FDA already reviewed in depth. As you recall, delivery at less than 37 weeks gestation was evaluated as the primary efficacy endpoint in Trial 002.

Now, moving on to Trial 003, I'll point out that in this confirmatory trial, two efficacy measures were assessed. One was the clinical endpoint, namely the neonatal outcomes, and the other a surrogate endpoint, which is delivery at less than 35 weeks gestation. Delivery at 35 weeks gestation was chosen as a co-primary efficacy measure because this trial was initiated in 2009, two years before the agency came to the conclusion that late preterm birth was also consequential in terms of neonatal outcome.

The second point I want to call your attention to is the temporal distance between Trial 002 and Trial 003, with Trial 003 finishing 16 years after Trial 002 had been completed, and this illustrates the challenges in conducting large clinical trials in obstetrics, possibly because obstetrical practitioners tend not to deviate from existing clinical guidelines.

As you have already seen, Trial 003 was more than three times larger in size than Trial 002, with a U.S. subset in 003 almost approaching the entire 002 sample size. Makena did not differ from placebo for either the clinical endpoint of neonatal outcome or the surrogate endpoint by gestational age at delivery at 35 weeks. No difference between Makena and placebo was discernible for delivery at 32 weeks or 37 weeks gestational age.

In addition to the trial failing to meet its primary objectives, in no subgroup analyses that we conducted did we observe any difference between Makena and placebo, and those subgroups included race, previous number of spontaneous preterm births, and region U.S. versus non-U.S., as already discussed.

These findings bring us to the concept of what constitutes a standard for regulatory approval. According to the regulations, all drugs, including those approved under the accelerated approval pathway, must demonstrate substantial evidence of effectiveness, and the regulations refer to evidence consisting of adequate and well-controlled investigations, including clinical investigations.

You'll notice that I highlighted here in red the phrase, "adequate and well-controlled investigations" with the word "investigations" in plural, because the agency has generally interpreted the regulation as referring to more than one clinical study being used to support approval, and here in the case of Makena, we now have two adequate and well-controlled clinical investigations.

There is Trial 002, showing convincingly, based on a surrogate endpoint, that Makena reduced the proportion of preterm birth before 37 weeks. But now we also have a much larger trial, 003, that evaluated not only a surrogate endpoint but a clinical outcome as well.

In Trial 003, the size of the U.S. subgroup, which was 391, is almost as large as the entire cohort of Trial 002, which was 460. This larger trial, 003, also convincing, showed that Makena conferred no treatment benefit whatsoever. Importantly in Trial 003, Makena had no treatment effect based on the surrogate endpoint of delivery in less than 37 weeks gestation, the same endpoint that was positive in Trial 002.

Here's a schematic of the two regulatory pathways to obtain FDA's approval for a drug. On the left is the accelerated approval pathway, where the agency grants accelerated approval based on a surrogate endpoint that we believe reasonably likely to predict a clinical benefit.

The advantage of the accelerated approval pathway lies in providing patients earlier access to promising therapy without waiting for a large preapproval confirmatory trial. However, at the time of the accelerated approval, when the decision is granted, there's less certainty in being able to translate the observed treatment effect into clinical benefit. And because of the uncertainty, a post-approval, confirmatory trial is required to verify the clinical benefit.

Contrast that to the traditional approval pathway on the right. Typically, we rely on a clinical endpoint that directly measures how a patient in question, in our case, the neonate, feels, functions, or survives. Alternatively, if the surrogate endpoint has been validated to actually predict clinical benefit, the surrogate endpoint can be used to support the traditional approval.

What could explain the conflicting results from these two adequate and well-controlled trials? At the minimum, we envision these three scenarios. In the first scenario, Trial 002 was falsely positive, and in the second scenario, Trial 003 was falsely negative. In the third scenario, the discrepancy is attributable to differences that we haven't explained; and if the panel has other hypotheses, we would be interested to hear them as well.

So having discussed the results from both trials and the possible reasons for conflicting findings, we're asking the panel to weigh in on the questions of the day. With Makena, has substantial evidence of effectiveness been established?

As Dr. Nguyen showed this morning, we would like to hear the panel opine on two issues of concern. The first issue relates to the conflicting results, based on the surrogate endpoint, the gestational age at delivery. In Trial 002, less than 37 weeks gestation at delivery produced a positive result, but in Trial 003, the same surrogate endpoint produced a negative result, as did the less than 35 weeks delivery surrogate endpoint.

If the treatment effect, based on the surrogate endpoint of gestational age of delivery, is not substantiated, do we have substantial evidence of effectiveness to support approval? Furthermore, there is issue of concern number two; namely, the clinical benefit has not been verified. Here we have Trial 003 that did not show any improvement in neonatal outcome. Again, given this concern, can we conclude that there is substantial evidence of effectiveness to support approval?

With that, I'll conclude my presentation and bring the FDA's overall presentations to a close. The FDA team stands ready to respond to any questions the panel might have, and we look forward to a productive discussion.

Clarifying Questions to FDA

DR. LEWIS: Thank you. We'll now take clarifying questions for the FDA. If possible, please indicate the person to whom your question is directed, and if possible, the slide number from the FDA. Please remember to state your name for the record before you speak. I'm going to start actually with Dr. Gillen.

DR. GILLEN: Thank you. This is a question pointed at Dr. Guo, and thank you for presenting the subgroup analyses. That would have saved me the long, labored question that I asked previously of the sponsor, which I think should have been presented there.

Just in completeness, I guess, I agree completely and wholeheartedly with the FDA's position on subgroup analyses, but I think what we're looking for here is the elimination of some of these pathways. I agree with you it's either a false positive, a false negative, or it's some change in the distribution between the two subpopulations where we have effect modification.

So I guess in completeness of that, I know that you looked at the baseline risk factor sub analyses, but another way, possibly a more sophisticated and maybe slightly more efficient way to do that, is to, for lack of a better term, develop a propensity score for being in one study or the other, and then match or adjust on that propensity score.

Was that done? And if that was done, did it produce any similarities between the first trial and the PROLONG study?

DR. GUO: This is Jia Guo, statistician from FDA. We didn't do that propensity score analysis. We came up with this analysis using the composite risk profile, which was constructed by the applicant. So basically, we look at how many risk factors they have, kind of like generally define the risk groups, like no risk, and at least have one factor or two factors. I also look three factors, at least three factors. But of the subgroups, the size is too small, but the trend is still the same. You don't see the benefit even with the risk increases.

DR. GILLEN: I understand that the subgroups become small as you do that. That's exactly why I'm asking about, somewhat, the weighted average, if you will, of all the composites as you go through for the propensity.

So the answer is we haven't looked at that, but as we've broken down the baseline risk factors, we don't see anything that would bring the two studies closer together in terms of the effect that was observed.

DR. GILLEN: Right, yes.

DR. LEWIS: Thank you. Dr. Orza?

DR. ORZA: My question is for the FDA clinical reviewers about study 003, in terms of study 003 was 10 to 20 years later than 002. And what we wind up with is lower than expected rates of premature birth in both groups.

Could that be due to the fact that these women were being seen every week, of which seems, even in a high-risk pregnancy, is unusual. So there were all kinds of other aspects to their care. Could that be a factor for driving down both the premature birth and the negative outcomes in the babies?

DR. NGUYEN: Hi. Christine Nguyen, FDA. That's an excellent question. I would point out that the more intensive care usually occurs in all clinical trials, including 002 and 003. So I don't believe that there was, perhaps, a differential in the attention to the subject trials in 003 compared to 002.

DR. ORZA: There wouldn't be in terms of the attention paid, but 10 and 20 years later, do we know more or do we do different things in those encounters that could explain part of the difference between 002 and 003?

DR. NGUYEN: Christine Nguyen again. Again, this is why we have a prespecified protocol, and we did our best to keep the design and hopefully the conduct of those trials very similar, so that we can really try to isolate the effect of the drug itself and neutralize other factors, so to speak.

DR. WESLEY: This is Dr. Wesley. I'd like to just add that whatever changes occurred over time would be equally distributed between the control group and the intervention group, so that would not be any different between those two arms.

DR. ORZA: Is there any way to test for that?

DR. WESLEY: Well, the purpose of a randomized-controlled trial is to eliminate those factors.

DR. ORZA: Right. I understand that, but if something in the randomization failed or the misclassification across groups was differential, that would affect it even if there was randomization.

DR. CHANG: Christy Chang, FDA. Could I also add that when 002 was being conducted, the participating centers were from the MFMU Network, and these are tertiary academic centers. So patients were receiving the highest level of intense monitoring they possibly could have.

DR. LEWIS: Thank you --

DR. NGUYEN: To answer -- I'm sorry. I don't think we answered your question. Christine Nguyen again. So that's why we look at the demographics and baseline factors between the two treatment arms, and they were balanced, in actually both 002 and 003.

DR. ORZA: But not the factors of the clinicians or the centers, just of the patients. Is that correct?

DR. NGUYEN: Well, the centers that are invited and accepted to participate in the trial have to pass certain criteria, and they do have to follow the same protocol.

DR. GUO: This is Jia Guo, statistician. I just want to add one point, that in Trial 003, the randomization was stratified by site. I think any influence from the site could be evened out.

DR. LEWIS: Thank you. Dr. Bauer, and then Dr. Davis.

DR. BAUER: I have two quick questions, and I think the first one goes to Dr. Guo as well. That is that your analyses all used absolute risk, which is a perfectly valid measure of association, but it does make it a little bit difficult to compare that with what the investigators thought that they were going to get before the study, and that is their power calculation.

I'm just wondering if you verified the relative risk estimates that they have presented to us today, specifically the hazard ratio of 0.95 for the PTB less than 35 risk with a confidence interval of 0.71 to 1.26. The reason that I point that out is that the sponsor plans to exclude at least a 30 percent reduction in that outcome; therefore, the number of events really can't be used as an explanation for the fact that they didn't get positive results. In fact, they got the results that they estimated they would get based on their power sample.

So did you actually confirm those relative risk reductions?

DR. GUO: I didn't do the analysis, but we confirmed the data. The dataset we used is the same.

DR. BAUER: Okay.

DR. GUO: So the reason why --

DR. BAUER: There's no reason to think it would be wrong.

DR. GUO: -- yes.

DR. BAUER: Okay.

DR. GUO: The reason why we use absolute risk reduction is because when you talk about relative risk reduction, it is relative to the placebo background rate. But the two trials have very different background rates. So when you do the comparison across the two trials using relative risk reduction, even though they may have the same relative risk reduction -- just assume -- it means very different for the absolute risk reduction, which tells you the percentage of patients that actually can benefit.

DR. BAUER: I understand. That definitely impacts the public health. And I'm just wondering if someone at FDA could actually comment on the meta-analysis that was discussed in the sponsor's slide CO-27, with a point estimate of 0.58 and confidence intervals that went from 0.38 to 0.9.

Did FDA look at that meta-analysis, and was that part of the data that was reviewed in terms of what's the prior probability of one of the trials being wrong, either 002 or 003?

DR. NGUYEN: Hi. Christine Nguyen again. We did not formally analyze this meta-analysis, and it was used as a concept for Trial 002. Given that we have two adequately designed and powered studies, we wouldn't typically rely on something of lesser evidence, or let's say lesser strength of evidence such as a meta-analysis, particularly when you're looking at studies that were done in the '60s and '70s with very small sample sizes.

So I do not think that this meta-analysis would influence the way we interpret the evidence that we have today.

DR. WESLEY: One other comment. Dr. Wesley. Some of the indications for treating were very different in those studies. Some of them had cerclage and some of them had ruptured membranes. There were different scenarios and clinical scenarios, whereas these two trials were pretty much exactly alike.

DR. CHANG: Christy Chang from FDA. If I could also add to that, the CO-27, some of the studies were done evaluating preterm labor, not necessarily preterm birth, reduction risk.

DR. LEWIS: Dr. Davis, and then Dr. Reddy?

DR. DAVIS: Jon Davis from Tufts. Thank you for your presentations. I guess my question is, does it really have to be that one is a false negative and one is a false positive? I think you have two well-designed, well-controlled, well-conducted clinical trials done 15 to 20 years apart, in different populations, in different countries, with different outcomes, and the data are what the data are.

Preterm birth has clearly been a holy grail that we've all worked for most of our careers to try to see if we can figure out. And maybe we don't understand exactly why the trials are different, and we can't demonstrate it statistically, but I suggest that they are.

You're probably aware there was a large, randomized, multinational trial of antenatal steroids done recently, and underdeveloped countries finding that the steroids not only didn't help neonatal morbidity and mortality, but made it worse. So we're not going to stop using antenatal steroids because it was a different trial and doesn't necessarily pertain to this.

I'm just curious how you're looking at that. In other words, since the second trial, 003, is more recent, does that mean that it's more impactful? Should we be weighting these two trials differently? What are some of your thoughts about that?

DR. CHANG: Christy Chang, FDA. I'll turn the table back to you. That's what we want to hear from the panel.

DR. LEWIS: Thank you. Dr. Reddy, and then Dr. Smith.

DR. REDDY: I am trying to grapple with this data, having just delivered a 25-weeker on labor and delivery when I came on. This is really difficult, I agree. Both trials were well done, so what do we do with this data?

I wanted to go back to the gestational age of the qualifying pregnancy. I'd be very interested in understanding, between the Makena and the placebo group, the difference in additional days and weeks gained in pregnancy, because the MFMU did do a study of the Meis trial, and they showed 34 weeks and beyond, that those women who had an index pregnancy or qualifying pregnancy 34 weeks and beyond gained less time and the benefits were for women who are earlier than 34 weeks.

So I'd like to see this data focusing on the PROLONG U.S. population, not the non-U.S. population, because as you showed, it's closer to the Meis trial population, the PROLONG U.S. population, except, like I mentioned before, there's a 1 and a half week difference in the qualifying pregnancy, and it's like around 32 weeks. For the Meis trial, it was 30.6, and the PROLONG U.S. trial was 32.5. That difference in morbidity at that gestational age, what we can hear from our neonatal colleagues is huge.

So I'd like to understand the days gained. I'm not a biostatistician, but how could we understand that between Makena and placebo in the PROLONG U.S. population, specifically?

Then another question I guess I have to ask is the primary outcome, preterm birth less than 35 weeks, in the PROLONG U.S. population, it looks like there is 11 percent difference. It's 15.6 versus 17.6 in the placebo group, so that's a 2 percent difference favoring Makena. So that's about an 11 percent difference. What would the sample size have to be to demonstrate that difference? It's massive, but I'm just curious.

Then the last question is, did anyone ever talk about the UK and progesterone use? My impression is they don't use 17-OHPC; they use vaginal progesterone if they use anything.

Sorry, I kind of --

DR. NGUYEN: That's okay. Christine Nguyen again. Well, I can answer the UK question. We have not looked into the practice guidelines that the UK, number one, but there were not that many subjects enrolled from the UK, or if any, I'm not sure. As far as Trial 003, that certainly wouldn't affect the findings that we saw.

As far as looking at days prolongation in the U.S. subgroup, I have to ask my stats colleagues to see if we had done an analysis on that particular question.

DR. GUO: In addition to the five factors, the subgroups we presented here, I think also the applicant part, and we both looked at numerous other factors, including the gestational age at the qualifying delivery, and we couldn't find anything really convincing that Makena showed efficacy results in that specific subgroup related with the gestational age at the qualifying delivery.

Back to the U.S. versus the non-U.S. question, you see that 2 percent difference, but the thing is that is a point estimate. You cannot rule out that is different from zero, so that's the problem.

DR. REDDY: No, I was asking what would the sample size be needed to do that?

DR. GUO: Another question is, to other experts here, if you plan another study, that 2 percent is what you want to expect to see in that trial. So that's back to the power issue. When people are saying the study is underpowered, you need to know is underpowered for what; what's the hypothesis?

Trial 003 is preplanned to see that 30 percent reduction, the relative risk, translate to 6 percent absolute difference on neonatal, but the study is not underpowered to detect that difference, but you are not really powering your study to detect your observed results.

DR. REDDY: Yes. I was focused just on the

U.S. PROLONG patients and their outcome of 35 weeks.

DR. NGUYEN: Right. This is Christine. I think it's fair to say that to adequately power a study, to look at a 2 percent difference, we would need to know a few factors, what's the baseline preterm rate, and that would drive some of it. But certainly, assuming everything being equal and based on the findings we saw from 003, it would require a very large trial. And I won't put a number on it, but I can tell you it's going to be huge.

DR. REDDY: Right. So then, back to the other question, you said you looked at the age of the qualifying delivery. You said there was no significant difference, depending upon the gestational age of the qualifying delivery. So did you just look at the cutoffs, 35, 32, 37, or did you do it looking at time of prolongation?

DR. GUO: Jia Guo from FDA again. You can refer to the two tables in the FDA briefing document, in the appendix. We presented all the subgroup analysis results that we have looked at. From there, we look at the gestational age of qualifying delivery with 20 to 28 weeks, 28 to 32, 32 to 37, and 35 to 37. We couldn't find any convincing evidence.

Also, it's hard because we did a lot of post hoc subgroup analysis here, so it's really hard to -- sometimes you see -- just like I present on the slide, some evidence you see may be due to chance only because we have a really high probability of the type 1 error because there's no multiplicity control here. So even if you see some difference, that may be because it's just randomly -- it's just due to chance.

We are kind of looking for convincing, consistent evidence across the two trials and also across the two efficacy endpoints, together. We don't find any convincing evidence for the subgroup defined, based on the gestational age of qualifying delivery.

DR. LEWIS: Okay. One other person from the FDA; please state your name.

DR. BAER: This is Gerri Baer. I'm a neonatologist at the FDA, and I appreciate your question, and my mic just got cut. I'll address the endpoint question that you had about the date and the potential benefit in prolonged pregnancy by days, or even a week.

One of the biggest challenges that we have struggled with internally is how to best measure this. If you prolong a pregnancy, as you know, at 24 weeks by a number of days, that might be a clinical benefit, but if you prolong that pregnancy at 34 weeks by a number of days, there might be a benefit, but it's a much smaller benefit.

So if we could look and say that prolonging pregnancy by 5 days, it was effective and that was a true effect, that would be fantastic, but it's not a straight forward endpoint, and we continue to deliberate on how to look at gestational age because of that.

DR. LEWIS: Thank you. Dr. Smith?

DR. SMITH: Brian Smith. My question is for Dr. Chang. I think just to clarify your last couple of slides, after accelerated approval of a molecule, is the ultimate goal of the confirmatory trial, where you say verification of clinical benefit, to show benefit for the surrogate endpoint, preterm birth, for which the molecule has the indication, or the clinical endpoint neonatal morbidity?

DR. CHANG: I'm sorry. Could we pull up the last couple of slides from my presentation? I think it would be 12 and 13. Would it help if I go over the processes again?

Here again, I think Dr. Nguyen also mentioned this morning that we're grappling with two issues of concern here. The first issue is that from 002 and 003, we have different results based on gestational age at delivery, based on the surrogate endpoint alone. So now having reviewed these two clinical investigations, do we have enough to support substantial evidence for effectiveness, given the conflicting endpoint findings?

Next slide, slide 13. Now, with issue number two, clinical benefit was only measured in 003 and not in 002. So our question to you is, has the clinical benefit been verified as required by law?

DR. LEWIS: Dr. Shaw, final question.

DR. SHAW: This will be a verification question, and this will be for Dr. Chang. This was your slide 4, where I'm trying to understand your definition of substantial evidence of effectiveness.

And it seemed that you equated it with evidence that has to come from multiple clinical investigations. Is that the definition of substantial evidence? And if not, maybe you can clarify.

DR. NGUYEN: Hi. Christine Nguyen, FDA, and, actually, I'll take this question. That's another really good question. As written by law, when the Amendments Act of 1962 went through, that established the requirement to establish efficacy before approval because before 1962, all you needed was to show that your drug is safe enough.

The way that the law is written, we at FDA traditionally interpret that as requiring two adequate, well-controlled trials; so it's both the quantity and the quality of the trials. Now, the scientific principle behind the two trials is that they allow for independent substantiation of the drug's benefits, so substantial evidence.

That said, over the years, we have accepted -- or rather, we've considered trials from adequate and controlled single trials with persuasive findings -- and there are other criteria with that, but

I won't belabor that -- as substantial evidence. So the question is, we must require that you have two adequate and well-controlled trials, but when we do, we do need to take into account the data from both trials.

Does that answer your question?

(Dr. Shaw gestures yes.)

DR. LEWIS: Dr. Eke, last question.

DR. EKE: Thank you. So my concern was -- actually, I have a couple of them, but the one that concerned me the most was enrollment into Trial 003. After the advisory committee talked about this in 2006 and the FDA considered it and agreed to enroll patients into Trial 003, was there any kind of foresight that there were going to be problems with enrollment, given that when the drug gets approval, patient enrollment gets low, especially when societies endorse the medication?

Have there been other conditions in medicine, other trials, where subsequent trials did not enroll as much because of this situation? Because I feel it kind of played some role into why Trial 003 rolled out low in the U.S..

DR. CHANG: Christy Chang from FDA. I could try to answer some of that question from Dr. Eke. The second review cycle for Makena resulted in a not approval action, precisely because FDA had concerns about whether this trial could be feasible and could be completed successfully. So at the time of the 2009 action to not approve the application, we asked for the applicant to agree to enroll at least 10 percent of the total subjects from the U.S. and Canada, and also we needed them to show that the IRB approval could be obtained from at least 15 investigation sites.

Also, enrollment had to be greater than 15 subjects at any U.S. clinical sites. That was all built in, in a very thoughtful discussion at the time of the second review cycle, something that we did consider.

DR. LEWIS: Thank you. I know that some people have follow-up questions. There will be a little time after lunch to address those, as well as certainly some questions that begin to touch on things that are really discussion points, and we'll certainly build in lots of time for that.

We're going to now break for lunch. We will convene in this room in one hour, at 1:05, at which time we'll begin the open public hearing session. Please take your personal belongings with you at this time. Panel members, please remember no discussion of the meeting contents during lunch amongst yourselves, with the press, or any members of the audience. Thank you, and, panel members, there is a small conference room for us to have lunch.

(Whereupon, at 12:04 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:05 p.m.)

Open Public Hearing

DR. LEWIS: If people could take their seats, I'd like to begin the program again.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure transparency at the open public hearing, the FDA believes it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this information may include sponsor's payment of travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Would speaker 1 please step up to the podium and introduce yourself? State your name and any organization you are representing for the record. Welcome.

DR. ALADDIN: I'm Meena Aladdin, a health researcher at Public Citizen's health research group, and I have no financial conflicts of interest. Public Citizen strongly urges the committee to recommend that the FDA withdraw approval of Makena from the market, as there is a lack of substantial evidence that the drug is effective. Public Citizen has petitioned the agency to take such action.

During the initial review of the NDA for Makena, the lead FDA statisticians strongly recommended against the drug approval, noting the following regarding the single, seriously flawed, premarket, phase 3 clinical trial. From a statistical perspective, the level of evidence from study 17P CT002 is not sufficient to support the effectiveness of 17P. The primary reason is the absence of a second confirmatory study. Study 17P CT002 was not designed for drug approval. The statistician further says the results of the analyses of the 32- and 35-week endpoints suggests that false positive rates could be as great as 1 out of 40.

The PROLONG trial was a well designed, appropriately powered clinical trial, the design of which was mutually agreed upon by both the sponsor and FDA. It did not suffer from the multiple flaws seen in the premarket trial. Most importantly, the PROLONG trial failed to show a statistically significant treatment effect for Makena on any primary or secondary endpoint.

The FDA concluded, in summary, Trial 003 did not demonstrate a treatment benefit of Makena on reducing the neonatal composite index or the rate of spontaneous preterm birth prior to 35 weeks gestation, and nowhere is there evidence of a treatment benefit on the rate of spontaneous preterm birth prior to 37 weeks or 32 weeks gestation.

Furthermore, the FDA concluded that the unplanned exploratory subgroup analyses conducted by the sponsor do not provide convincing evidence of efficacy over placebo with any subpopulation, and there is no statistically significant interaction between Makena and any of these risk factors.

Maintaining approval of Makena in the absence of any demonstrated clinical benefits would make a mockery of more than a 50-year FDA legal standard, requiring substantial evidence of a drug's effectiveness. Therefore, Public Citizen strongly urges the committee to recommend that the FDA withdraw approval of Makena from the market, as it fails to provide any clinical benefit. Thank you.

DR. LEWIS: Thank you. Speaker number 2, please.

DR. URATO: Hello. I'm Dr. Adam Urato. I'm an obstetrician/gynecologist and the chief of maternal fetal medicine at Metro West Medical Center in Framingham, Massachusetts, and a co-petitioner with Public Citizen. I have no financial conflicts of interest.

I'm here today to strongly urge the FDA to withdraw approval of Makena, based on the recent definitive findings that it is ineffective for preventing preterm birth. As a clinician, I counsel patients with prior preterm birth regularly. I have delivered lots and lots of babies in my career, many of whom were premature.

Preterm birth is a major problem caused by many different factors, but this drug is not the solution. Approval of this drug was based on a single study that had many significant flaws, relied on a surrogate efficacy marker, and did not show meaningful clinical benefit. Furthermore, the FDA mandated postmarket study, the PROLONG trial, showed Makena to be ineffective in preventing preterm birth. This makes continued use of this drug indefensible.

I must add here that it was noted today that the American College of OB/GYN and Society of Maternal Fetal Medicine have recently made statements supporting Makena. It should be noted that these groups are funded by AMAG Pharmaceuticals.

Proper counseling of patients involved reviewing risks and benefits of Makena. The risks are injection site reactions, possible increased risk in pregnancy complications, including stillbirth, and unknown long-term adverse effects from in utero exposure. And benefits, the drug has no proven benefits. I'm certain that when patients are properly counseled, they would never agree to be injected with it.

I would also like to highlight that the drug is a synthetic hormone that crosses the placenta and enters into the fetus during development. It enters cells in the fetal brain, the reproductive organs, and throughout the body. The long-term effects of a fetal exposure to synthetic hormones are not known, but we have been down this road before.

Diethylstilbestrol, DES, was used by millions of women across three decades. Fetal exposure to this synthetic hormone resulted in severe and terrible long-term health effects for many who were exposed. Part of the tragedy of DES is that despite how it was promoted to the public, the drug was not effective in preventing abortion, miscarriage, and preterm birth.

The lesson we learned from DES was clear. We would never again expose pregnant women and their developing babies to a synthetic hormone that did not have good evidence of proven effectiveness, and yet, 50 years, we're making that same mistake. History will judge us poorly if we do not pull this drug from the market and if we continue injecting this synthetic hormone into pregnant women. Thank you for allowing me to speak to you today.

DR. LEWIS: Thank you. Speaker number 3, please.

DR. FOX-RAWLINGS: Thank you for the

opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Stephanie Fox-Rawlings, the center's research manager. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policy makers. We do not accept funding from drug or medical device companies, so I have no conflicts of interests.

The mortality and morbidity associated with preterm birth is a serious issue, which puts children at risk for long-term developmental problem. Treatments that decrease risk for preterm birth and improves neonatal outcomes are needed, but any drug given for this purpose must accomplish this purpose without undue risk.

Based on the evidence being discussed today, there is not consistent evidence that Makena actually does this. When the FDA approves a drug, even if it's based on accelerated approval, there's a lot of pressure to keep it on the market regardless of postmarket data, but in this case, there's no evidence that this drug decreased neonatal death or morbidity, which are the most important outcomes and the outcomes required for full approval.

Although the first study showed a statistically lower rate at birth before 37 weeks, from 55 percent 37 percent, that could still have occurred by chance. In the confirmatory study, the rate of births before 35 weeks was 11 percent instead of 11.5 percent, and a similarly small difference for births before 37 weeks, both of which were not statistically significant and would not have been sufficient merit approval. At the same time, there were almost twice as many stillbirths for babies whose mothers took Makena, 2 percent versus 1 percent in the first trial and 1 percent versus half a percent in the confirmatory trial.

FDA's reputation depends on admitting when a promising new treatment is later found to be not so promising. The purpose of an advisory committee meeting is to provide objective advice to encourage FDA to stick to the science and admit when there is not evidence that the benefits outweigh the risks for a product, such as the case with Makena.

At most advisory committee meetings, the sponsors recruited clinicians and/or patients to speak on behalf of their product. As scientists, physicians, and patient and consumer representatives, please keep in mind that just because a patient has a good outcome after using a medical product, it does not mean that the medical product caused that good outcome.

As you already know, randomized, double-blind, controlled clinical trials give us a much more accurate assessment of whether a product works than just antidotal information, however heartbreaking or compelling. Makena may possibly reduce preterm births for some pregnant women who have previously had a spontaneous preterm birth, however, with the conflicting results in the two studies, the sponsor needs to determine if there is a subgroup of pregnant women who are likely to have benefits that outweigh the risks, and if so, to be able to define that group for an indication.

But the benefit also has to be clinically meaningful. The sponsor needs to demonstrate a clinically meaningful impact for neonates, such as improved survival or health outcome. Unless the sponsor can do these two things, approval for this product should be rescinded. Thank you.

DR. LEWIS: Thank you. Speaker number 4, please.

DR. HILL: Good afternoon. I'm Dr. Washington Hill from Sarasota, Florida, and I've practiced OB/GYN or MFM 55 years. AMAG supported my travel and hotel, but not my time or my opinion. Preterm birth is a significant problem in the U.S., especially in African Americans.

In 2003, Meis reported it could be reduced through weekly injections of 17P. Subsequently approved and marketed as Makena for patients with prior spontaneous preterm birth. Last year, ACOG reaffirmed patients with this indication should be offered 17P, now a current clinical guideline. Last Friday, ACOG reaffirmed again it is not changing these recommendations.

17P should not go away because of PROLONG, as it has been a part of the OB/GYN's care prevention of preterm birth for years, resulting in less preterm birth, especially in African Americans disproportionally affected and at significant risk, as Dr. Owens pointed out this morning.

The populations of these studies were markedly different. Putting a finer point on it, demographics matter, as pointed out in the Meis study conclusion. Her study included the highest of the high risk for preterm birth: black, under stress, or unmarried, smokers, underweight, history of previous preterm birth, and no prenatal care; far different than PROLONG patients, who were predominantly neither American, or African American, but European and without social determinants of health, so important in causing preterm birth.

Let's not eliminate this effective intervention from our preterm birth prevention toolbox because of PROLONG, a non-comparable, negative trial. If we do that, we would be ignoring results of the landmark positive Meis study, the 2019 positive meta-analysis, and over 15 years of positive clinical use showing safety and efficacy in reducing preterm birth. We would also be doing less than we could for our patients with prior spontaneous preterm birth.

Makena is the only FDA-approved treatment for patients with prior spontaneous preterm birth and needs to be available for us doing all we can to prevent preterm labor and preterm birth. There is insufficient evidence and data today for its removal. We need 17P, as pointed out Friday and today by SMFM, so we can make the best decision with our patients and choose what is in their best interest. Thank you for your time.

DR. LEWIS: Thank you. Could we hear from speaker 5, please?

DR. BARTON: Good afternoon. I'm John Barton, a maternal fetal medicine specialist in private practice in Lexington, Kentucky. For disclosure, AMAG Pharmaceuticals has agreed to pay for my travel expenses to this meeting. I did not, however, have a financial arrangement concerning my presentation, nor do I have a financial interest in the outcome of this presentation.

I've been in practice in our community hospital for 27 years. Three of the greatest problems in current obstetrical care are hypertension, hemorrhage, and prematurity. Over the past five years, obstetrical societies have made great end roads in reducing complications from hypertension and hemorrhage. Prematurity, however, remains a significant clinical problem.

Several of our previous treatments for prematurity prevention have been withdrawn from use, including ritodrine, terbutaline, and prolonged IV magnesium sulfate therapy. Intramuscular 17-alpha hydroxyprogesterone has been shown to be beneficial in reducing the recurrent risk of spontaneous preterm delivery as one of the few approved interventions to reduce the incidence and burden of spontaneous preterm delivery in our patients and on our healthcare system.

In my office electronic medical record, I have a standard counseling note for patients with a history of a previous spontaneous preterm delivery. I state that a spontaneous preterm delivery in a previous pregnancy is well documented as placing the current pregnancy at risk for prematurity. I then discuss some of the specific theories as to why 17P may result in reduced rate in preterm delivery.

Finally, based on the literature and some of my own previous publications concerning 17P therapy, I affirmed that women who are candidates for this therapy should have progesterone supplementation initiated between 16 and 24 weeks gestation and continued through 36 weeks gestation.

Finally, in providing an analogy, in protocols to reduce infection in hospitals, patients transferred with an IV or to have their IV removed and replaced once are performed under known sterile conditions.

From a clinical standpoint, it's important, however, not to remove a good IV until you've replaced it with one of equal or better quality. Similarly, as a practicing physician at a community hospital, I believe we should be reluctant to remove FDA-approved 17P therapy unless we have another therapy of equal or greater ability to reduce the recurrence, risk, and burden of spontaneous preterm delivery. Thank you.

DR. LEWIS: Thank you. Speaker 6, please.

MS. OSMAN: Good afternoon. My name is Robin Osman. Danielle Boyce asked me to read her testimony on her behalf. She planned to be here today, but unfortunately had a last-minute issue arise, and had to stay home to care for her premie today. This is her testimony.

"Good afternoon. My name is Danielle Boyce. I'm here to share my personal perspective. I have been on an FDA advisory committee and have served as an FDA patient representative. I have been in your shoes and appreciate the weight of the decision that you need to make. I consider it my civic duty to participate because I have a premie.

"I want to share with you my belief that pregnant women should have access to Makena if they are at risk for having another preterm birth. My son Charlie was born in 2010 at 34 weeks after a significant struggle with preterm labor.

"When Charlie was born, I was under the impression that 34 weeks was no big deal. That is the public perception, but that is not the case. Despite his decent birth weight, 5 pounds 8 ounces, Charlie had many of the conditions of prematurity, including respiratory distress syndrome, jaundice, breastfeeding challenges, and temperature regulation problems. We faced a 10-day NICU stay.

"The long-term consequences of Charlie's premature birth continue to this day. He developed infantile spasms, a catastrophic form of epilepsy, has had two brain surgeries, autism, and has profound cognitive impairment. He was born at 34 weeks, but I will take care of him for the rest of his life.

"I did not take the decision to have another child lightly. I reviewed the safety and efficacy evidence on my own. I have a master's in public health with a concentration in epidemiology and spoke to top maternal and fetal medicine doctors. I asked for their clinical experience. All agreed that I should take Makena.

"I took their advice, and to my amazement, 34 weeks came and went, and I was still pregnant; then 35, 36, and 37 weeks. With each day that went by, all I could think of was the organ development, weight gain, and all the other benefits of keeping him cooking one day at a time. In May 2017, I had a full-term, 7-pound baby boy named Nash. I remember looking down at his perfect little face in the delivery room and saying, 'Thank God I took those shots.'

"I don't know for sure that it was Makena that gave me a full-term baby, but given the lack of side effects, I would never forgive myself if I hadn't done everything that I could possibly do to prevent preterm birth. If I ever have another child, I will be devastated if I do not have the means of potentially preventing another premature birth. Thank you very much for your time. I wish you the best in your deliberations."

DR. LEWIS: Thank you. Speaker 7, please.

DR. NORTON: Thank you. Good afternoon. My name is Dr. Mary Norton, and I'm a practicing perinatologist and director of maternal fetal medicine at UCSF. I'm here representing the society for maternal fetal medicine as past president and current chair of the publications committee. I have no conflicts of interest to disclose.

We all know that preterm birth is a major public health problem, that prior preterm birth is a significant risk factor, and 17P has been used in an attempt to decrease the risk of recurrence. In 2003, Meis, et al. reported a 34 percent reduction in recurrent preterm birth in women given 17P and also demonstrated reductions in some neonatal complications.

After the Meis publication, ACOG and SMFM have recommended progestogens for women with a prior spontaneous preterm birth. In 2017 SMFM reaffirmed a recommendation that pregnant women with prior spontaneous preterm birth receive weekly 17P. However, as we've heard today, the PROLONG study found no benefit of 17P compared with placebo in reaching either their primary outcomes.

An important difference between PROLONG and Meis involve the study populations. As we have heard over the course of the day, PROLONG patients had a much lower baseline risk, and this complicates interpretation of the results. Both Meis and PROLONG found no increase in congenital anomalies or evidence of teratogenic effects. Long-term outcomes are unknown, although long-term adverse effects have not been reported.

Preterm birth is clearly a complex disorder. While factors such as race and the number and gestational age of prior preterm births are associated with recurrence, specific criteria to quantify risk, the interaction between risk factors, and optical management of at-risk women are not well understood. Patient level criteria to determine potential response to 17P have not been confirmed.

Based on the evidence of effectiveness of 17P demonstrated in the Meis study, which is the trial with the largest number of U.S. patients, SMFM believes that providers should continue to have access to 17P for women at high risk of recurrent spontaneous preterm birth. The risk-benefit discussion with such women should incorporate shared decision making, taking into account the lack of short-term safety concerns, but uncertainty regarding benefit.

We recognize that 17P is associated with significant healthcare costs, discomfort from the injection, and extra patient visits, and that long-term potential maternal and neonatal effects are unknown. The lack of benefits seen in PROLONG raises questions regarding the efficacy of 17P, and SMFM recommends that additional studies are needed to determine if there are populations or subgroups in which 17P may provide a benefit. We are aware of ongoing studies, including the large IPD meta-analysis discussed today, and will continue to closely follow advances in this area to assure optimal care for women and provide guidance for maternal fetal medicine subspecialists. Thank you.

DR. LEWIS: Thank you. Speaker 8, please.

MS. CHIAVERINI: Hello. My name is Amelia Chiaverini. I will be reading the testimony of Anabel Jimenez-Gomez, as she couldn't be here today.

"I support Makena for families that are considering using it. I really wanted to be here in person because Makena helped me bring home the baby that my husband and I so wanted and prepared for. After losing my first baby at 20 weeks to preterm birth, it was critically important to me to do everything I could to make it to full term.

"My first pregnancy was a rough one. When I was 20 weeks along, I was feeling lower back pain and was really uncomfortable. After an ER visit, the doctor said a UTI was the cause of my discomfort. I was prescribed antibiotics and muscle relaxers. Within

24 hours, I got a lot worse and ended up back in the hospital. I went into preterm labor.

"Our baby girl was stillborn. The whole birth was a very traumatic experience, which I still have nightmares about. The doctors ran tests but couldn't find an exact cause for my preterm birth. They asked, 'Did you hurt yourself? Did you fall, lift something heavy?' They couldn't pinpoint exactly what caused it. It was really stressful to both my husband and I.

"About five months later, I found out I was pregnant again. We were scared and wished we had waited a little longer. My doctor told me we would take different precautions because my pregnancy was considered high risk. I had biweekly doctor visits with a different goal for each appointment. The main goal was to make it to 20 weeks, so my doctor suggested Makena.

"At first, I was terrified to try something new. She gave us statistics and also let us know that other women had gone through similar experiences. This gave us hope, so we decided to try it out. The medical team was really good at teaching my husband to administer the shots. He administered them for me at home once a week for 16 weeks. They were painful, but looking back, I realized it was all worth it.

"I delivered my baby boy, Mateo, at 39 weeks and 5 days, which was just 2 days before his due date. The delivery was a little less stressful, but I had an amazing team that could take care of me and calm my nerves the entire time. It took 2 days of labor, but Mateo finally came out in a smooth delivery. He was 8 pounds even, 20 and a half inches long.

"Even though it was scary to lose my first baby and then go through my second pregnancy, I'm really glad that we did, and have Mateo today with the help of Makena. I didn't know if it would work or not, but I was willing to try anything that could help me carry a pregnancy to full term. Makena had a significant impact on us.

"I believe Makena can help a lot of women carry their rainbow babies to full term safely. I recommend it to women who have gone through a similar experience as mine. Thank you for listening to my story. Anabel Jimenez-Gomez."

DR. LEWIS: Thank you. Speaker 9, please.

DR. MOLEY: Hi. I'm Dr. Kelle Moley. I'm the chief scientific officer and senior vice president of the March of Dimes. Before this, I was at Washington University in St. Louis as a practicing OB/GYN for 30 years.

On behalf of the March of Dimes, I'm pleased to provide comment on the state of maternal and child health in the U.S.. March of Dimes, a nonprofit, nonpartisan organization fights for the health of all moms and babies. We advocate for policies to protect them. We work to radically improve the health care they receive. We pioneer research to find solutions, and we empower families with programs, knowledge, and tools to have healthier pregnancies.

March of Dimes does not offer recommendations on medical treatments, however, we do rely upon the leading medical societies and organizations, such as ACOG and SMFM to make such recommendations. March of Dimes then supports and communicates these to all stakeholders.

We do this all because today in America, we face an urgent maternal and infant health crisis. Approximately every 12 hours, a woman dies due to complications resulting from pregnancy, and more than 50,000 others experience dangerous complications that could have killed them, making our country among the most dangerous places in the developed world to give birth.

For women of color, the dangers of giving birth or even more acute. Black mothers are more than three times as likely to die from pregnancy related to complications as white peers. But this crisis isn't only about moms; it's also about their babies. It's about the continuum of care for all moms and babies as their health is intertwined. In fact, the U.S. prematurity rate may have increased for the fourth consecutive year. Each year in the U.S., 22,000 babies die; that's 2 babies every hour, and approximately 1 in 10 babies are born preterm.

Preterm birth increases from 9.63 percent in 2015 to more than 10 percent in 2018. In a few days, on November 1st, we will mark the start of Prematurity Awareness Month, and November 4th will be the nationwide release of the March of Dimes report card, which highlights the collective factors that contribute to maternal and infant mortality and morbidity. The report card grades the nations, all states, and the District of Columbia and Puerto Rico, based on the latest data on preterm birth rates, and spotlights the issues contributing to poor health.

March of Dimes' mission is to fight for the health of all moms and babies. Consistent with our mission, when an evidence-based intervention like 17P becomes available, our overwhelming interest is to increase access so that all eligible women receive it no matter what their income or insurance status. For many years, we've advocated for access to 17P for all eligible women due to the evidence about its effectiveness in reducing preterm birth. We've educated women and providers about the importance of 17P.

In conclusion, the U.S. needs to be aggressively paying attention and looking for ways to solve the national maternal and infant health crisis of increasing preterm birth rates. We stress the need for more therapies, more solutions, more devices, and everything possible to address the birth crisis we're experiencing.

Therapeutics for preterm births such as 17P and all future therapies should be available so that physicians can use their discretion to prescribe them to the correct subset of patients with these complex and multifactorial conditions.

The accelerated approval pathway is critical to achieving this goal, as preterm birth disproportionately affects underserved populations in the U.S. We applaud the FDA's history of continuing effectiveness therapies of preterm birth as worthy accelerated drug approval, and trust this will continue to be its practice.

It's essential that the U.S. do everything possible to ensure that moms and babies are healthy. We thank you for the opportunity to comment during today's meeting. March of Dimes stands at the ready to serve as a resource to this committee.

DR. LEWIS: Thank you. Speaker 10, please.

MS. JOHNSON: My name is Allison Johnson. My travel is being reimbursed by AMAG Pharmaceuticals, however, I'm not being compensated for my time, and this testimony is my own.

I'm a mom to three beautiful little boys. In July of 2018, my third son Andrew joined our family, and I credit Makena with helping to bring him into our lives. But in order to tell my story around Makena, I need to take you back to the birth of our second son Teddy.

My water broke at 34 weeks 6 days with Teddy. It was a very complicated delivery. The doctors tried for nearly 40 minutes to first get a spinal, then epidural in place for my repeat C-section. Both were unsuccessful, which eventually led to me being put under general anesthesia. His birth was traumatic, and this is a story that I wait to tell my pregnant friends until after they've given birth. But I know we were lucky. Teddy was born at 5 pounds, 12 ounces, and he thankfully had no complications. He required some early intervention services up until the age of 2, but now he's a healthy, thriving, and rambunctious 4 year old.

Following Teddy's birth, if you had asked my husband and I whether we were done having kids, I almost always said yes. I'd been told almost right away that once you have a spontaneous preterm birth, your chances of having another are much higher. However, my husband and I knew in our hearts that our family wasn't complete. There was still a missing piece, but I was nervous about another pregnancy.

So my husband and I decided to meet with my doctor, who was confident that I could have a successful pregnancy if we chose to have another child. She explained to us that in order to help with preterm birth, there was an injection, Makena, that she would recommend. My husband and I talked through our options following that appointment, and we decided to try to expand our family once more.

A few months later, I was pregnant with Andrew, and I began the Makena injections as prescribed. My husband learned from the nurse how to administer them at our home, and each week, from 16 weeks to about 35 weeks, he helped give me those shots in our upstairs bathroom, and it actually became a family affair. Sometimes our two other boys wanted to help, too, and they were in charge of the band-aids.

I was fully prepared for Andrew to arrive before my scheduled C-section date. I had my bags packed and ready to go by 32 weeks, but it never happened, and he was born at a healthy 8 pounds, 1 ounce. He had made it to full term, and I thank Makena for helping us to get there.

I'd like to ask that the FDA take my experience into consideration when you evaluate Makena and its effectiveness. While I wasn't in either of the clinical trials discussed earlier today, Makena helped me and my baby, and I hope that you will give that hope and chance to other anxious and excited families as well. Thank you.

DR. LEWIS: Thank you. Speaker 11, please.

MS. JOHNSON: So again, my name is Allison Johnson, and I will be reading the testimony of Glory Joseph.

"This is my story and my most recent encounter with Makena. Through the use of Makena injections, I was able to deliver a healthy baby girl. Because of the success I had my husband and I have decided that we will be using Makena again once we decide to become pregnant. Because I was unable to present today, I have attached some photos of my beautiful family, including Grace Marie Joseph, whom we often refer to as our Makena baby, which I will be sharing with you today.

"With my first ever pregnancy, everything seemed to be going well, but too soon into my pregnancy, I started experiencing painful contractions. I went to the ER. All tests were normal. Ultrasound had shown a viable fetus. I was discharged home with undiagnosed, unknown cause for my symptoms to experience premature rupture of membranes shortly, 4 days later, without any known cause.

"The loss came just a week after we had announced the pregnancy and made it public. It was almost shameful to have to go and tell people we weren't pregnant anymore. I'm fortunate to have a very supportive family and friends who helped me get through it, but it was definitely a tough time. I'd get emotional seeing other pregnant women or other babies around the time we had delivered.

"My husband and I both really wanted to build a family, so we decided to try again. In the back of my mind, I was scared I couldn't carry a full-term pregnancy. We knew we wanted another child, but it was scary. When I became pregnant again, I asked my general OB to refer me to a high-risk specialist because of my history. She agreed, and I saw the specialist at 12 weeks.

"She told me that there was a medication we could try once I reached 15 weeks, Makena. I discussed it with my husband and family and did my own research. There didn't seem to be many side effects, so I decided I may as well try it and see if it worked. Once I got to 16 weeks, it was both scary and exciting. I knew there was hope once I started taking Makena, but I wondered if the shop would even work for me.

"The major side effect that I experienced was pain at the site of the injection. With the combined continuous prenatal care, plus weekly Makena up to 36 weeks, I was able to deliver a healthy, beautiful, baby girl, Grace Marie, at 37.4 weeks. She weighed

7 pounds 10 ounces.

"I would highly recommend Makena to any other mothers like me who had preterm births. Thank you for this opportunity to share my story. I truly support Makena. Glory Joseph."

DR. LEWIS: Thank you. Speaker 12, please.

DR. JACKSON: Hi. I'm Marc Jackson. I'm an MFM and the vice president for education at the American College of Obstetricians and Gynecologists. We represent more than 58,000 physicians and other partners dedicated to advancing women's health. I have no personal financial relationships to report, but in 2019, AMAG provided a grant to ACOG to support medical student projects, but not our practice activities or our clinical guidance.

In the time since we submitted our written comments to the committee, the PROLONG trial, Trial 003, has been published. This multinational RCT of patients with a prior preterm birth found no difference in recurrent preterm birth prior to 35 weeks or the neonatal composite outcome between women treated with 17 hydroxyprogesterone caproate or placebo.

Several comments about the study need to be made. Although the study design was similar, the PROLONG study 003, as executed, was fundamentally different from the MFMU trial, 002, that was published back in 2003. This is evidenced by the large difference in the baseline preterm birth rates less than 37 weeks, 23 percent versus 55 percent.

Thus, the study population in Trial 003 was a lower risk population than in 002, and substantially so. Differences in the 002 and the 003 populations, with respect to the number of prior preterm births, smoking rates, social, ethnic, and racial differences, and national differences in healthcare delivery, makes plain at least some of the discrepancy. Because of these differences, a head-to-head comparison of the two trials is inappropriate.

Despite the PROLONG study's findings, the results do not indicate that the initial U.S. based Trial 002, the MFMU trial -- they do not indicate that it was wrong or that its conclusions are misleading in some way. Rather, the data from Trial 003 should be examined as part of the body of literature on placebo-controlled trials using 17-OHP in preventing preterm birth.

It is that broader examination of the literature that should be used to determine whether there is substantial evidence of effectiveness, not the recent Trial 003 alone. Until a comprehensive analysis can be done, ACOG will continue to recommend that physicians offer 17-OHP to pregnant women with a prior preterm birth.

We will continue to monitor this topic and to evaluate additional data and analyses when they're published, and we'll address new findings in the review process for our clinical guidance as needed. Continued access to 17-OHP is important for our patients, and ACOG respectfully encourages this committee to table any decision on whether to withdraw drug approval until a complete meta-analysis using patient-level data from all the available studies can be done. Thanks for the opportunity to speak.

DR. LEWIS: Thank you. Speaker 13, please.

MS. CHIAVERINI: Thank you for giving me time to speak today. Again, my name is Amelia Chiaverini.

I am being reimbursed by for my travel expenses by AMAG because I wanted to personally tell you about my experience with Makena. I believe this product must be available to women that face similar situations to prevent further emotional and financial stress. I am taking time away from my responsibilities as a mother and wife to be here today. It is that important to me.

In January 2011, I went into preterm labor. I was given several medications to help me and my baby. Unfortunately, after 5 days, I was in labor again and was rushed to the operating room for an emergency C-section. On February 2nd, my first son was born at 27 weeks, 1 day, weighing only 1 pound 14 ounces. It was a terrifying experience.

I briefly saw Duncan before he was transported to a children's hospital. He was so tiny, and the tubes seem to engulf him. My room was near the waiting area to reduce the constant reminder of his absence from the maternity ward. Duncan spent 3 and a half months in the NICU. He received many medical interventions, including oxygen, phototherapy, feeding tubes, PICC line, blood transfusions, and a surgery.

I had to get past all these issues to focus on giving Duncan care and breast milk. The emotional toll was much more difficult to overcome. Here are some memories that stick with me: finding out that a young mother I was talking with had experienced the NICU two times previously; hearing the anguished cries of grief from a mother because her child had died while I quietly held my tiny boy and cried for her and for me; and the worst day, March 21st, when the staff had to manually resuscitate Duncan. Though it was stressful for me and my family, we made it through. Duncan came home on May 19th weighing 8 pounds 1 ounce.

Before my next pregnancy, my husband and I talked with my obstetrician about preventing preterm birth. He told us about Makena. Together, we decided it was a great option for us because it did not come from a compound facility. By receiving the shots, I felt empowered. I was doing all I could to help my baby, and it also eased my stress. On December 12, 2013, Donovan was born at 38 weeks 6 days, weighing 6 pounds 7 ounces. I believe Makena made his full-term birth possible.

There are many women with similar stories that need Makena to help prevent preterm birth, which could also reduce their emotional and financial stress that preterm birth creates. Makena should be available to these women as it was for me. Thank you again for letting me tell my story with Makena.

DR. LEWIS: Thank you. Speaker 14, please.

DR. RANDELL: Good afternoon. My name is Dr. Michael Randell. Thank you for allowing me to speak to you today during the public hearing on Makena and 17P. In my brief comments, I will focus on my concerns if the FDA decides to withdraw Makena from the market. I do not have any conflicts. AMAG Pharmaceuticals has paid my travel to be here, but I have not been compensated for my time.

I am an OB/GYN in Atlanta, Georgia. I'm a fellow of the American College of Obstetricians and Gynecologists and a diplomat of the American Board of Obstetrics and Gynecology. I've been in private practice for more than 24 years following my training. I've delivered thousands of babies and have managed preterm labor, including using progesterone for pregnancy prolongation in my patients with a documented history of a previous spontaneous birth at less than 37 weeks of gestation.

While preterm birth affects about 10 percent of births in the United States, Georgia's preterm birth rate is higher than the national average. Therefore, preventing preterm birth in my patients has been a major focus of my Atlanta practice. I began using 17P in 2008 following the recommendation of ACOG and the Society for Maternal Fetal Medicine that stated, "Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes."

Last Friday, ACOG announced it is not changing its clinical recommendations at this time, and it continues to recommend offering 17P.

In each pregnancy, there are two patients, the mom and the baby. This precious package requires OB/GYN to provide their patients with the safest and highest quality of care. I was always concerned with having to obtain compounded 17P that is not made under FDA-approved conditions, so when Makena was approved, I immediately began prescribing Makena instead of compounded 17P. I've observed several of my patients not have another preterm delivery when using Makena, and I saw it improve neonatal outcome. In my experience, Makena is effective. I've seen the benefits.

Few physicians understand the difference between compounded and FDA-approved medications. In 2014, I wrote an article, Risks and Liabilities of Prescribing Compounded Medications. In this article, I stated, "The potential for patients to suffer serious harm from substandard medications prepared by compounding pharmacies is very real."

Healthcare professionals should be aware of the potential liability to which they expose themselves whenever they prescribe or administer compounded products. Patients injured through the use of compounded medications that do not meet FDA requirements for safety, efficacy, or quality may file lawsuits against the pharmacy, alleging product defects, as well as against the prescribing physician and medical facility, alleging professional negligence. That is breach of the applicable standard of care.

While understanding the PROLONG study showed that Makena is no better than placebo in preventing preterm birth, I don't believe that this study will change the current standard of care to prescribe 17P to pregnant women at risk. If the FDA decides to withdraw Makena, which I strongly urge the FDA not to do, OB/GYNs will return to using compounded 17P, potentially placing their patients and themselves at significant risk.

Few physicians have the training or experience to suitably evaluate a compounding pharmacy's ability to maintain an accepted technique and consistency of drug concentrations, or to investigate how the pharmacy ensures the potency and purity of their active pharmaceutical ingredients and finished products.

FDA regulation serves an extremely important role in keeping America's drug supply safe. Therefore, I believe that for now, it is in the best interest of patients and my profession that the FDA does not withdraw Makena. Thank you very much.

DR. LEWIS: Thank you. Speaker 15, please.

DR. CARITIS: Hello. My name is Steve Caritis. I am a professor of obstetrics and gynecology in reproductive sciences at the University of Pittsburgh, and a specialist in maternal fetal medicine. I have a few comments that I hope the committee will find useful in their deliberations.

First, I'd like to establish my credentials. My colleague, Dr. Venkataramanan, who you see up there, and I have published 27 research papers on 17-hydroxyprogesterone caproate, which I will refer to as 17-OHPC, including the first paper on the assay of 17-OHPC and the first pharmacokinetic and pharmacodynamic studies of 17-OHPC in both Singleton and twin gestations. These studies were supported by the Maternal Fetal Medicine's Units Network and the Obstetrical Fetal Pharmacology Research Centers. None of these studies were supported by industry.

Our research that is most relevant to your deliberations is our pharmacodynamic study of 17-OHPC in women with singleton gestation. In that secondary analysis of data from the MFMU Omega 3 study, we reported concentrations ranging from 4 to 56 nanograms per mL; that's on the left there. That is despite the subjects all receiving an identical dose of 250 milligrams weekly.

The figure on the right indicates a linear relationship from these same data between log transform 17-OHPC plasma concentrations and the rate of preterm birth. Clearly, those women with higher concentrations had lower rates of preterm birth. These data suggest 17-OHPC efficacy for preterm birth reduction.

The possibility that a higher concentration of 17-OHPC might be associated with lower rates of preterm birth led us to initiate a prospective study within the Obstetrical Fetal Pharmacology Research Centers. We will randomize 300 women with a prior preterm birth across 5 university centers to either 250- or 500-milligram weekly doses of 17-OHPC. This will provide a pharmacodynamic analysis of 17-OHPC that may assist in establishing a pharmacologically based dosing regimen.

Despite FDA approval of 17-OHPC in 1956 and the recent approval of Makena, a dose-ranging study had not been reported; neither had a dose or concentration response study been reported for 17-OHPC and the rate of preterm birth. The weekly dose of 250 milligrams for preterm birth prevention is not based on any pharmacologic data or principle, confounding any meaningful assessment of drug's efficacy.

In the way of disclosure for myself and Dr. Venkat [ph], the 17-OHPC for this study that I referred to earlier is being provided by AMAG Pharmaceuticals without charge to the OPRC. The data obtained and publication rights are retained by the investigators. In addition, we are also negotiating to perform a study for AMAG, comparing intramuscular and subcutaneously administered 17-OHPC. Thank you.

DR. LEWIS: Thank you. Speaker 16.

DR. THOM: Good afternoon. My name is Elizabeth Thom, and I do not have any financial relationships with the sponsor. I'm a research professor of biostatistics statistics and bioinformatics from George Washington University biostatistics center, and the center has been the data coordinating center for the NICHD MFMU networks since the beginning of the network, and as such, I was involved in the Meis study, and I was the principal investigator of the coordinating center and oversaw the conduct of the trial.

The data coordinating center was responsible for assisting with the development of the protocol, creating the data, the case report forms, providing the data management system, monitoring protocol adherence, and doing weekly editing and auditing. I believe that we did a good job because we were very familiar with obstetrics and obstetrical trials. So overall, I think the data were very good quality and the protocol adherence was good.

I was actually present at the interim monitoring meeting when the Data and Safety Monitoring Committee recommended early termination of the study, and I have no doubts that the trial was truly positive. The data had been consistent at the previous interim look, and I'm pleased of that, and although the outcome rate was higher than expected, the women who agreed to the trial were at very high risk.

To change subjects, in the last few years, I have also been a member of the Secretariat for individual participant data meta-analysis funded by the PatientCenter.com Research Institute, which was referred to earlier today, and that is comparing vaginal progesterone, oral progesterone, and 17-OHPC with control or with each other. It is known as EPPPIC.

As a member of the Secretariat, I helped design the overall study, but I have had no involvement in the actual analysis. The meta-analysis itself was conducted by an independent but very well respected group in the UK. None of the members of that team have been a part of a previous progesterone trial or progesterone meta-analysis and were considered to be unbiased.

This is the largest and most comprehensive individual participant data meta-analysis to date. They looked at 30 trials in about 10,000 women, and about half of them were trials of 17-OHPC. They included 84 percent of the data of randomized trials in 17-OHPC. Those that weren't included are mainly small, unregistered, or single center. The results have not been published, so I can't talk about that, but I believe that these data are important and should be taken into consideration.

Finally, on a personal note, I was the mother of a preterm baby of 32 weeks gestation, and although it was 5 years ago, I can tell you the experience never goes away. After my son was born, we had several difficult years; and although it was not nearly what some families go through, it certainly factored into my decision not to have another child, as 17-OHPC was not available then, and if it had been, things might have been different.

So on both a scientific and personal level, I ask that the FDA panel and the FDA do not negate the results of the Meis trial by the results of the PROLONG study, but consider the fact that the original trial is more relevant to the U.S. population, that high-risk women might very well benefit from 17-OHPC, and to take into account the results of the EPPPIC meta-analysis when it becomes available. I believe that 17-OHPC should be an option for high-risk women with a prior preterm birth and shared decision making between the doctors and women who could potentially benefit from it. Thank you.

DR. LEWIS: Thank you. Would the final speaker please approach the podium?

(No response.)

Clarifying Questions to Applicant or FDA

DR. LEWIS: Okay.

We have time for some clarifying questions for the FDA and the sponsor by the committee members.

Dr. Gillen, I think you're up first. You had a question left over from this morning.

DR. GILLEN: Yes, thank you. My question is primarily to Dr. Wesley, and it's really around clarification of the 37-week endpoint that was used in the first study. As you'll recall and was stated earlier, in that 2006 advisory committee meeting, there was pretty strong consensus that the 37-week was not a quote/unquote, "adequate surrogate," adequate surrogate I presume meaning satisfying the Prentice criteria.

So what was stated about that -- and this is really a follow-up, to some degree, to Dr. Shaw's question about substantial evidence for efficacy. Part of that is the quality of the endpoint and the clinical relevance of the endpoint, I would argue.

The question is, when you described the timeline about new information coming out on the 37-week endpoint as, quote/unquote, "becoming an adequate surrogate," how does that impact our view of what is substantial evidence for efficacy, as described by the sponsor, to be honest, in their presentation?

What's the FDA's point of view?

I'm trying to get a feel for where you are on the 37-week endpoint and what the timeline was, because it seems like the PROLONG study was already underway at the time that you had made that decision that the 37-week now is, quote/unquote, "adequate."

Can you fill me in on this?

DR. WESLEY: Well, it's somewhat difficult because nobody knows exactly the best surrogate to use for this. At the time when the data came out -- and it wasn't just a publication; it was also states made a law that you couldn't induce somebody before 39 weeks, if you recall. You're not a clinician, but 39 weeks, you had to wait to induce somebody because of the morbidity occurring in the late preterm birth.

So because the results were so persuasive at 37 weeks, even though they weren't at 32 and 35, we decided to give it a chance and go ahead and do the provisional approval. It's not clear exactly, but I wanted to show a slide to show you the population in 002.

Can you pull up slide 20? It is an older population of preterm births, and that might be why, because you had so many more of them in that population, you see the median -- I don't look at means, but the median preterm birth rate in the treatment arm was 37 and a half weeks, and in the placebo arm, it was 36 and a half weeks; only one week difference.

It seems as though because the population was older in that thing, it might have been affected. I don't know. This is not written in stone with us. We keep looking. We keep looking at the literature, we keep up with changes, and we make decisions based on that. That's the best I can say.

DR. GILLEN: My question is somewhat pointed to your slide 14, which says, "FDA concluded that delivering at less than 37 weeks of gestation was an adequate surrogate endpoint." Is that still the position of the FDA? I'm just trying to get -- if we're asked to come back and judge the first study based upon its merits, which we already did once in 2006 -- I happened to be there. So now if we're asked to judge it again, I want to know where the FDA stands on this as an endpoint.

Given what I'm reading here, is that the official stance of the FDA?

DR. WESLEY: There is no official stance. We decided at that time, with the people there, to do that -- to use that gestational age. But I can't say there's an official stance. I mean, it's something that we keep evaluating all the time.

DR. NGUYEN: Hi. Christine Nguyen, FDA. Let me try to address your question. You're asking whether, in 2019, we would consider the gestational age of delivery less than 37 weeks an adequate surrogate endpoint for accelerated approval, and the answer would be yes.

DR. LEWIS: Thank you. Dr. Orza?

DR. ORZA: I have some questions about the safety side. In their comments and also in their petition, Public Citizen commented on and did some analysis of the rate of stillbirths, which was higher in both studies in the treatment group. I was wondering what FDA's analysis of that had shown.

Also, the sponsor recommended to describe data that they had on the long-term effects, out to an average of, I think they said 4 years. And I was wondering if the FDA had analyzed those data and what your conclusions were.

DR. CHANG: Hi. Christy Chang from FDA. Your first question was about the safety findings from both 002 and 003. You're correct that from the 002 study, there appears to be a signal in increasing early fetal loss and early infant deaths from study 002. But in study 003, based on our review, it appears that the incidences for these findings were similar in both treatment groups. Furthermore, the 003 study was designed to rule out a twofold increase in adverse neonatal outcome, and was shown in 003.

DR. ORZA: They were similar overall, but specifically for stillbirths, they were higher in the treatment group in both studies, and that was what the Public Citizen analysis referred to. There was also a concern about where in the 16- to 20-week window the treatments were started, and they seemed to suggest that there was a difference between early in that window and late in that window, potentially, on the rate of stillbirth.

Did you do similar analyses?

DR. WESLEY: Can you pull up slide 24? This shows the two studies, and if you look at stillbirths, you have a 2 percent rate in the treatment arm of 002 and zero percent of the placebo arm. Then in 003, you have a 1 percent stillbirth rate and a 0.5 percent.

So these are very small numbers. The percentages are not that dramatically different. No, we didn't really look at the time of starting of the drug and the relationship of stillbirth because the numbers are so small, it would be hard to really do that analysis, but that is something that's worth considering in the future.

DR. LEWIS: Thank you. I think sponsor wanted to say something to that point.

DR. ORZA: And also the long-term data, the long-term safety data.

DR. KROP: We evaluated the stillbirth rate very carefully and had an independent maternal fetal medicine physician, who was blinded, to review the details. I'd like to call up Dr. Sibai who reviewed these himself.

DR. SIBAI: Baha Sibai, UT Houston. I reviewed the data for both the Meis trial as well as the PROLONG. For the PROLONG, this was blinded. For the Meis study, I had the data because it's already published and available. I looked through every one of these, and as you see from here, from the PROLONG study, there was only one unexplained. For the others, I identified 11 factors.

The way I did it, I used the publication from the stillbirths, which is the NICHD network, where they had several factors there. I evaluated maternal, fetal, placental, cord abnormalities in making my decision. And it is reassuring to see that, really, in either one of these studies, there was no signal that 17P increases stillbirth.

DR. LEWIS: Thank you. Dr. Davis?

DR. WESLEY: Was there a question on long-term follow-up?

DR. LEWIS: I'm sorry. That's right. I apologize.

DR. WESLEY: Can you pull up slide 30 and 31? The follow-up of children on 003 is not complete, so I'll just show you the results of 002. This is a screening. The ASQ scores are screening for developmental problems. If you look at the treatment arm and the placebo arm -- and remember, this is a 2 to 1 ratio, so they had to look at percent -- you see that the treatment arm had 27 and a half percent positive screens; the placebo arm 28 percent positive screens.

Can you bring up slide 31? These are the people with a positive screen who also had a diagnosis of developmental delay. Those in the treatment arm had 2.6 percent developmental delay -- no, I'm sorry -- 6.7 percent developmental delay. Those in the placebo arm, 9.8 percent.

So there really isn't much difference -- this is a safety study only, between the treatment and the placebo arm -- when it came to screening and developmental delay. If you look at the percentages now, there are some differences, but they're not that significant.

DR. DAVIS: How old were these children?

DR. WESLEY: They're about 18 months old.

DR. DAVIS: And do you know why they used this test versus a Bayley, which is more --

DR. WESLEY: That was used in terms of the diagnosis, yes. The Bayley is more diagnostic and not a screen, so it was used for the diagnosis.

DR. LEWIS: Before you get to your question, Dr. Davis, is this the entire population of 003, or --

DR. WESLEY: No. This is only 002. Because it was not set up beforehand, if you look at slide number 28, it tells you how many. Fourteen of the original 19 study sites in 002 were able to participate. This was post hoc set up and done, so you didn't get everybody, but it had a good percent. Eighty percent of the mothers who participated in the study had this screen and diagnostic testing.

DR. NGUYEN: Hi. Christine Nguyen. Let me just clarify, the infant follow-up for 003 is ongoing, and the results are blinded. So we're not able to show you those results, and I believe there are data on about 200 children.

DR. LEWIS: Just one more. I will get to your next.

So this is 14 of the original study sites children were eligible to participate. Was there a good distribution of sites throughout the country or were they skewed in terms of a preponderance of one study site?

DR. WESLEY: From my recollection, it was fairly widely distributed. These are 14 sites that were able -- but they were in different parts of the country. There was no particular segregated group of them, no.

DR. LEWIS: Dr. Davis?

DR. DAVIS: Thank you. Jon Davis from Tufts. The definitions of your neonatal morbidities were a little perplexing, so in other words -- and it may be a moot point because the rates were so low and the average delivery time was 37 weeks, so that's why you may not have had very many. But certainly some of the definitions were bronchopulmonary dysplasia, which was defined as oxygen use for 28 days, which I think I stopped using about 20 years ago.

So I didn't know how those were drafted and whether those are viable, and whether we should be relooking at the definitions and potentially reanalyzing the data with more updated definitions.

I had one more question.

DR. CHANG: Christy Chang from FDA. Some of these may be better addressed by the company. If we could pull up Dr. Sibai's slides from CO-38.

DR. NGUYEN: I'd like to remind the committee that this neonatal index was based on data of when 002 was conducted, so this is 1999. It is about 20 years old. When we proceed with a confirmatory trial, we like to be as consistent as possible with the trial that gained initial approval. So I think that's one explanation.

DR. WESLEY: These definitions were developed by the Maternal Fetal Medicine Network Units, not by us.

DR. CHANG: I'm wondering if Dr. Sibai has any more comments about this slide, which shows the long-term neonatal follow-up on the babies, whose mothers participated in 002.

DR. KROP: Dr. Sibai, do you want to go up and comment?

DR. SIBAI: Do you want me to comment on this or there's a question? Sorry.

DR. CHANG: I'm just wondering if you had any comments, any additional comments, besides what you already talked about this morning. Based on what the slide has shown, of all the infants that were enrolled in the follow-up study, there didn't appear to be any differences in motor development.

DR. SIBAI: Correct. I would like to point out that, really, the median age at follow-up was 48 months, and you can see the 75th percentile. The other thing I want to emphasize, really, there was no gender differences, which was one of the endpoints. We looked at 12 points for masculinity and 12 points for femininity in this evaluation, and there was no significant difference.

In regard to the question about BPD, this is really the definition that was used in the neonatal research network among the various studies.

DR. DAVIS: My final question to FDA is, in your market scan data, we've been told you can't do another trial because everyone's using this already, and it's an established treatment. I was curious if we actually know -- most neonatal trials, we can see that 85 percent, 90 percent of our mothers have gotten antenatal steroids before the babies deliver.

Do we have any idea what the market use is? I'm not sure if you would know or maybe the sponsor. How many of these mothers who actually have had a previous preterm birth are receiving the medication? Because it was my sense that it was still relatively low throughout the United States. So whether that really does preclude doing another study, I wasn't sure.

DR. TSAI: This is Huei-Ting Tsai from FDA. Can you clarify? Are you asking the utilization among the people using the injectable HPC, how many have the preterm delivery?

DR. DAVIS: Yes. So in other words, if we're being told that this is now standard of care being used widely throughout the United States and would preclude doing another study, is that true? I mean, are 80 or 90 percent of all the mothers who are now pregnant, who have had a previous preterm delivery, are they receiving 17P?

DR. TSAI: If we look at slide 10 I think for the Sentinel -- for the drug use slide, slide 10 in drug use slide, FDA drug use slide, but you probably have the information, basically in the Sentinel analysis, it does include the Market Scan data, and that's a major data planner. You can refer the data we got from the Sentinel analysis to see how the use might be in Market Scan.

DR. NGUYEN: Can you pull up drug utilization slide 10, please?

DR. TSAI: Slide 10 in drug use presentation.

DR. NGUYEN: The next FDA slide.

Christine Nguyen. To answer your question, we have to know the universe of all eligible women in the U.S., and then figure out how many of those receive Makena. So I'm not sure -- well, Market Scan, we will not be able to get the information on that denominator.

DR. KROP: We do have some data on utilization that was from a chart review. I don't know that that would be helpful in your question. It was a thousand patients that we went back and tried to get the denominator that you're referring to. And what we found was, based on that, those were all indicated patients, that about 75 percent of them were taking 17P. This was in 2017.

I'm sorry. I don't know why it's not coming up. But it included both 17P compounded, as well as 17P Makena. The combination was 75 percent, the vast majority of that being Makena, and then there was some off-label use of vaginal progesterone in about 10 percent of patients, and about 15 percent of patients were not being treated.

DR. LEWIS: Okay. Dr. Hunsberger, go for it.

DR. HUNSBERGER: I just had a question for the applicant. They were discussing why, potentially, another study couldn't be done maybe as a randomized study between another treatment. On slide 83, you put up different treatments and said, well, none of these are beneficial, but if you look at the odds ratio, that's pretty much the odds ratio or the relative risk you saw in your study.

So it's not quite consistent to say the PROLONG study or we should approve this, when these are given as evidence of not being beneficial, and maybe also a discussion of why you couldn't do a randomized study between one of these treatments.

DR. KROP: I'd like to call up Dr. Blackwell to address that question.

DR. BLACKWELL: Thank you. Sean Blackwell from UT Houston, Houston, Texas. I think, certainly, any group of trialists can do a trial. The question is on whether or not it would be informative for this particular question. Certainly, we could do a comparative trial, a randomized-controlled trial of 17P to any therapy. The question is, would it be informative based on the information that we have already?

This is three large placebo-controlled trials, adequately powered with a very high-risk patient population similar to the Meis study, again, different than what I would describe in a PROLONG population, that showed no difference related to treatment effect. Certainly, it's possible to do a trial. The question is whether or not it would be informative and confirmatory. That was the point that I was making in my presentation.

DR. LEWIS: Thank you. I think at this point, we do have a lot of material to get through this afternoon in terms of discussion, and some of the points that are bothering people perhaps you'll have an opportunity to air those concerns. At this point, let's take a 5-minute break, 5 minutes. We'll reconvene at 2:30.

(Whereupon, at 2:25 p.m., a recess was taken.)

Questions to the Committee, Discussion, and Voting

DR. LEWIS: We will now proceed with the questions to the committee and panel discussion. I'd like to remind the public observers that while this meeting is open for public observations, public attendees may not participate, except at the specific request of the panel.

We will have three discussion questions and three voting questions. Some of them have subparts. We'll start with the first discussion question. If you have a comment to offer, please raise your hand to be recognized.

Discussion question 1, discuss the effectiveness of Makena on recurrent preterm birth and neonatal morbidity and mortality. Dr. Shaw?

DR. SHAW: Hi. Thank you. I guess this is a comment and potentially discussion, that the sponsor might like to respond to this comment. I can refer, actually, to Jia Guo's slide number 3, which has the Trial 003 study design. When I think of the effectiveness of Makena, we have these two trials. I've heard a couple people talk about Trial 003 as a well-powered, well-designed trial. But when I look at the trial design that's on Guo's slides, number 3, that was powered based on a baseline rate that did not apply.

I understood earlier that the DSMB did look at overall event rates, lumped, and they would have known early on that the baseline rate was off; that instead of the expected 17 percent for the neonatal composite index, they were seeing a background rate of about 5 percent, so a third. And the same thing for the reduction of the preterm birth; instead of the background rate of 30 percent, they were seeing something maybe lumped at around 11.

Over the 9 years that enrollment took place, I'm sort of confused as to why that might not have been -- it must have been evident that it was no longer set up to be a confirmatory trial. It was underpowered. It was terribly underpowered.

So I feel like I can only consider the evidence of the first trial in terms of a trial that was adequately powered to detect efficacy. So we're sort of sitting in a very similar place in the sense of one adequately powered trial. That's basically just a comment.

DR. LEWIS: Others, discussion?

DR. NGUYEN: May I respond to that comment? Christine Nguyen.

DR. LEWIS: Yes.

DR. NGUYEN: When we power a confirmatory trial, the best evidence we go on is the treatment effect that we see in the approval trial. We can't predict in advance what the results of the confirmatory trial would be. I mean, you can't look into the future. I can't answer why the data were not reviewed formally and assessing about event rates and what have you.

But it doesn't make 003 not an adequate and well-controlled trial. It was powered based on the best available evidence. So again, when we're looking at 003, we're trying to find a drug effect, so I think it's important to look at all the data in front of us.

DR. SHAW: Absolutely. I think speaking from what I -- and I might have misunderstood, but a lot of times DSMBs, we have to monitor event rates because we all do the best we can. And frequently, especially when we go into a new population, we need to realize we may have powered on the wrong thing, and generally background event rates would be considered, and maybe it wasn't. But that's still a piece of the trial, and its hindsight could be 20/20, but it's just something to be aware of.

We can't refer to that -- you did the best you could, and that's not in question, but this was a trial powered for a different population than the one it was inevitably --

DR. NGUYEN: So I would comment that the eligibility criteria was the same as 002. So the intention there is that you enroll the same population. And again, we can't predict in advance what the results will look like for 003.

Another thing I would also clarify is we approved Makena based on the findings of 002, so we expect the treatment effect to be similar. So we're not looking at a totally different population or somehow looking for different outcomes. We're looking for a verification of the drug's effect.

DR. LEWIS: Okay.

DR. GUO: Jia Guo from FDA. I have a comment on that.

Could you please get my slide 27? Go back one to 26. When we talk about a power of the study, that's a very important concept at a design stage. We know the power is the conditional probability, but at that time we have an expectation of the treatment effect we will observe in this trial.

We're not talking about the retrospect -- when people say the study and the power, we commonly think about the retrospective calculated power based on the study results.

DR. SHAW: I'm sorry. I just want to be clear that that was not my question about retrospective power. It's just understanding a baseline rate used for the power.

DR. GUO: Yes. And if you look at Trial 003 results and look at a confidence interval based on applicant's relative risk reduction, you see for the neonatal composite index, the relative risk reduction, actually, for the neonatal is positive 12 percent, and the confidence interval, the lower bound, is minus 28 percent, which actually does not cover that 35 percent, what they expect to observe in the study. So in that way, this study is not underpowered to detect their original plan for the relative risk reduction.

DR. LEWIS: Okay. If we could show the discussion point again, and I think Dr. Reddy was next, the first discussion question for the committee.

DR. REDDY: Just to build on what Dr. Shaw said, they did not look at the event rate. I just wanted to make sure -- the DSMB for 003, because I asked that question.

DR. SHAW: There were two different answers, actually. It was confusing.

DR. REDDY: When I asked, one of my first questions was, for 003, did they at any point go to the DSMB about the event rate or to the FDA because the event rate was lower than expected, and the answer was no.

DR. KROP: [Inaudible - off mic] -- charged to look at efficacy and did not comment to us about event rates. That was not their charge for the committee.

DR. SHAW: But I was confused because at one point, I thought I heard you say the overall rate was looked at, not the efficacy, which would be by arm.

DR. KROP: I think they knew the overall rate, but that was not -- I mean, they weren't telling the sponsor you're underpowered; you need to go do something. I think at this point, this is a rare disease, and the idea that even if we were powered to go do 3500 patients, it wouldn't have even been possible. It would be another 10-year study. So I'm not sure whether that would help the situation.

DR. REDDY: I wanted to clarify that. But in terms of question 1, to me, the focus is preterm birth. I think it's an important outcome because we know preterm birth gestational age is directly related to neonatal morbidity/mortality. So I think, to me, I'm focusing on preterm birth and gestational age at delivery because we know that is directly related to morbidity and mortality.

Then for me, I'm interested only in the 003, the U.S. portion. I feel the other portion is not applicable to us here in the U.S. So given being focused on 002, which was a well-done RCT of American population and U.S. PROLONG, which more reflects the U.S. population, I think there is evidence that Makena is effective.

DR. LEWIS: Dr. Bauer?

DR. BAUER: I'm going to be the devil's advocate here because I'm going to take just the opposite. I'm going to suggest that actually 003 was actually the more properly done trial, and that you can't just ignore the fact that the trial enrolled people at a lower risk. In fact, the right question is, was there any evidence that the drug had differential effect in the lower risk people as opposed to the higher risk?

Both in 003 and in 002, there was no evidence that the drug had any better or any worse effect, depending on what the baseline risk was. It's a very important issue that Dr. Shaw brought up about the event rate because if you're studying a lower risk population, you have less of a likelihood to show a meaningful difference. But remember that the power calculation for 003 said that they wanted to find a 30 percent or greater reduction in the risk of their primary endpoint. In fact, their confidence intervals excluded that interval.

So I would not argue that that was an

underpowered trial. In fact, I'm going to take just the opposite. I think that there are questions about the much older trial. Really, an event rate that's almost twice in the placebo group of what you would expect, based on other populations, to me is not yet explained, and there are also differences in randomization that we can't account for, particularly that purports to women that had more than one preterm labor. So I think we could call into question the validity of actually 002 as much, or in my opinion more than 003.

DR. REDDY: I understand your concerns. I'm worried about 003 in terms of the neonatal morbidity and mortality was so low. We can't poo-poo we do not know the underpinnings of preterm birth in this country. We heard about all these risk factors, but even if you count for all these risk factors, there's still an elevated rate controlling for all these things.

Really, Ukraine and Russia to base majority of patients in 003, it makes me feel very uneasy because they had a very low rate. I want my neonatology colleagues to comment on the extremely low rate from very preterm births in this study.

DR. LEWIS: I know Dr. Davis is up next, but if somebody wants to quickly comment on Dr. Reddy's observation? Is there a neonatologist in the house?

DR. DAVIS: I think we agree that the primary reason to use this drug is to prolong pregnancy and minimize neonatal morbidity and mortality. None of that was shown in either trial because the rates overall were quite low.

We as neonatologists see the bulk of our morbidity and mortality in babies delivered less than 30 weeks gestation. I think most NICUs in the United States have survival rates well over 90 to 95 percent in babies over 30 weeks gestation, and we have the most concerns and see the most severe illness in preterm infants who are delivered less than 28 to 30-weeks gestation.

Most of our neonatal trials studying major morbidity and mortality are limited. Usually we go from 23 to 29 weeks gestation, and we don't enroll anyone over that because the rates of complications get much lower, and then you can't get enough patients and power your trials properly.

So I would suggest that even if you were to do another study, the rates here are so low that you could never power a study to find a significant difference, at least in my mind from looking at these data. If you look at the deliveries at less than 28 weeks gestation, which is what we really worry about the most, if anything, it was slightly higher in both 002 and 003 in the Makena group. It doesn't look like it was statistically significant, but there was certainly no benefit.

What it suggests, we've talked about the multifactorial nature of preterm delivery, and it may be that more mothers at less than 28 or 30 weeks have inflammation, infection, et cetera, Which we tend to see after delivery, and maybe the pathogenesis is somewhat different at older gestational ages. But I think from this standpoint, the rates are incredibly low, and if you're using the drug in order to improve neonatal outcome, you can't demonstrate that.

I do agree that late preterm infants do have higher rates of long-term morbidity and mortality, but the question then, which we talked about earlier, if you're getting us from 36 weeks to 36 and five-sevenths, is that a meaningful clinical outcome that you're going to be able to demonstrate a significant difference in that 6-day period, and is the risk of injecting this medication -- and I feel better about seeing the 4-year follow-up that there is no obvious signal of any differences, but does the risk potentially outweigh the benefits of that extra 5 or 6 days when you're talking at somewhere around 36 to 37 weeks?

I would have a really, really difficult time either designing that trial or figuring out how to interpret those data.

DR. LEWIS: Thank you. Dr. Gillen?

DR. GILLEN: Thank you. I'll take what I would consider to be the easier one first on this, and that, no, I don't believe that effectiveness for neonatal morbidity and mortality has been established. I think gestational age has been and is a surrogate here for neonatal morbidity and mortality.

There have been changes in evolutions in what we would define as an adequate surrogate, depending upon the time frame for the gestational age at the time of birth, but neither study has demonstrated, in my mind, anywhere close to efficacy on neonatal morbidity and mortality.

Now, with respect to preterm birth, I agree wholeheartedly with Dr. Bauer in that there are still questions remaining about the placebo control rate in the first study. It's an anomaly that has yet to be explained as to why it was so high, and the observed rate at less than 37 weeks was effectively around where previous studies, placebo arms, were sitting, and that has not been explained.

If one is going to say that the reason that there's a lack of replication, which this is the underlying argument here, and this is where I began my very first question of the day, is because there's a difference in the patient populations, I have yet to see one subgroup where the two started to be compatible with one another.

Even in a data-driven world, we can't find one subgroup where there's effect modification or evidence of that effect modification that's sitting here. Cutting it by U.S. population, black versus non-black population, that is yet to be demonstrated to me. So I believe that even with respect to preterm birth at this point, that there is fairly weak evidence, I would argue, in terms of effectiveness.

DR. LEWIS: Anyone else? Question 1?

(No response.)

DR. LEWIS: So on the question of effectiveness of Makena on neonatal morbidity, there seems to be no one commenting that Makena does affect neonatal morbidity and mortality on recurrent preterm birth. There's some range of opinion in terms of whether you should value 002 or 003 more so; or whether either of them show effectiveness.

Dr. Lindsay?

DR. LINDSAY: I just wanted to weigh in on the issue of the efficacy of Makena recurrent preterm birth, and I really wanted to ask a question based on a couple of things I've heard about the independent patient meta-analysis data that's going on.

My question is -- and this is just a general comment -- when we get the results from independent patient meta-analysis, will that trump the results of what we get from the randomized clinical trials?

One speaker made the comment that maybe we should wait for our deliberations until we have those results, and I would agree. I have to be candid. I've been prescribing the medication for a number of years, but in terms of looking at the evidence and looking at the data, it's really kind of hard to say that it's been very effective if you look at the data very critically.

I'm just asking is that meta-analysis going to be a tiebreaker, or I wanted someone to kind of make a comment about whether the independent data meta-analysis will trump the results of these two well-conducted, randomized-controlled trials, because that would help me in my deliberations.

DR. LEWIS: Well, that's a good question, and it kind of does feed into our discussion question 2 about a confirmatory trial, if that's to be designed. So I think, if you don't mind, we'll kind of fold that in.

Oh, I'm sorry. Go ahead, FDA.

DR. JUNG: Hi. My name is Dr. Taehyun Jung from FDA, Office of Biostatistics. I authored the meta-analysis of the two published studies in the briefing document. The FDA reviewed two published studies. One is a published in the American Journal of OB/GYN in 2018, authored by Romero, et al. This study used vaginal progesterone, and the dose was ranging between 90 to 200 milligrams daily. There were 5 studies that was used for meta-analysis, and that was administered by intravaginal.

This study was limited because the study population was different from study 003. The Romero study had spontaneous preterm birth, but it was only 30 percent. All of the subjects had 100 percent short cervix that was defined as cervical length less than 25 millimeters. And the Romero study didn't use the approved dose, that is 250 milligrams weekly.

Also, the authors conducted a post hoc analysis on U.S. and non-U.S. white population and black population. The white population showed a higher risk reduction compared to the black population. The black population showed a relative risk of 0.86, but it crossed the reference line, so there was no difference. the U.S. population and both non-U.S. showed significant risk reductions, but the U.S. population had a higher risk of preterm birth compared to the non-U.S.

DR. LEWIS: I'M sorry. Could you just clarify that again? So you're talking about vaginal progesterone in a meta-analysis? Was Makena in this?

DR. JUNG: The study published in 2008 was using vaginal progesterone only.

DR. LEWIS: Vaginal only. Okay. Thank you.

DR. KIM: I'm Clara Kim from Office of Biostatistics. I just wanted to clarify that the meta-analysis that Dr. Jung is talking about is the one that's included in the backgrounder. I think the patient-level meta-analysis that you're referring to, we haven't gotten a chance to review it. So how much we rely on that, I think that would be a review issue.

DR. NGUYEN: So if I may provide some guidance, we rely on the most robust strength of evidence when making our decision. So unless we think that the individual patient data meta-analysis, which I suspect is going to be a little more heterogeneous than the two adequate and well-controlled prospectively designed trials, it will be hard for us to think that would trump the very robust evidence from the two trials we have in front of us.

So I can't answer it for sure, but you just kind of eyeball the robustness of the evidence that are generated from the two different analyses, that that would sort of guide how we handle those data.

DR. LEWIS: Dr. Orza?

DR. ORZA: One possibility I think that could come out of the IPD meta-analysis -- and again, I haven't seen the results either; I'm not privy to those -- is that it might not contribute to these questions specifically, but it might identify, for example, a legitimate comparator to get us out of the jam of having to use a placebo.

DR. LEWIS: Dr. Eke, did you have a comment as well on this question? No?

Okay. Are we ready for question 2? Question

2, if a knew confirmatory trial were to be conducted, discuss the study design, including control, doses of the study medication, efficacy endpoints and feasibility of completing such a trial.

Don't all speak at once. Yes?

DR. JARUGULA: As the industry representative here, I'd just like to comment. Having seen the evolution of this development, the study 003, how long it took to complete the study, given the recommendations of the societies and also about the ethics of using placebo in this, I think it would be extremely hard for any company to conduct such a study. You've seen that study 003 background rates were much, much lower than anticipated, and yet we tend to use that study as a basis to utilize the findings of the other study.

So I don't know. I'm still conflicted on that. But leaving that aside, I think conducting another's study, a well-controlled, double-blind study would be extremely difficult. I would venture to ask the committee and others to discuss other possibilities here, either finding a subpopulation or any other possibilities.

DR. LEWIS: Dr. Gillen?

DR. GILLEN: Possibly controversial thinking out loud here, but the sponsor has very clearly articulated that they don't believe that another study would be feasible given the fact that accelerated approval was already granted, and it is very hard to recruit from the same patient population. I would conjecture maybe that accelerated approval was potentially given too quickly in this case and has convoluted this problem.

I guess a question for some of my clinical colleagues around the table is, if approval was withdrawn, could this study be done, and done appropriately, with a representative patient population to attempt to confirm, if you will, Trial 002, which is what the purpose of 003 was, and what I've been told is that could not be done because of the changing patient population and the difficulty of recruiting.

I'm not really giving an answer here on the feasibility, but I understand the logistical difficulties, and I think we've been conditioning upon the fact that the accelerated approval is granted and will stay granted. And I think we need to think about the two hypotheticals to say, what if it wasn't there, could we do an adequately controlled trial and actually get to an answer?

DR. LEWIS: That's kind of what we're asked to talk about in question 3. What are the potential consequences?

Dr. Orza, and then Dr. Wing.

DR. ORZA: I'm having trouble articulating this idea, so bear with me. But in study 003, I'd like to see data about a control group, what was going on out there with women at high risk for premature birth outside of the study to understand what the baseline might have been because the women in this study weren't just getting an injection of placebo. They were getting weekly attention and care. And it could be that because both of them got that, regardless of whether or not they got the drug, that that actually is the answer to why the rates were so low, both in the placebo group and in the control group.

So we might have in fact discovered the way to make this better, completely independent of the drug. So I would like more information about what was going on outside of the trial to try to understand better what was going on inside of the trial, and to help us think about what the next study should look like.

DR. LEWIS: Thank you. As I understand it, in 002, though, the same thing, their placebo group also got weekly attention. No? Yes, they did.

DR. ORZA: Right, kind of setting that aside because I don't know what happened there.

DR. LEWIS: Oh, okay. Dr. Wing?

DR. WING: So my thoughts are all over the map, so please bear with me. I'm going to talk to issues related to both questions 2 and 3. I'm going to leave an open-ended question, first, for people who are more informed than myself, which is one of the elements of question 2, which, is 250 milligrams of this drug the right dose? And it's perhaps what we're seeing in the differences of these trials related to the dosing.

I'm going to throw another variable in here, in the discussion, because I really am going to stir it all up, is whether or not the timing of administration of these drugs also affected the results and can account for the discrepancies in the two trials. So that's me as a clinical trialist talking about design.

I think feasibility, we're going to bash it around quite a bit. I think the ethics of doing a placebo-controlled trial when this drug has had FDA approval is a non-starter, at least in my opinion. It's just not going to happen.

So then we have to go to the alternative, then, which is if you pull the approval of the drug and say we're going to conduct the trial, then you've got to consider the legal implications, which the FDA I think has argued, at least in my mind, appropriately that that would be an okay thing to do. But there will be clinical and political consequences of that because, clearly, the clinical consequences, as a clinician, we're desperate as MFMs. Perhaps, I'm less desperate now because I've walked away from the bedside, but we don't have anything that's really good; just stop this problem that causes insufferable pain. So we succumb to emotion as a result of that.

I think Sean said it best, that the clinical response out there in the field is going to be that our brethren will start prescribing other versions of progesterone, whether it's vaginal, or oral. or some other compounded injectable, and they may all at once; that that could happen or they could put in more cerclages that were unnecessary. So in that regard, I think we're also looking at other ethical implications here, where we're doing harm where we shouldn't be.

As physicians, we take these oaths to do good and also do no harm, so I think we have to ask ourselves what good are we really doing here? Then I think the political implications are clearly, we know that there are disadvantaged populations in this country, and we have data. The black and white says that the 17P somehow prevented some recurrent preterm birth in a disadvantaged patient population. That to me stands above all else in considerations of these trials.

DR. LEWIS: Dr. Hickey, a new confirmatory trial?

DR. HICKEY: Well, I'm going to say Dr. Wing stole much of my thunder --

(Laughter.)

DR. WING: I didn't mean to.

DR. HICKEY: -- pretty much all of it. I would agree we are fairly desperate in terms of finding solutions for people, and that was, I think, our difficulty in the PROLONG trial when you try to enroll a patient and say we have a potential preventative agent for you or you can roll the dice and do placebo. So I think feasibility of a placebo arm is almost nonexistent.

I do like Dr. Caritis' idea of looking at different dosing agents, and that would probably be my goal, would be to do dosing, but also to really follow the PK/PD and see if we see is there a threshold level that we need to reach in women; because I can tell you, looking at our practices versus other practices, that people really ramp up that use of progesterone when it's not working beyond that recommended dose, and they do see benefits, so they keep doing it.

So clearly, I think there's some anecdotal evidence that perhaps looking at dosing may be part of our issue, and I'm really hoping that some of the individualized data helps us pull out that subgroup that really is going to be the beneficiaries of this work.

DR. LEWIS: Thank you. Dr. Reddy?

DR. REDDY: I agree, A placebo-controlled trial cannot be done in this country given everything that's been said. Patients, they'll go to compounding. They'll use other means to try to decrease their risk of preterm birth. But we definitely need more evidence. So even if we can't do an RCT, I agree with PK/PD studies, dosing studies. There have been studies where they use 500 bid in France and found, in fact, it did not work; it did not decrease. So there is some literature out there.

I think the EPPPIC meta-analysis that was mentioned, we need a well done IPD of Makena, not vaginal progesterone. If a trial is desired, there are some options. You could have a control group using vaginal progesterone; it's not great. Also the UK, like I mentioned, I don't think they're using Makena, so that's another population.

If there's some way to gather more

information, so a registry of patients who've had previous spontaneous preterm birth, the data that was presented, it was previous preterm birth. So the question was how come only 39 percent of women are getting Makena if they've had a previous preterm birth? So 30 to 40 percent of preterm births are iatrogenic; they're not spontaneous. So we need high quality data, which we're lacking, so the eligible women, an and observational study.

As physicians, as a clinician, we have to counsel patients. We have to incorporate this PROLONG information. And it is going to change counseling because there is evidence. We have to incorporate that level of uncertainty. We can't be this clearly decreases the rate of preterm birth by a third; now, it has to be nuanced based on other factors.

DR. LEWIS: Thank you. Dr. Drake?

DR. DRAKE: Matthew Drake for the Mayo Clinic. Unfortunately, I also think this is an unfeasible trial unless you can, a priori, identify a group that is going to have a 55 percent risk of preterm birth. If you can't, a priori, identify that group, which it sounds like it's probably going to be hard to do, then I think it's going to be essentially impossible to do this.

One thing we haven't really heard about is whether this -- maybe we did, but I don't recall hearing it, whether 17P undergoes any metabolism and whether that's different between any patient populations; whether it is or isn't metabolized faster in an African American population, versus a Caucasian population, versus an Italian population, versus anything like that.

Some presented from the audience, looking at pharmacodynamic/pharmacokinetic data, but whether that metabolism is important and leads to differences in the level of 5 up to 56 that they measured is, I think, perhaps very important and may underlie some of these findings. So if there was a way of identifying and addressing some of those issues, it could be important.

DR. LEWIS: Thank you. Ms. Ellis?

MS. ELLIS: Hi. Thank you. I came to this meeting. I'm the patient representative. I'm the only one at this table without an advance degree or any degree at that moment, but what I do have is a personal history of preterm labor, and I was able to, with things that are not approved anymore and bed rest, bring my second daughter to deliver at 38 weeks. Then she herself has had a preterm labor. So my grandson, we've had some early intervention and difficulty.

So this is a topic very near and dear to my heart, so I'm trying to bring in the personal, human element as we talk about this. Reading through the briefing materials, the statistical considerations were just really over and above what I could comprehend, and I came here seeking clarity and more confused than I was when I showed up, as I'm sure many people here are.

This trial seems to me to be about time. Whether or not that time actually is clinically meaningful is something that's kind of debatable here as well. And something that Dr. Reddy said earlier today was about what's missing for me is for the people who have had a previous preterm labor, how did this drug help them get more time?

I mean, as a whole group, we've got those results, but what are the results if people are starting this at different times? So we don't know -- it's hard to tie everything together. So if there were some kind of registry or something, that you brought up, having this information might be useful going forward. Thank you.

DR. LEWIS: Thank you. Dr. Davis?

DR. DAVIS: I would agree that it's going to be impossible to do the same trial for a third time, nor since the first two trials didn't have dramatic impact on neonatal outcome, I don't know that I would want to do that. But if there are opportunities to enrich the population that you're studying -- and I think Mat mentioned before was appropriate -- maybe one previous preterm delivery alone is not adequate to predict, in a meaningful way, the impact of preterm delivery.

We now have an obesity epidemic that's different between the two studies. We have a more substance use problem than we had before. And maybe you're identifying high-risk populations and doing it in a way that, okay, you had a previous preterm delivery at less than 35 weeks, that's one point; less than 28 weeks, that's two points; you're African American, and that's a point; you're obese, that's a point; your smoking history, that's a point.

Maybe there's a way of enriching that population so you can get to a much higher risk group because maybe that will have an impact at that stage. And I do like the idea of either a dose escalation trial, which then might preclude use of a placebo, or potentially a placebo trial with a different population and a different trial, but I definitely would not necessarily do the same trial over again.

DR. LEWIS: Thank you. Dr. Eke?

DR. EKE: Thank you. I kind of wear three hats, being an MFM, a clinical pharmacologist, as well as a clinical trialist. I keep scratching my head because looking at what we have facing us right now, I could not agree more with my colleagues, it's going to be very difficult another trial, basically looking at the logistics, and the ethical as well as the legal aspects to this.

What we have left would be to see how to get that subset of patients who benefit from this drug. I believe that there are some people who benefit; not everyone, some who do benefit from the drug, and our job should be to look for those patients to give this drug to.

Dr. Caritis talked about the dose response, which I totally agree with. When he discussed that idea a couple of years ago, I was on board with it as well. I was surprised that there was no PD aspect done for this drug, so that is one aspect.

An aspect, which no one has talked about, which Dr. Drake kind of mentioned briefly, is the pharmacogenetics of this drug. Tracy Manuck, who is at UNC, there are two landmark papers that she's published. One of them, she actually used samples from patients from the Meis trial.

She went back, collected samples from these patients and looked at their genetics. Is there something within these patients that actually make them respond more, which she called responders versus non-responders. That study showed that some people that actually responded more, they had some genes that were over-represented versus those that were not.

So that is something as well we could look at, and see patients who really need this drug, and whether we can say a patient who gets this drug will be African American, has these kind of genes, blah, blah, blah, and that will kind of help us streamline whichever kind of study we need to do in the future.

DR. LEWIS: Thank you. Dr. Smith?

DR. SMITH: Sure, just a comment. Neonatologists are guilty of this, but it seems a little bit late in the drug development pathway to be talking about trying to find the right dose of the medicine after two huge randomized-controlled trials. I also worry about the feasibility, especially if you start looking at randomizing against a non-FDA approved therapeutic approach. If anything, that group is going do a little bit better than maybe placebo, and your sample size is just going to have to be that much bigger.

DR. LEWIS: Dr Shaw?

DR. SHAW: Hi. Yes. I guess I just wanted to comment on the potential design if we could do a trial for further study. I feel like I'm hearing discussion of what might be an observational study, some kind of pragmatic study of people or registry. But I would say that a study in which we want to gain information can't be observational. I think these two well-controlled trials showed us when we equated the care on the two arms, we couldn't see a difference between black and white or education, high or low

So if we can't see any large differences in these pretty big groups of well-studied people, I'm not sure how we could imagine using regression and adjust our way out of the obvious confounders if they're going to be in an observational study. So I don't have confidence that we'll get clarity from a study that's not a controlled study or some kind of observational registry.

DR. LEWIS: Anyone else? Yes? Dr. Wade?

DR. WADE: Before we move on to question 3, I would just second what others have said, but I do believe there is lots of exposure out there. We saw that in the Sentinel review, so it would at least steer us to how much we're going to work towards a randomized-controlled trial if we looked at the observational data. We haven't heard anything specifically about all this. exposure leading to any reductions in preterm birth, so it seems like that exposure data is out there, whether or not we've looked at it on a state-by-state basis, or not.

Then I agree with everyone that we are trying to figure out who this highest risk population is, and in reviewing about the progesterone levels and how there is this broad variation of progesterone levels, almost 10-fold across women that were receiving 17-OHPC, it feels like there may be some more information there about what's driving the variation. Is that something inherent to the patient or is it something inherent to the dose of the drug? So there may be more information there that we could tease out.

Lastly, I looked at table 22 in the appendix, which looked at the U.S. subset of Trial 003, comparing Makena to placebo in all these different high-risk stratification groups. Although, I'm sure these differences are not necessarily statistically significant, the earliest gestational age of the prior preterm birth being in the 0 to 20 weeks or 20 to 28 weeks, that seems like a huge risk factor. The Makena group actually had more.

So there isn't even a balance of -- when my eyes go to what are the highest risk women in these groups using Trial 003 U.S. subset, the Makena is not performing well in what I'm drawn to as my highest risk groups. So I think there still is really a lot more work to be done to even figure out how to design what the next step would be.

DR. LEWIS: Thank you. Dr. Hunsberger?

DR. HUNSBERGER: I just have to say I agree with Dr. Shaw. I don't know how we'd figure anything out without a randomized study. And especially after listening to this whole discussion, I'm in equipoise, and I guess I wonder how the clinicians are kind of not in equipoise given we have these two randomized studies where they give very different results. How do counsel a patient given this data and not be in equipoise?

So to me, it seems like you have to have a randomized study to figure this out. I just think the data doesn't help us right now.

DR. LEWIS: Thank you. Dr. Reddy?

DR. REDDY: Well, to answer the point about being a clinician, unfortunately, in OB, that's a lot of what we have to do. A lot of the medications we use have not been studied in pregnancy. Even something as basic as chronic hypertension in pregnancy, we're like, well, you could be on meds, but there is no evidence that that works. In fact, quality evidence, the American College of OB/GYN says you should be taken off your medicines.

So I think we've gotten used to that. I think the PROLONG data is important, and it will be incorporated, and it will be explained, there's this one trial that shows this, there's another trial that shows that, and what the level of certainty is.

But one thing Michele Orza said, that now it's been bothering me for the past few minutes, is you were talking about weekly visits, the Ukraine and Russia, what else do they do? Do they put in cerclages, monitor the cervix every week? I have no idea what else they're doing for these women, so it may not be a study of just that medication, of just Makena, because the way they practice is completely different than here. Even in the neonatal outcomes, what we call NEC, at least in the Maternal Fetal Medicine Units Network, there are strict definitions. The data is rigorously collected, but I'm not sure what happens in those countries.

DR. LEWIS: Thank you. Anyone else?

(No response.)

DR. NGUYEN: Dr. Lewis -- I'm sorry; Christine Nguyen -- I just want to remind everybody the clinical practice can vary, especially when we have so many sites. Please remember that there is a protocol in place to standardize practices. For example -- and I don't have details for the protocol -- certainly, I can't imagine Russia putting a cerclage and not the U.S. So just to let you know, there's a protocol in place that's standardized the care as much as possible.

DR. REDDY: Well, I think that's really important to ask then, was their standardized management? Probably not. Can someone from PROLONG answer about the management?

DR. KROP: Yes. I'd like to call up

Dr. Blackwell.

DR. BLACKWELL: Hi. Sean Blackwell from Houston, Texas. The research protocol for PROLONG specified research procedures, but clinical care was at the discretion of the treating attending clinicians. So there was not a standardized protocol for things such as screening for transcervical length; the management if there was a short cervix, and the nature or degree of tocolysis, or other obstetrical management options. It would be the randomization process, they would account for that, but the research protocol -- much in the same as in the Meis study, we did not standardize clinical protocol related to these obstetrical interventions.

DR. KROP: I think it's important to remember -- you brought up the differences between Russia, Ukraine, and the United States -- there is a very different healthcare system. It's a universal healthcare system. There's a social safety net that exists in those countries that doesn't exist here, and there is also preventive measures that are put in place that are far more extreme than we have in the United

States. They have nurses go out to patients' houses. They have pre-pregnancy counseling and getting patients on vitamin early. In the U.S., we of course have a bias in the other direction of putting on these healthier patients into the study just because of the existing standard of care.

DR. LEWIS: Thank you. Well, maybe I'll just weigh in that it's not just what the doctors do, it's what the society is like. A single pregnant woman in the United States is not necessarily the same as a single pregnant woman in the Ukraine or Europe: what kind of family support they have, what kind of neighborhood support they have, how much they have to work to make a living, food security, and housing security. All of those things I think have bearing.

Anybody else on question 2?

(No response.)

DR. LEWIS: Okay. Question 2. I think that there is pretty much agreement about the feasibility of completing a randomized-controlled trial being extremely difficult, as some feel that that's the only valuable data, really, that we're going to get, that an observational data kind of study is not going to be helpful; and several people weighing in on the importance of getting pharmacokinetic data, which we really don't have, and that perhaps some sort of comparative trial with other kinds of progesterone could be a type of study design that might be useful, being a feasible thing.

In terms of other kinds of ways to design the study, maybe looking at an enriched population of high-risk patients as they exist today. We have a much more obese patient population than we did before. Substance use rates are different. Other ways to identify a group that might be helpful or might benefit from the drug, pharmacogenetic studies, dose-response studies; that, really, we just don't have data at this point that might help us understand the differences between the outcomes in study 002 and 003.

DR. GILLEN: At least from my standpoint --

DR. LEWIS: Sorry.

DR. GILLEN: -- the infeasibility of a randomized-controlled trial, what I am seeing is that's conditional upon the current accelerated approval still being in play. I think the dynamic changes dramatically if you pursue removal of that approval. So that's me personally; I'm seeing that.

DR. LEWIS: Sure. So that could be, in fact, one of the potential consequences of withdrawing Makena on patients, and a clinical practice, one could be it's feasible, then, to do a placebo-controlled trial.

Does that reflect your view?

(Dr. Gillen gestures yes.)

DR. LEWIS: Okay. So we'll move on to question 3, which I just sort of summarized some of what you said a couple of times, discuss the potential consequences -- a very important point -- of withdrawing Makena on patients and on clinical populations, clinical practice. Let's have more of a discussion there.

Dr. Orza?

DR. ORZA: Just a technical question. It was referenced that if this were taken off the market, that people would be compounding it anyway. How does that work?

DR. LEWIS: FDA?

DR. NGUYEN: Christine Nguyen. This is where we need your input, particularly patients who are caring for pregnant women and how they're counseling their patients, based on the data from the two trials.

DR. LEWIS: Ms. Ellis?

DR. ORZA: I didn't understand that. My question was if this is -- so it's the withdrawal of this specific drug, but legally people are still allowed to compound it? Is that how it works?

DR. NGUYEN: I'll give you a very brief answer. Under certain circumstances, hydroxyprogesterone caproate, so the active ingredients, may be compounded. But that's pretty much all the details that I can provide regarding compounding. I think it does answer your question.

MS. ELLIS: So my follow-up question to Dr. Orza's is, do we have any data or any idea of what was the compounding usage prior to the accelerated approval, from the 2006 meeting when people were discovering that this might be helpful to the approval in 2011?

DR. NGUYEN: Christine Nguyen again. If I may just remind the audience, I understand the compounding issue is important, however, it is not before the committee today, so that is not something we could be prepared to discuss.

MS. ELLIS: I'm just curious because one of the questions is what happens if approval is withdrawn, and it just is something that makes sense that it might happen. So I was just curious about that time frame, if we anything, if anybody knows anything about what was happening.

DR. LEWIS: I'll give FDA a minute or I'll give sponsor a minute. Are you ready? Go ahead.

DR. TSAI: Huei-Ting Tsai, FDA. Can we put up slide 22 in drug use, slide 22? This slide, the brown color shows the form of HPC use. If we look at usage before 2008 through 2011, in our data, the Sentinel analysis showed around less than 5 pregnancies per thousand pregnancies used the compounded HPC during the second or third trimester.

DR. KROP: So in 2005, there was a survey done of 572 maternal fetal medicine practitioners, and 67 percent of the respondents use progesterone at that time to prevent preterm birth. This is before Makena was on the market, so this is obviously all compounding. Then there was a 2007 survey done of 345 OBs that showed 74 percent recommended or offered progesterone, and 92 percent of users began recommending it within three years of the Meis trial. There were two publications. One was by Nest in AJOG, and one was by Henderson in AJP.

DR. LEWIS: And that was any progesterone or that was HP?

DR. KROP: It doesn't specify. I think it was 17-hydroxy.

Dr. Sibai, can you comment on that?

DR. SIBAI: In the study that I mentioned about 5,400 women, every single one of them received the compounded. Makena wasn't approved by that time. In addition, during this time, I received a grant from the CDC to study responders, and we used the compounded. So if Makena is not available, I assure you every physician in the United States will find every way possible to use the compounded, or much worse, they're going to see start offering cerclage to these women, which in my opinion is going to be catastrophic.

DR. LEWIS: Thank you. Dr Hickey?

DR. HICKEY: I was just going to say, clinically, when Makena was first approved, the price point also wasn't at an appropriate level for some people if they were paying out of pocket, so people continued to use the compounding form. And that would be, my expectation, if this was taken off the market and is not approved, then people are going to look for that equivalent wherever they can find it. Based on what we know with safety and poor outcomes, compounding pharmacies are not regulated, and I think that poses a serious health risk. But people will look for progesterone wherever they can find it. They won't just say, I'm not going to treat you.

DR. LEWIS: Dr. Lindsay?

DR. LINDSAY: Yes, I would second that comment. For years in our state, Makena was not approved, and you're going to see patients who are going to present with a history of preterm labor were using the compound. I think if it disappears tomorrow, that would be the same course that we would take. We would be giving patients compounded 17-OHP.

DR. LEWIS: Dr. Shaw?

DR. SHAW: I'm thinking about this question about the potential consequences of withdrawing, so I'm thinking of the population that bears the higher burden of preterm birth, mainly a disadvantaged population that tends to be lower education, lower economic status, perhaps self-pay insurance. This is a population that we're seeing -- we have two trials now for which we're debating the efficacy results in. We're concerned about 002. We can't explain the really high background rates from the placebo. We have 003. There's a lot we can't explain there.

We're going to tell this disadvantaged population that this evidence is good enough for you. In some ways, if we can turn this political piece around and argue that side of the story, how do we give this population the best chance at hard scientific evidence? Because I can tell you, people are terrible at judging risk. It's an emotional decision. You can have the conversation, but you're going to take that population that's not used to doing math and you're just going to start throwing statistics at them, and they're just going to not hear most of that.

So one consequence of withdrawal is a huge signal for concern. We're not sure. A consequence of not withdrawing is keep doing what you're doing; everything's fine. So I think the consequence of withdrawing allows for a deeper dive into this question. It's just not going to be possible. There is at least one, I think, advantage for this population, the very vulnerable, premature babies who aren't going to be able to weigh their options independently. So I think it's really important to think about the vulnerability of this population.

DR. BAUER: I agree with that; excellent and well said. I would argue also that this is going to be an opportunity, if it is withdrawn, for the professional societies to really look at their responsibility, and ethical responsibility, not only to their patients but to their members to really say, in fact, at least according to the FDA, it was inadequate evidence to say that we're doing net benefit for this.

There is an ethical responsibility not to provide ineffective treatments to a large proportion of the population, and then feel good that we've done everything we could do. In fact, it sounds like to me -- and again this is not my field, but there must be lots and lots of things that we don't understand about this disease because the rates vary so much over the world.

So that just suggests some of them are probably endemic to our society, but maybe there are others that can't be. I think this is an opportunity for us to really point that out. Again, I would hope that the professional societies would lead the way as opposed to opposing it.

DR. LEWIS: Ms. Ellis, and then Dr. Orza?

MS. ELLIS: I think what's missing here for me is just solid information that would help me vote with confidence. I think the only way to get that information -- it's very uncomfortable to say this; I feel like it's the Kobayashi Maru -- is to do a trial that stratifies, that is taking a lot more into consideration. And the only way to get that trial is for this drug to be withdrawn. However, it's a great deal of discomfort because of the women who have access and who will not have access for whatever time it takes to get that going.

So whatever the usage was in 2006 for people going off and getting it on their own, it's going to be more because of social media and mommy blogs. People are going to be talking about this. So whatever path is taken going forward, I hope that we consider the gap. And for people who are in need or at high risk for preterm labor while things are happening, that somehow something is put in place so that they don't fall through this gap.

DR. LEWIS: Dr. Reddy?

DR. REDDY: I'd argue against withdrawing it. There are subsets of this population, very high-risk patients who probably do benefit from it, women who had more than 2 preterm births; women who have delivered below 28 weeks. So I don't think withdrawing it just to do a trial makes any sense.

I think, though, it's clear -- I think everyone agrees we need to do more research and get better information on which patients could it be a benefit for. I think we're going to just have to -- the professional organizations, the best thing they can do is help us in counseling patients properly and getting them the right information, which they can do a good job with. But I think withdrawing it would be a disaster because it would be unethical for the patient populations who could benefit the most from it.

DR. LEWIS: So we do have an opportunity to vote, so it's not that you have to weigh in yes or no, but we are thinking of potential consequences, trying to get the views out there before we actually make up our minds,

Did you have a comment, Dr. Gillen? No?

DR. GILLEN: I always have a comment.

(Laughter.)

DR. GILLEN: I do, actually.

(Laughter.)

DR. GILLEN: I think certainly the way I view my job, as a public health practitioner and a clinical trialist, is to increase the prevalence of truly beneficial drugs. I think our job is to not only give patients choices, but to give them well-informed, empirically driven choices that we can stand behind. I think that the horse has been let out of the barn on this, and we need to pull it back in. And the only way that we can pull it back in and get to an answer on this is by having a randomized clinical trial. The only way I see that happening is to remove that approval.

There's no other way to build upon that, and we are at a place right now, you can see it on this committee, in my mind, that we don't have an answer. I mean, we hear words like "it probably works in a subset of a population" or "this works in a subset of a population." I have not seen that subset of a population yet. It has not been quantified.

DR. LEWIS: Thank you. Anybody else on consequences of withdrawing Makena for patients and clinical practice?

DR. SHAW; This is just a clarification. Dr. Reddy. I wasn't sure about if there was a study we were referring to in terms of women who have more than 2 preterm births. You said that those, we know that works. Was that coming from a different study than we saw today or -- just to get clarity.

DR. REDDY: There's a paper about the index pregnancy, the qualifying pregnancy. So the earlier the qualifying pregnancy, the more beneficial the effect of Makena; so that's published. In terms of women with 2 preterm births, that needs to be analyzed. That, I don't know. Those women are very high risk. Those are women who, if you counsel them, having counseled women like that, you tell them the data. You can tell them about the PROLONG study. They will take it because of the fact that there's one study that shows that there could be a benefit to them.

But I feel like we do have a lack of information. I would like to see an IPD with Makena only, not vaginal progesterone, and then also prolongation and pregnancy in both groups, based on what their index pregnancy delivery was.

DR. HUNSBERGER: Just to clarify, on the paper that you were discussing, was that from the 002 study or was that from the 003 study?

DR. REDDY: No, 002.

DR. HUNSBERGER; Okay. Thanks.

DR. LEWIS: So in terms of potential consequences of withdrawing Makena on patients in clinical practice, I think Dr. Wing summarized some of that under the prior discussion, political consequences in terms of some of the high-risk pregnancies among groups of minority races, low socioeconomic status, and emotional consequences. Patients really are in a desperate situation in that setting. They may have had a friend who's used it or they just feel like they want to do everything for their pregnancy.

One other hard consequence, of course, other types of progesterone will certainly be used, and we had a lot of discussion around what those constitute, primarily compounded forms of the medication. We don't know what the price point of those is going to be, and, of course, the risk-benefit status in terms of lack of not necessarily common practices creating a quality product.

So on the positive side, consequences of withdrawing the drug could be the opportunity to get higher quality data, avoid unknown risks from Makena use, which certainly long term, we don't have a lot of data on, and the opportunity for professional societies to take the lead in creating better quality evidence going forward.

We now have three voting questions to start to look at. If there's no further discussion on the question, we'll begin the voting process. We will be using an electronic voting system for this meeting. Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

We're going to go around the room for these voting questions and ask each person to weigh in. If you just are agreeing with the last person, you don't have to state everything the last person said. You can just say I agree with the last person, but I will ask for a rationale from each person.

The first voting question is question 4 from your booklet, do the findings of Trial 003 verify the clinical benefit of Makena on neonatal outcomes? And provide a rationale for your vote. You have the option of yes, no, or abstention.

(Voting.)

MS. BHATT: The voting results, zero is yes; no, 16; abstain is zero.

DR. LEWIS: Thank you. I'm going to start on my left with Dr. Eke, and we'll go around the room.

DR. EKE: Thanks. We've seen the data presented over and over again, here today. Based on what we see on both the 17-OHPC group and the placebo group, there was no evidence that there was increased benefit for the unit.

DR. LEWIS: Thank you. Dr. Hickey?

DR. HICKEY: I concur.

DR. LEWIS: Dr. Lindsay?

DR. LINDSAY: I concur.

DR. REDDY: I concur.

DR. WING: I concur.

DR. DRAKE: Agree.

DR. LEWIS: This is easy.

DR. BAUER: Yes, I agree.

DR. SHAW: Agree.

MS. ELLIS: I concur.

DR. ORZA: I concur.

DR. GILLEN: Agree.

DR. HUNSBERGER: Agree.

DR. SMITH: Agree.

DR. WADE: Agree.

DR. DAVIS: Agree.

DR. LEWIS: Thank you. So the committee's unanimous on that question, no evidence of neonatal benefit.

Question 5. Based on the findings from Trial 002 and 003, is there substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm births? And please provide a rationale for your vote; yes, no, or abstain.

(Voting.)

MS. BHATT: The results for question 5, yes is 3; no is 13; and abstain is zero.

DR. LEWIS: Okay. We'll do the same thing, but this time, each person please state your name into the microphone for the record when you provide the rationale for your vote.

Dr Eke?

DR. EKE: Thanks again. So I voted based on what we have with us, which is the FDA definition of substantial benefit, which based on what we have defined, Trial 003 does not meet that standard.

DR. HICKEY: Kim Hickey. I voted no because I felt the data in the study populations were disparate, and you couldn't come to a conclusion that both had substantial supporting evidence.

DR. LINDSAY: Michael Lindsay. I voted no for the similar reason. If you combine the two trials, there is no substantial evidence there is effectiveness.

DR. REDDY: I guess I have a lot to talk about. I voted yes. Substantial I guess is subjective, though, I feel that there is evidence, based on 002 clearly, and then in 003, if you focus on the U.S. PROLONG trial and the primary outcome, although the difference of the benefit was small, that's why I voted yes, taking it all together.

DR. WING: I'm Deborah Wing. I voted no for reasons previously stated.

DR. DRAKE: Matthew Drake. I also vote no for reasons previously stated. Unfortunately, the 003 trials is just not confirmatory for what was nicely seen in 002.

DR. LEWIS: Thank you. I voted yes, basically, the same reasons as Dr. Reddy.

DR. BAUER: Doug Bauer. I voted no, much for reasons that have been already stated, but I was also impressed with the consistency of the subgroup analysis across both studies, which showed no consistent subgroup where there was an effect. I was also swayed by the fact that 002 is a 20-year old trial, and I didn't feel like we were able to really understand the dynamics of that trial as well as we were able to pick apart 003.

DR. SHAW: I think Dr. Bauer stated a lot of my reasons for voting no, and just really not being able to identify the patients reliably as to which ones you would counsel to take this versus not.

MS, ELLIS: Annie Ellis. I voted yes. I felt that Trial 002 was still very compelling, although Trial 003 was not confirmatory.

DR. ORZA: Michele Orza. I voted no for similar reasons that have already been stated.

DR. GILLEN: Daniel Gillen. I voted no for reasons I've previously stated and those that have been also stated around the room.

DR. HUNSBERGER: Sally Hunsberger. I voted no, and I'd like to just affirm Dr. Bauer's comments in just that the consistency of the negative findings in the subgroups really swayed me.

DR. SMITH: Brian Smith. I voted no for the previously stated reasons.

DR. WADE: Kelly Wade. I voted no for the same reasons, and agree a lot with Dr. Bauer.

DR. DAVIS: Sean Davis. I voted no. While I, too, believe the results in 002 and do think this was a viable and quite important trial, it wasn't confirmed in 003. And in both trials, there was a lack of any detectable impact on the neonates, which is really what anyone really cares about.

DR. LEWIS: Thank you. Okay. Next question.

This is where it gets complicated.

(Laughter.)

DR. LEWIS: So FDA approval, including accelerated approval of a drug, requires substantial evidence of effectiveness, which is generally interpreted as clinically and statistically significant findings from two adequate and well-controlled trials, and sometimes from a single adequate and well-controlled trial.

For drugs approved under the accelerated approval pathway, based on a surrogate endpoint, the applicant is required to conduct adequate and well-controlled, post-approval trials to verify clinical benefit. If the applicant fails to conduct such a post-approval trial or if such trials do not verify clinical benefit, FDA may, following an opportunity for a hearing, withdraw approval.

Should the FDA, A) pursue withdrawal of approval for Makena; B) leave Makena on the market under accelerated approval and require a new confirmatory trial; C) leave Makena on the market without requiring a confirmatory trial? You're going to provide rationale for your vote, including the following:

Vote A if you vote to withdraw approval. That may be appropriate if you believe the totality of the evidence does not support Makena's effectiveness for its intended use, and under those circumstances discuss the consequences of Makena's removal if not previously discussed in discussion point 3.

Vote B, require a new confirmatory trial. That may be an appropriate vote if you believe the totality of evidence supports Makena's effectiveness in reducing the risk of preterm birth, but there is no substantial evidence of effectiveness on neonatal outcomes, and you believe a new confirmatory trial is necessary and feasible.

Discuss how the existing data provides substantial evidence of effectiveness of Makena in reducing the risk of preterm birth, based on surrogate endpoint of gestational age at delivery, and also discuss key study elements, including study population, control, doses, and efficacy endpoints of the new confirmatory trial, if not previously discussed under discussion point 2, and approaches to ensure successful completion of such a trial.

Vote C, leave Makena on the market without a new confirmatory trial. That may be appropriate if you believe Makena is effective for reducing the risk of preterm birth and that it is not necessary to verify Makena's clinical benefits in neonates. Discuss how the existing data provides substantial evidence of effectiveness of Makena in reducing the risk of preterm birth and why it is not necessary to verify Makena's clinical benefits in neonates.

Do people need a little extra time to digest this before they vote? Dr. Reddy?

DR. REDDY: So when it says trial, does it mean specifically RCT or does that mean research, further research?

DR. LEWIS: FDA, please, weigh in.

DR. NGUYEN: Hi. Christine Nguyen, FDA. So when we're talking a trial here, we are looking for a trial that will provide the robust evidence needed to verify the clinical benefits of Makena. That's the overall objective.

DR. LEWIS: Is that a randomized trial or not? Is it some other kind of study --

DR. NGUYEN: Sure.

DR. LEWIS: -- because we talked about other kinds of studies.

DR. NGUYEN: Yes. Certainly a randomized trial would be the design that we would think about, but, obviously, we are always open to other ideas that can achieve the same objective.

DR. LEWIS: When you say randomized trial, do you mean randomized placebo-controlled trial?

DR. NGUYEN: Same answer as previously. Here, we're trying to verify the benefit of the drug. So however that trial could be set up to help us identify the effect of the drug to the extent possible. So again, I think traditionally we think of a randomized-controlled trial, but is that the only trial? And if any of you have creative ideas of other trials that can give us the same information.

DR. REDDY: Sorry. I think this is an important point. Let's say you vote C, does that mean that the sponsor would not have to do any more research?

DR. NGUYEN: Correct, as far as verifying the drug's benefit.

DR. REDDY: So if you want further research done, then that's B, but you're saying it has to be the trial. We talked about various research ideas.

DR. NGUYEN: Yes, so let me just clarify B. There are two things that need to be considered for B. So when we're talking about considering the new confirmatory trial is necessary and feasible, it's necessary if you believe that Trial 003 was significantly flawed in such a way that the results either should be discounted or the results are not usable, so that we actually need another trial. It's not because we can't figure out or we don't have all the explanations of the results.

So that's the first one. And B would also reflect the fact that you think a trial is feasible, and such a trial should provide robust evidence to verify the clinical benefit of Makena. So I will stick my neck out there and say probably a PK/PD won't verify the clinical benefit of Makena.

DR. CHANG: This is Christy Chang from FDA. Could I also add another point of clarification? If you're contemplating a confirmatory trial with an active comparator, because nothing is approved by the FDA for the same indication, how do we make that comparison?

DR. LEWIS: Dr. Orza?

DR. ORZA: I believe for comparative effectiveness studies, there is not a requirement that it be FDA approved, but only that it be in widespread use. So if it were possible to identify a comparator that wasn't widespread use, that would be, I think from a funder's point of view, acceptable. Whether it would be acceptable to the FDA is another question.

DR. NGUYEN: Christine Nguyen, FDA again. Our task is to ensure that the drugs we approve have substantial evidence of effectiveness and usually compare to a placebo. We do not usually accept as an active comparator, if I may use that term. That has not been demonstrated to be safe and effective for the intended use because we don't know how to interpret the results.

If Makena performs, say, the same as vaginal progesterone, is it because neither are working, or are they both working? We can't really interpret the results.

DR. ORZA: So it might not help the FDA, but it might help the clinical community.

(Pause.)

MS. ELLIS: There's no abstain button.

(Laughter.)

DR. LEWIS: There's no button, but you can abstain.

(Laughter.)

DR. LEWIS: Dr. Lindsay?

(No audible response.)

(Voting.)

MS. BHATT: For question 6A is 9; B is 6; and C is zero.

DR. LEWIS: Thank you. Let's go in the opposite direction just for variety's sake here. So we'll start with Dr. Davis.

DR. DAVIS: I was interested, as I mentioned previously, on a trial to try to better define a higher risk population of mothers at risk of delivering preterm that potentially could have a more significant impact on neonatal outcome. I think those would be the ways that I would approach it with potentially dose escalation and other pharmacokinetics and pharmacometrics, and looking at dosing levels, and serum levels, and outcomes.

I recognize FDA's need to have a second confirmatory trial. I am concerned about putting the genie back in the bottle when it becomes standard practice and you have every major obstetrical organization supporting the continued use. I might suggest to FDA that they work with the sponsor to more narrowly limit the label and potentially indicate the non-confirmatory nature of the trial, though limited benefit to neonates, and the potential of limiting it to a higher risk population until another trial is done.

DR. LEWIS: Thank you. Dr. Wade?

DR. WADE: I voted no. I followed the outlined requirements of the accelerated approval process and what was outlined at the task at hand for

003, which I did not think verify -- unfortunately didn't verify the findings as 002. I am significantly worried about the consequences of that decision, though. and I think we could all spend a lot more time thinking about how to accelerate through another trial to get the data that we desperately need to safely treat women.

DR. LEWIS: Dr. Smith?

DR. SMITH: Brian Smith. I voted for option A. I would echo the comments made by Kelly Wade. I would also add that I heard one of the concerns with withdrawal of the molecule was that OBs would use unproven therapies like vaginal progesterone or cerclage, and to me I think the consideration there is that OBs have an obligation to their patients to do no harm.

DR. LEWIS: Thank you. Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger. I voted A. I just don't believe the totality of the evidence supports this, and I think this might be the only way to do a study where we will actually get the data that we need. And I think we really need data to understand what's going on.

DR. LEWIS: Thank you. Dr. Gillen?

DR. GILLEN: Dan Gillen. I definitely think that there are many, many repercussions to the withdrawal, and I don't make that choice lightly, but for me it's a logical process of elimination. I do not believe that substantial evidence has been established, given the results of the two studies. And by the sponsor's own admission, they believe that we can't trust the second study because the first study was on the market and leads to a bias population, which means that if you're going to do an honest assessment of this drug, it would have to be removed.

DR. LEWIS: Dr. Orza?

DR. ORZA: Michele Orza. I voted B, although I felt that my votes on questions 4 and 5 inexorably led to a vote of A. So I am voting B with a couple of conditions. I'm assuming that the clinical societies will, as Dr. Bauer rightly suggested, lead the way. The new evidence is still under consideration by them. The IPD meta-analysis, which could be updated with the new data on Makena, has yet to be released, and they will have to take that into consideration.

I think if they are moved to a position of equipoise so that a randomized, placebo-controlled, hopefully also with an active comparator -- if one is identified and can be done. then I think you can leave it on the market. But if that doesn't happen, then I think the FDA does need to withdraw it in order to make that study possible, because I do think that more compelling confirmatory evidence does need to be generated. I'm very compelled by Dr. Shaw's point about saying that this level of evidence is good enough for some people.

DR. LEWIS: Ms. Ellis?

MS. ELLIS: Yes. My heart wanted to vote C because mothers want nothing more than to have healthy babies, and the longer that we can keep them growing with our protection, the better. But I was prevented from doing so because choice B had the word "feasible," and if it's all false -- if one part's false, it's all false. So I could not vote that way.

I also had to consider the regulatory framework with which we are here and with which we function, and accelerated approval requires confirmation. And this vote, depending on what the decisions are made later on, may prevent my own daughter from accessing this drug. However, I got lucky with my second pregnancy, using something we don't use anymore and bed rest. And I think that mothers and babies shouldn't have to rely on luck. We need data. Thank you.

DR. SHAW: Pamela Shaw, and I voted A, and I spent most of the day knowing I had to answer this question, thinking about this particular question. And if there's any way I could have chosen B -- but I can't think -- I'm thinking noninferiority, is there a active comparator? No. I just cannot think of a feasible trial, so picking B, to me, is just going to prolong this painful process even longer. So I'm thinking A was the best practical choice for finding something that will work in neonatal infants as fast as possible.

DR. BAUER: Doug Bauer. Unfortunately, I also voted for A with a lot of trepidation, probably from the patient standpoint, which I think Ms. Ellis just eloquently summarized for us. But also, I really feel for the providers who are in the trenches, that are going to have to answer to their patients that are just demanding something for something. It's really an awful condition that we have no other choice for. But I really feel in the long run that removal of the drug is the right thing to do, and at least we'll have some possibility that then there'll be a properly done trial to finally answer the question.

DR. LEWIS: I voted B, reluctantly. I almost wanted to abstain because I think that the data are conflicting, and it's certainly not terribly persuasive one way or the other. I think that we would definitely benefit from additional data. I don't know that -- it's not going to be the quality of a randomized, placebo-controlled trial. I think it will shed some light, though, on perhaps understanding a population for whom this might be beneficial and ways that the drug's usefulness can be limited in some way, the labeling can be limited in some way that would help us find a better population who could use it.

DR. DRAKE: I'm Matthew Drake. I also voted for A. I think it's a very challenging situation we've been tasked with. I feel for those patients. I feel for the practitioners who will have to deal with them. But ultimately, I tried to be objective and just look at the efficacy requirements as spelled out by the FDA, and I just, unfortunately, didn't think that those were met. So for that reason, I vote A.

DR. WING: I'm Deborah Wing, and I struggled with my vote, and I voted A. I put on my clinician scientist hat and looked only at the data, and I do not believe there is substantial evidence of effectiveness based on my read of both of the trials and listening to the deliberations today and through this afternoon. I fully appreciate and have experienced the agency's requirements to adequately powered, appropriately designed trials to move products out onto the market.

I agree with Dr. Gillen. I think this drug likely got to market a little bit early, so we are hamstrung because of lack of results in a validation trial that was spread across the world. Obviously, one of the things we try to do when we impart our clinical trials to the world is generalize them. We actually generalized Makena and got negative results, which is, I think, not what we anticipated, but we do the science because we don't know. We asked a question and we didn't get an answer; we didn't get an answer we anticipated.

I'll come back to the ethical principles of doing good and doing no harm. I think the doing good here is continuing to ask the questions and asking are we doing good by the patients. And I think the only way by which to get the results of a confirmatory trial is to actually do another placebo-controlled trial.

As hard as that might sound, I know that the societies, the agency, and the sponsor will work together to try to figure out how to cover the gap we just created for the clinicians, and hopefully for the patients, because this is what we call in business, a big hairy audacious problem, and we have to put heads together and do something differently. But I'm not convinced that leaving Makena on the market as is, is the right thing to do.

DR. REDDY: I voted for B because I see A as untenable. I think withdrawing it from the market, you're not going to have a randomized-controlled trial.

It will be very difficult because, still, we are obligated to tell patients what the evidence is there.

002, the fact that it's 20 years old, I don't think that makes a difference because spontaneous, preterm delivery hasn't changed. It was a well done randomized-controlled trial. Why the rate was so high in the placebo group; who knows? But on the surface of it, it's a very supportive trial, and then you take 003, and, to me, it's apples and oranges.

The U.S. subgroup, there wasn't a significant difference. I get that. We can talk about power and the risk of it, but I do not think our RCT, a placebo randomized-controlled RCT will be done in the U.S. Patients are very smart. They have the information as physicians. I cannot say, oh, it's not FDA approved, so I'm not going to recommend it or I'm not going to discuss it, because all the medicines we use in pregnancy are not FDA approved. What we do is we counsel patients, and that's what we'll continue to do.

So I didn't vote for A because I think it's a big step backwards. I think by voting for B, we're getting additional information. I would only vote for

A if I thought the medicine was a danger, there was a safety issue, and I think 003 has resolved that. And at the least, I'm very happy about that, and I thought had no use whatsoever. So I think A is a vote for -- there's not going to be an RCT. Patients will not -- and physicians also. It's going to be very difficult to get patients into an RCT, placebo RCT.

DR. LINDSAY: Michael Lindsay. I voted for B. I agonized over this decision when I got the background information. I've been reading it over the last couple of weeks, and it was really clear that the evidence was conflicting, and I knew it was going to be conflicting today.

The reason why I chose B is I agree with Dr. Reddy. I didn't think A was really a valid choice. In terms of a clinician, I think one of the things that I struggle with is tomorrow I'm going to be seeing patients, and I have to give them some guidance of what they can do when they've had preterm delivery. I realize that this information is conflicting, and when you counsel people, you offer them the information, and then they make a choice.

I realize that doing another randomized-controlled trial may be the ideal way to kind of resolve the problem, but in the real world, as clinicians, we don't deal with idealism every day; we sort of deal with reality. I agree there probably are some subpopulations that are impacted in a positive way by this medication. We just haven't identified them, and I think that that would be one of the directions that I would encourage the FDA to pursue, encouraging investigators.

I think the reality, though, is as we let the genies out of the bottle and people know that there are medications that have been used for patients who had preterm deliveries, they're going to still want to get access to those medications. Clinicians like myself who've been out there for decades and have used compounding medications are going to give their patients compounding medications, and that's a reality.

So I think by following the rules -- and I say this to my trainees. I know the rules. I haven't followed them consistently, and I think this is an exercise that we really need to follow the rules, and

I'm not against that. But I think you also need to know the consequences, is that the problem is not going to go away, and people are going to seek other treatments and there'll be other methodologies of treatment.

DR. HICKEY: Hi. Kim Hickey. I also voted for B. I thought the idea of removal of the drug was, just like Dr. Reddy said, not feasible, and much like Dr. Lindsay said, our patients know it's there, and if I don't find them some sort of progesterone, they'll find someone who will. So I think doing the RCT placebo-controlled trial is not going to be feasible, and I feel there is a subset that have benefited from this.

I think it will be hard to look at someone who had a preterm delivery that had a term delivery on Makena, and then tell her, but it doesn't work, because we can all agree, and we all have, that the data's conflicting, and we don't like things about each trial. But to just toss it out and say we're going to go back to ground zero and put people at risk from potential compounded 17P, I don't think is worth it.

DR. EKE: I voted for B. Just like most of us said here, I struggled with this for days. Since I got the notification to go through this, I read through both trials. I struggled. The clinical trialist in me would say go for A, but when I look at the totality of the evidence, and especially what the consequences of this is going to be to all my patients and for people to take care of, if I look at what we have currently for treating -- this is not being sentimental, it's just looking back at why I voted for B. If we look at what we have, this is the only pharmacotherapy we have for preterm birth that has been shown to work in some populations.

The next thing, if we withdraw totally, people will be placed in cerclages, which studies have shown increases preterm birth in this population, and there are no other pharmacotherapies out there, so we'll see patients scrambling to get this. And I just worry about what that will be.

So why I looked at that, it was we keep this while we get -- I want to see a trial that will tell me which patients would benefit from this drug because I know and I believe that there are populations or patients that will benefit from this drug. I want to see those populations. I want to see an increased -- or a better outcome in units. Those were the things that kind of drove me to vote for B. Thanks.

DR. LEWIS: Before we adjourn, are there any last comments from FDA?

DR. WESLEY: This is Barbara Wesley. I'd like to make one clarification about who makes what rules. The FDA doesn't make the rules. The Congress makes rules about the statutory requirements. We carry out the rules. I think Congress consults with the Institute of Medicine, if I'm not mistaken. But they make the rules and set the statutory requirements. We carry them out. I just want to clarify that because I think sometimes that gets confusing.

DR. LEWIS: Thank you all for your attention and your -- I'm sorry. Dr. Nguyen, yes?

DR. NGUYEN: Actually, Dr. Lewis, I have the last comments.

DR. LEWIS: Sorry.

DR. NGUYEN: I would like to add, on behalf of FDA, we really thank everyone here today. We thank the applicant for their excellent presentation and their professionalism. I'd like to thank, obviously, all the FDA review staff who have worked tirelessly and very quickly to bring this to a meeting, and certainly our presenters. I'd like to acknowledge team members who worked very hard behind the scene, Christina Chang, who is our team leader and our two project managers, and Kalesha Grayson and Jeannie Roule.

Certainly last but not least, I want to express our gratitude to all of our AC staff members and all of you sitting at the table today. We appreciate how difficult this was for you, and it was very difficult for us as well. We also appreciate our decisions will affect each individual patient and their families. We're not just looking at facts, but we do owe it to the public to do the right thing, which is to put out drugs that are safe and effective, and we need to consider both.

So thank you very much again. Thank you, Kalyani. Thank you, Dr. Lewis, and we'll see some of you back tomorrow morning, so thanks.

Adjournment

DR. LEWIS: Yes. Thank you all for a productive day. Thanks to the FDA, sponsors, and of course the public for their contributions. We appreciate it. We are adjourned. Panel members, please take your personal belongings. The room will be cleaned at the end of today. Any material left on the table will be disposed of. Please leave your name badges, though, on the table; that I do want to remind you. So we're now adjourned. Thank you.

(Whereupon, at 4:26 p.m., the meeting was adjourned.)

October 29, 2019, Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) - Webcast Recording

The Center for Drug Evaluation and Research (CDER) provided a live webcast of the October 29, 2019, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee.

A recording of the webcast can be found at the following address:

- Start of Meeting to Morning Break: https://collaboration.fda.gov/pfdj6tbjng8i/
- Morning Break to Lunch Break: https://collaboration.fda.gov/pkmoqz9f1alj/
- Lunch Break to Afternoon Break: https://collaboration.fda.gov/pktdgjodgvx6/
- Afternoon Break to End of Meeting: https://collaboration.fda.gov/pel10yotagt7/

The webcast was broadcast using Adobe Connect. You can make sure your computer has the correct plug-ins to view the webcast at this web site:

https://collaboration.fda.gov/common/help/en/support/meeting_test.htm

Appendix 3

CDER Review Trial 003 CDER's Stats Review Evaluation, NDA 021945, Makena 20220707

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	021945
Supplement #:	
Drug Name:	Makena (Hydroxyprogesterone Caproate Injection) 250 mg/mL
Indication(s):	To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth
Applicant:	AMAG Pharmaceuticals, Inc.
Date(s):	Submitted: 9/11/2019 PDUFA: 7/11/2020
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Jia Guo, Ph.D.
Concurring Reviewers:	Mahboob Sobhan, Ph.D., Acting Team Leader Laura Lee Johnson, Ph.D., Director, Division of Biometrics III
Medical Division:	Division of Urology, Obstetrics and Gynecology, HFD-580
Clinical Team:	Barbara Wesley, M.D., Clinical Reviewer Christina Chang, M.D., Clinical Team Leader
Project Manager:	Kalesha Grayson

Keywords: NDA review, subgroup

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1 EXECUTIVE SUMMARY

Makena, hydroxyprogesterone caproate (HPC), received accelerated approval in 2011 for the reduction in the risk of recurrent preterm birth (PTB) in pregnant women with a history of a singleton spontaneous PTB (sPTB). For effectiveness, the new drug application (NDA) relied on data from the Maternal Fetal Medicine Unit (MFMU) Network Trial 002, in which, compared to placebo, Makena reduced the proportion of women delivering prior to 37^0 weeks gestation (i.e. 37 weeks 0 days), a surrogate endpoint reasonably likely to predict clinical benefit to neonates. As a condition of the accelerated approval, the Applicant conducted a confirmatory trial to verify and describe Makena's benefit on neonatal outcomes from reducing the risk of recurrent birth.

Initiated in 2009 and completed in 2018, the confirmatory trial (Trial 003) was an international, randomized, double-blind, placebo-controlled study that enrolled women with eligibility criteria like those of Trial 002. The trial's co-primary efficacy endpoint was (a) delivery < 35^0 weeks gestation and (b) a neonatal morbidity/mortality composite index.

In Trial 003, Makena did not demonstrate a statistically significant treatment effect compared to placebo on the co-primary efficacy endpoint. There was also no evidence of a treatment effect on either the proportion of PTB prior to 37^0 weeks gestation or on the proportion of PTB prior to 32^0 weeks gestation. However, the Applicant asserted that Makena could still be potentially beneficial in a subgroup with high risk of PTB based on their exploratory analyses.

The approach to this review is to evaluate the overall effectiveness first, followed by exploratory subgroup analyses, although results for exploratory subgroup analyses are not generally considered supportive of product effectiveness when the results in the overall population are negative.

Based on our analyses, we conclude Trial 003 failed to confirm the clinical benefit of decreased neonatal mortality and morbidity as measured by the neonatal composite index. Trial 003 also failed to substantiate Makena's treatment effect on the surrogate endpoint that supported the 2011 accelerated approval (gestational age at delivery) at the three cut points found in Makena's current prescribing information (delivering at <32^0, <35^0, and <37^0 weeks gestation). Furthermore, exploratory analyses did not uncover a subgroup in which Makena provided evidence of efficacy.

2 INTRODUCTION

2.1 Overview

Makena, hydroxyprogesterone caproate (HPC), received accelerated approval based on a single trial (Trial 002) in pregnant women with history of previous singleton sPTB. In Trial 002, compared to placebo, Makena reduced the proportion of deliveries prior to 37^0 weeks gestation, a surrogate endpoint reasonably likely to predict clinical benefit to neonates.

- Trial 002 showed that Makena (HPC 250 mg) injection administered intramuscularly once weekly starting at 16^0 weeks (16 weeks 0 days) to 20^6 weeks (20 weeks 6 days) gestation and used through 36^6 weeks gestation or birth reduced the proportion of women who delivered <37^0 weeks gestation from 55% (placebo) to 37% (Makena). The treatment difference was -17.8% [95% confidence interval (CI): -28%, -7.4%].

- Trial 002 also showed the proportions of women delivering at <35^0 and <32^0 weeks gestation was statistically significantly lower among women randomized to Makena compared to placebo. The treatment difference was -9.4% (95% CI: -19.0%, -0.4%) for delivery <35^0 weeks gestation and -7.7% (95% CI: -16.1%, -0.3%) for delivery <32^0 weeks gestation.
- Overall, from the clinical perspective the treatment effect was sufficiently persuasive to support accelerated approval based on the findings of Trial 002.

A post-approval requirement was issued at the same time with the accelerated approval in 2011 that a confirmatory trial should be completed to verify and describe the clinical benefit of Makena. This trial was to include at least 15 investigational sites (US and non-US), with no single site enrolling more than 15% of the total number of subjects to verify Makena's clinical benefit on neonates. Also, at least 10% of the total randomized subjects would need to be from US and Canadian sites. This confirmatory trial (Trial 003) was initiated in 2009 and completed in 2018.

2.2 Data Sources

The study data, reports and additional information for these studies were submitted electronically. These items are located in the Electronic Document Room at \\Cdsesub1\EVSPROD\NDA021945 under the submissions dated 07/30/2019, 08/14/2019, 08/15/2019, 08/20/2019, 09/06/2019, 09/11/2019, 09/23/2019, 09/25/2019, 09/27/2019, and10/18/2019.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Applicant submitted analysis datasets and associated programs to generate analysis results for the Trial 003. Data sets were complete and documented. Pre-specified statistical analyses were carried out per the analysis plan. Post-hoc analysis results and responses to the Division's information requests were also submitted.

3.2 Evaluation of Efficacy

The current review focuses on the efficacy evaluation of Makena in Trial 003. The overall approach to this review is as follows:

- Evaluate the overall effectiveness of Makena in Trial 003 to confirm the Makena's clinical benefit on neonates.
- Perform exploratory analyses to determine whether the effectiveness varied by various demographics, baseline characteristics and composite risk level to justify the Applicant's assertation that Makena could be beneficial to any specific subgroup of patients.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Trial 003 was a multi-center, randomized, double-blind, placebo-controlled clinical trial in women with a singleton pregnancy, aged 18 years or older, with a history of a previous singleton sPTB. Trial 003 was conducted in the United States, Canada, Russia, Ukraine, Hungary, Spain, Bulgaria, the Czech Republic, and Italy.

Eligible subjects were randomized in a 2:1 ratio to receive either Makena or placebo and received weekly injections of study drug from randomization (16^0 through 20^6 weeks of gestation) until 36^6 weeks of gestation or delivery, whichever occurred first.

Randomized subjects were to be followed for efficacy outcomes through the date of delivery and for adverse events (AEs) up to the End-of-Treatment Period Visit, defined as 35 ± 7 days after the last dose of study drug. If the End-of-Treatment Period Visit occurred before the date of delivery, maternal and fetal deaths were to be reported until delivery. Neonates of randomized subjects were followed until Day 28 or the date of discharge from the NICU or equivalent, whichever occurred later.

3.2.1.2 Endpoints

3.2.1.2.1 Primary Efficacy Endpoint

There was a co-primary endpoint in Trial 003:

> **Surrogate endpoint:** PTB prior to 35^0 weeks of gestation; scored 1 if any of the following events occurred: a delivery occurring from randomization up through 34^6 weeks of gestation, including a miscarriage occurring from 16^0 through 19^6 weeks of gestation, and an elective abortion; 0 otherwise.
>
> **Clinical endpoint:** Neonatal morbidity and mortality composite index; scored 1 if the liveborn neonate had any of the following events occurred at any time during the birth hospitalization up through discharge from the neonatal intensive care unit (NICU): neonatal death, grade 3 or 4 intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), or proven sepsis; 0 otherwise.

3.2.1.2.2 Secondary Efficacy Endpoints

Two additional secondary efficacy endpoints were also evaluated.

- PTB prior to 32^0 weeks of gestation
- PTB prior to 37^0 weeks of gestation

3.2.2 Statistical Methodologies

3.2.2.1 Primary Analysis

For the co-primary efficacy endpoint, the number and percentage of subjects for the event were presented by treatment group. Statistical significance of the treatment effect between Makena and placebo for each component of the co-primary endpoint was tested using a Cochran–Mantel–Haenszel test (CMH) stratified by gestational age at randomization (16^0 to 17^6 weeks and 18^0 to 20^6 weeks). The two secondary efficacy endpoints were analyzed in a similar way as the co-primary efficacy endpoint.

The interaction between treatment and gestational age at the time of randomization was assessed by a logistic regression model of preterm delivery prior to 35^0 weeks of gestation with terms for treatment, gestational age at randomization stratum, and treatment-by-gestational age interaction term. A similar analysis was performed for the neonatal composite index.

3.2.2.2 Exploratory Analysis

Trial 003 failed to demonstrate efficacy with respect to both components of the co-primary endpoint. The Applicant conducted a series of post-hoc exploratory subgroup analyses to understand the potential reasons for the negative findings in Trial 003. Details are presented in section 4.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 1708 subjects were randomized to either Makena (n=1130) or placebo (n=578). Almost all (99%) subjects completed the study and completed treatment (93%). Russia, Ukraine and the U.S. were the three highest enrolling countries, randomizing 621 (36%), 420 (25%) and 391 (23%) subjects, respectively, followed by Hungary, Spain, Bulgaria, Canada, the Czech Republic, and Italy, which each had less than 100 subjects (16% of all subjects).

The Applicant defined the following efficacy analysis populations:

- Intent-to-treat (ITT) population: all randomized subjects. Subjects were analyzed by the treatment group to which they were randomized, regardless of the blinded study medication (active or placebo) the subject received.
- Liveborn neonatal population: all babies of randomized women in the ITT Population who were liveborn and for whom morbidity/mortality data were available.

Table 1: Trial 003 Subject Disposition

	Makena, N(%)	Placebo, N(%)
Subjects randomized (ITT population)	1130	578
Subjects who received at least one dose of study drug (safety population)	1128 (99.8)	578 (100)
Liveborn infant with morbidity data available (liveborn neonatal population)	1091 (96.5)	560 (96.9)
Subjects withdrawing from study	18 (1.6)	6 (1.0)
Subjects discontinuing study drug	80 (7.1)	43 (7.4)

Source: Applicant's study report

The Makena and placebo groups were comparable across all demographic and baseline characteristics (see Table 7). The mean age was 30 years and pre-pregnancy BMI was 24.4 kg/m^2. Of the randomized subjects, 88% were white, 7% were black, and the rest included Native Hawaiian/Pacific Islanders, Asian and American Indian or Alaska native, mixed race and other. Almost all black subjects were from the United States. Approximately 10% of women were never married or divorced/widowed/separated, approximately 8% smoked, approximately 3% consumed alcohol, and 1.3% used illicit drugs.

The treatment groups were also well balanced with respect to obstetrical characteristics in the current and previous pregnancies. Overall, the mean (SD) gestational age at randomization was 18.4 (1.5) weeks for the Makena group and 18.5 (1.5) weeks for the placebo group. Slightly more subjects initiated study drug between 18^0 to 20^6 weeks of gestation (56% Makena, 58% placebo) than between 16^0 to17^6 weeks (44% Makena, 41% placebo).

3.2.4 Results and Conclusions

3.2.4.1 Primary Analyses

The results for co-primary and secondary endpoints are shown (in descending order) in Table 2. An event listed in the neonatal composite index occurred (scored as a value of 1) in 5.4% and 5.2% of liveborn infants in the Makena and placebo groups, respectively, with a difference of 0.2% (95% CI: -2.0%, 2.5%) as shown in Table 2. The rate of PTB prior to 35^0 weeks gestation was 11.0% and 11.5% in the Makena and placebo groups, respectively, with a difference of -0.6% (95% CI: -3.8%, 2.6%). The treatment effect of Makena compared to placebo was not statistically significant for either component of the co-primary endpoint.

The rates of PTB prior to 32 weeks gestation and prior to 37 weeks gestation were also not different between the Makena and placebo groups.

Table 2: Trial 003 Efficacy Results

Efficacy Endpoints	Makena (N=1130)	Placebo (N=578)	Treatment Difference (95% CI)*	P-value*
Neonatal composite index	5.4% (59/1091)	5.2% (29/560)	0.2% (-2.0, 2.5)	0.84
PTB <35^0 weeks (%)	11.0% (122/1113)	11.5% (66/574)	-0.6% (-3.8, 2.6)	0.72
PTB <32^0 weeks (%)	4.8% (54/1116)	5.2% (30/574)	-0.4% (-2.8, 1.7)	
PTB <37^0 weeks (%)	23.1% (257/1112)	21.9% (125/572)	1.3% (-3.0, 5.4)	

Abbreviations: N: number of randomized subjects, CI: confidence interval, PTB: preterm birth
*Difference, 95% CI and P-value were from CMH method stratified by gestational age at randomization
Source: Statistical Reviewer analysis

3.3 Evaluation of Safety

Please refer to clinical review for safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

<u>Applicant's subgroup analysis:</u>
The Applicant conducted subgroup analyses for the co-primary efficacy endpoint by subgroups defined in Table 3 for the overall study population in Trial 003 and its U.S. subgroup. Cervical length and race subgroups were pre-specified exploratory analyses in the SAP and the rest of the subgroups in Table 3 were post-hoc for exploratory purposes.

Table 3: Trial 003 Subgroup Categories

Subgroup	Categories
Geographic region	U.S., Non-U.S.
Gestational age at randomization	16^0-17^6 weeks, 18^0-20^6 weeks
Gestational age at qualifying delivery*	20^0-<28^0 weeks, 28^0-<32^0 weeks, 32^0-<35^0 weeks, 35^0-<37^0 Weeks
Gestational age at earliest prior PTBs	0-<20^0, 20^0-<28^0, 28^0-<32^0, 32^0-<35^0, 35^0-<37^0
Number of previous PTBs	1, 2, ≥3
Cervical length at randomization	<25 mm ≥25 mm
BMI before pregnancy (kg/m^2)	<18.5, 18.5 - <25, 25-<30, ≥30
Any substance use during pregnancy	Yes, No
Smoking	Yes, No
Alcohol	Yes, No
Illicit drugs	Yes, No
Race	Non-Hispanic black, non-Hispanic non-black
Ethnicity	Hispanic, non-Hispanic
Years of education	≤12, >12

* Qualifying delivery is the most recent preterm delivery.

The Applicant's subgroup analyses results for the co-primary efficacy endpoint are presented in Table 8 and Table 9 in the Appendix. The Applicant's analyses found the overall event rates for PTB <35^0 weeks and the neonatal composite index were higher in the US relative to ex-US regions and the treatment effect of Makena was slightly greater in US. than ex-US region. CDER's analyses are described in section 4.1. The Applicant also concluded that the treatment effects of Makena vs. placebo were similar across categories for other subgroup variables listed in Table 3.

<u>Reviewer's exploratory analysis</u>

The statistical team reviewed all Applicant's subgroup analysis results and conducted subgroup analyses by region and race because these subgroups are evaluated by FDA routinely. In addition, the reviewer explored subgroups that differentiate the study populations between Trial 003 and 002.

For each of these subgroup analyses, the difference between the Makena and placebo groups was computed using two methodologies, a stratified Cochran Mantel Haenszel (CMH) method and shrinkage estimation through Bayesian modeling. The subgroup analysis using the CMH method evaluates a particular subgroup category independently from other subgroup categories and relies only on the data from the subjects in that particular category. The Bayesian shrinkage estimation analysis evaluates all categories of one subgroup variable jointly and borrows information across categories to reduce the variability of the estimates and prevent random highs and random lows.

Generally, CDER does not support subgroup analyses for inference of efficacy when the primary analysis result does not demonstrate efficacy. There are multiple reasons to not consider subgroup analyses to support establishing efficacy when the treatment effect in the overall population is not significant (FDA 1998; FDA 2017b).

The major statistical reason is the inflation of type I error probability, that is, the heightened probability of incorrectly concluding a treatment effect. When such subgroup analyses are used to search for evidence of a treatment effect, there is a high probability that any observed favorable subgroup results are due to chance alone. Therefore, CDER generally considers such analyses for hypothesis-generating purposes only.

4.1 By Geographic Region (U.S. vs non-U.S.)

In the U.S. subgroup of Trial 003, both the neonatal composite index and preterm birth prior to 35^0 weeks endpoints showed no evidence of a treatment effect using stratified CMH and shrinkage estimation. Although the point estimates of -2.2%, based on the CMH analytic method, for the co-primary endpoint in the U.S. subgroup are in the direction of a beneficial treatment effect, the 95% confidence intervals around these point estimates include 0, indicating no evidence of effect even in these exploratory subgroup analyses. Similarly, no evidence of a treatment effect was seen for the endpoints of delivery < 37^0 weeks or < 32^0 weeks. In addition, the interaction between treatment and region for each component of the co-primary endpoint was assessed by a logistic regression model with treatment, region, and treatment-by-region interaction; no significant interaction effect was noted. Therefore, Trial 003 did not show that Makena had a favorable treatment effect compared to placebo for either component of the co-primary endpoint nor on the secondary endpoints in either the U.S. or non-U.S. region (see Table 4).

Table 4: Trial 003 Results of Efficacy Endpoints by Region (U.S. vs non-U.S.)

Endpoint Subgroup (% (n/N))	Makena (N=1130)	Placebo (N=578)	Treatment Difference* (95% CI)	Treatment Difference** (95% CI)
Neonatal composite index				
U.S.	7.1% (18/252)	9.5% (12/126)	-2.2% (-8.3, 3.9)	-0.2% (-4.9, 2.8)
Non-U.S.	4.9% (41/839)	3.9% (17/434)	1.0% (-1.4, 3.3)	0.6% (-1.6, 2.8)
Preterm birth <35^0 weeks				
U.S.	15.6% (40/256)	17.6% (23/131)	-2.2% (-10.1, 5.7)	-0.8% (-6.0, 3.5)
Non-U.S.	9.6% (82/857)	9.7% (43/443)	-0.2% (-3.6, 3.2)	0.4% (-3.6, 2.8)
Preterm birth <32^0 weeks				
U.S.	5.5% (14/256)	9.2% (12/131)	-3.9% (-9.6, 1.7)	-0.6% (-8.4, 3.8)
Non-U.S.	4.7% (40/860)	4.1% (18/443)	0.6% (-1.7, 2.9)	0.5% (-1.8, 2.8)
Preterm birth <37^0 weeks				
U.S.	33.2% (85/256)	28.2% (37/131)	4.7% (-5.0, 14.3)	1.8% (-3.6, 9.0)
Non-U.S.	20.1% (172/856)	20.0% (88/441)	0.2% (-4.4, 4.8)	0.9% (-3.5, 5.2)

*Cochran–Mantel–Haenszel method
**Shrinkage estimation method
Source: Statistical Reviewer's analysis

4.2 By Race (Black vs. Non-Black)

Similarly, subgroup analysis by race (black and non-black) in Trial 003 did not provide evidence that Makena had a treatment effect on either component of the co-primary efficacy endpoint nor on the secondary endpoints in the black or non-black subgroups (see Table 5).

Table 5: Trial 003 Results of Efficacy Endpoints by Race

Endpoint Subgroup (% (n/N))	Makena (N=1130)	Placebo (N=578)	Treatment Difference* (95% CI)	Treatment Difference** (95% CI)
Neonatal composite index				
Black	8.7% (6/69)	7.5% (3/40)	0.8% (-9.9,11.5)	0.4% (-5.0, 6.2)
Non-black	5.2% (53/1022)	5.0% (26/520)	0.2% (-2.1, 2.5)	0.2% (-2.0, 2.4)
PTB <35 weeks gestation				
Black	23.6% (17/72)	19.5% (8/41)	3.0% (-12.5, 18.5)	-0.1% (-6.7, 9.6)
Non-black	10.1% (105/1041)	10.9% (58/533)	-0.8% (-4.1, 2.4)	-0.7% (-3.9, 2.5)
PTB <32 weeks gestation				
Black	11.1% (8/72)	9.8% (4/41)	0% (-11.4, 11.3)	-0.4% (-5.6, 5.5)
Non-black	4.4% (46/1044)	4.9% (26/533)	-0.5% (-2.7, 1.7)	-0.5% (-2.7, 1.7)
PTB <37 weeks gestation				
Black	37.4% (27/72)	34.2% (14/41)	2.1% (-16.2, 20.3)	1.3% (-7.1, 10.3)
Non-black	22.1% (230/1040)	20.9% (111/531)	1.2% (-3.0, 5.5)	1.2% (-3.2, 5.6)

*Cochran–Mantel–Haenszel method
**Shrinkage estimation method
Source: Statistical Reviewer's analysis

In Trial 003, the majority of Black subjects were from the U.S. Therefore, subgroup analysis by race was carried for the U.S. region only; results are presented below. No consistent treatment effect was observed for the three cutoff time points of gestational age at delivery or the neonatal composite index. The findings from this subgroup analysis by race in Trial 003 U.S. subjects were not in line with the findings from Trial 002.

Table 6: Trial 003 Results of Efficacy Endpoints by Race – U.S. subjects only

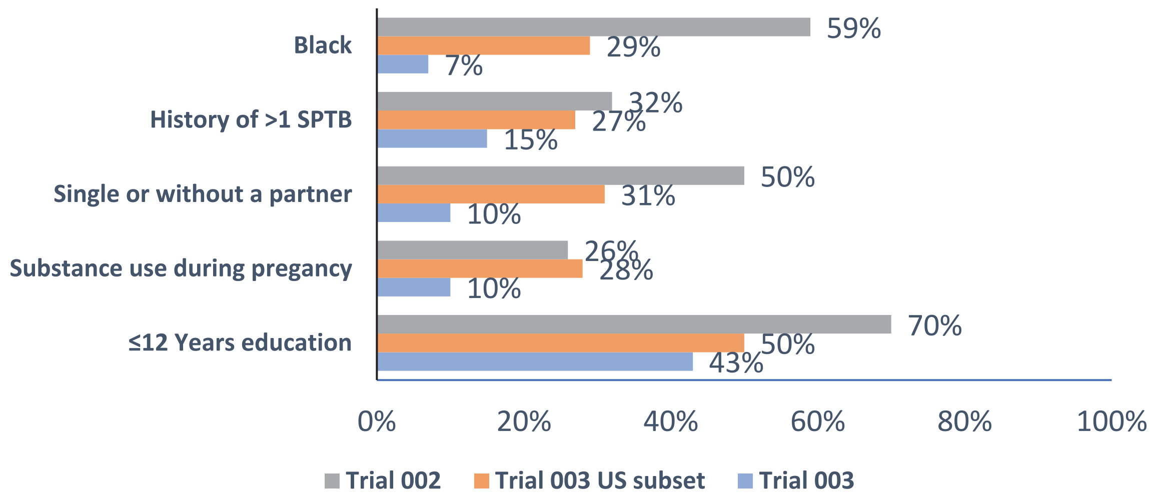
Endpoint Subgroup (% (n/N))	Makena (N=256)	Placebo (N=131)	Treatment Difference* (95% CI)	Treatment Difference** (95% CI)
Neonatal composite index				
Black	7.4%(5/68)	7.5%(3/40)	-0.7% (-11.1,9.7)	-2.0% (-8.5 5.0)
Non-black	7.1%(13/184)	10.5%(9/86)	-3.0% (-10.5, 4.5)	-2.3% (-8.1, 3.4)
PTB <35 weeks gestation				
Black	22.5% (16/71)	19.5% (8/41)	1.7% (-13.7, 17.1)	-1.6% (-10.9, 9.1)
Non-black	13.0% (24/185)	16.7% (15/90)	-3.7% (-12.8, 5.5)	-2.5% (-10.8, 5.3)
PTB <32 weeks gestation				
Black	9.9% (7/71)	9.8 % (4/41)	-1.5% (-12.6, 9.6)	-3.6% (-10.6, 4.2)
Non-black	3.8% (7/185)	8.9 % (8/90)	-5.0% (-11.5, 1.5)	-4.2% (-10.3, 1.4)
PTB <37 weeks gestation				
Black	36.6%(26/71)	34.2%(14/41)	1.0% (-17.3, 19.3)	4.1% (-8.5, 15.8)
Non-black	31.9%(59/185)	25.6%(23/90)	6.3% (-4.9, 17.6)	4.9% (-4.7, 15.4)

*Cochran–Mantel–Haenszel method
**Shrinkage estimation method
Source: Statistical Reviewer's analysis

4.3 Additional Subgroup Analyses

The Applicant asserted that differences in demographic and risk factors between Trial 002 and Trial 003 may have contributed to the inconsistent result between trials even though both trials were nearly identical in design. When comparing the demographics and baseline characteristics, notable differences exist between the two trials with respect to 5 factors including black race, history of more than one previous sPTB, single or without a partner, substance use during pregnancy, and no more than 12 years of education.

Figure 1: Demographics and Baseline Characteristics Comparison between Trial 002 and Trial 003



Source: Statistical Reviewer's analysis.

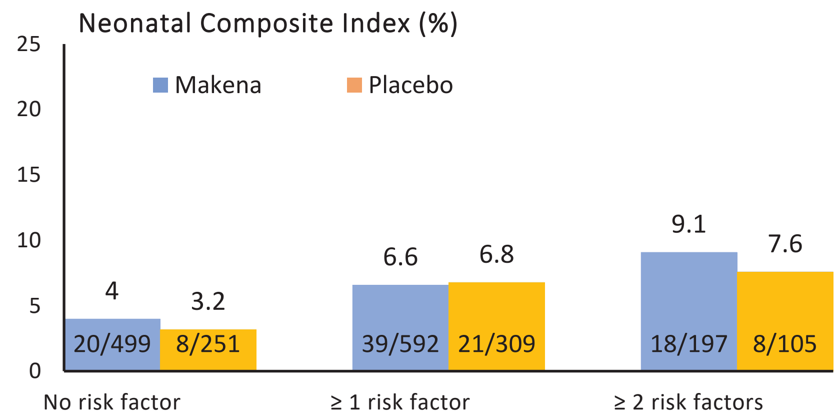
The Applicant concluded that it is possible that differences in baseline risk for PTB underpin the lack of correlation between the efficacy results observed in Trial 002 and Trial 003, where Trial 002 comprised of a higher risk population than Trial 003 (see Applicant's AC briefing material section 8: discussion).

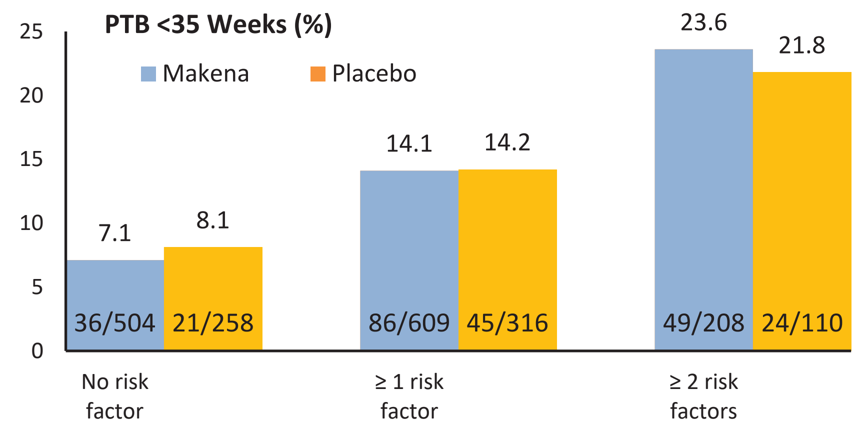
The statistical reviewer conducted subgroup analysis for the efficacy endpoints by the 5 risk factors which differentiated the two trial study populations and the results are presented in Table 5 and Table 10 to Table 13 (see Appendix). The statistical reviewer also conducted exploratory analyses using logistic regression models for each component of co-primary efficacy endpoint with treatment, region, each of the above 5 risk factors, and its interaction with treatment. These analyses did not provide - evidence of efficacy over placebo in any subpopulation and there was no statistically significant interaction between Makena and any of these risk factors.

The statistical reviewer explored the subpopulations defined by composite risk level defined by the 5 risk factors. Three subpopulations were defined as subjects had none of the risk factors, had at least one risk factor, had at least two risk factors. Figure 2 presents the subgroup analysis results by the composite risk level for the co-primary endpoint. In the top bar graph, the height of the bar represents the percentage of neonates who had at least one event defined in the neonatal composite index in each treatment group for that risk level subgroup. The difference between the blue bar and orange bar represents the treatment effect of Makena vs. Placebo for the neonatal composite index in that risk group. As we see from the bar graph, when the overall risk increases on the x-axis, the percentage of neonates who had at least one neonatal composite index event in both treatment groups increases as well. However, the treatment effect of Makena vs. placebo on this endpoint did not improve. In the group of subjects who had at least 2 factors, placebo was slightly favored instead. Similar results were seen for the PTB prior to 35^0 weeks, shown in the bar graph at the bottom.

In summary, although these risk factors may have impacted the overall PTB or neonatal composite index rate, there was no evidence in Trial 003 that these factors had an impact on the treatment effect, given that no suggestion of efficacy was seen even in groups with higher risk levels.

Figure 2: Trial 003 Subgroup Analysis Results by Composite Risk Profile





Source: Statistical Reviewer's analysis. the height of each bar represents the percentage of subjects who had the event in that subgroup group category. The "≥2 risk factors" category is included in the "≥1 risk factor" category.

Considering the Applicant's and the reviewer's subgroup analyses results, Makena did not demonstrate any favorable effect over placebo in the key efficacy endpoints in any of the evaluated subgroups either.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

CDER approved Makena under the accelerated approval pathway based primarily on the results of a single adequate and well-controlled clinical trial, Trial 002, in which the drug showed a treatment effect on the surrogate endpoint of proportion of women delivering at $< 37^0$ weeks. As a condition of approval, CDER required the applicant to conduct an appropriate post-approval study to verify and describe Makena's predicted effect on preterm birth and neonate morbidity/mortality. The applicant conducted such a study in Trial 003, an adequate and well-controlled trial evaluating the efficacy of Makena.

In summary, Trial 003 did not demonstrate a treatment effect of Makena on reducing the neonatal composite index or the rate of preterm birth prior to 35^0 weeks gestation, nor was there evidence of a treatment effect on the rate of preterm birth prior to 37^0 weeks or 32^0 weeks gestation. Comparing to Trial 002, although the two trial populations differed in certain risk factors for PTB (e.g., demographics and socioeconomic factors), CDER determined these risk factors were not effect modifiers. Exploratory subgroup analyses also failed to provide evidence of clinical benefit within any specific subgroup. Even if they did, the significant statistical limitations of these types of analyses would preclude reliable inference of efficacy based on their findings.

5.2 Conclusions and Recommendations

From a statistical perspective, we conclude that Makena failed to confirm clinical benefit for the intended indication.

APPENDICES

Table 7: Demographics and Baseline Characteristics: Trial 003

Variable	Makena (N=1130)	Placebo (N=578)
Gestational age at randomization, weeks (mean ± SD)	18.4 ± 1.5	18.5 ± 1.5
$<16^0$ (n,%)	6 (1)	4 (1)
16^0-17^6	495 (44)	236 (41)
18^0-20^6	628(56)	333(58)
$>20^6$	1(0)	5(1)
Number of previous preterm deliveries		
1 previous PTB, N (%)	964 (85)	494 (86)
>1 previous PTB, N (%)	166 (15)	82 (14)
Number with cervical length <25 mm at randomization, N (%)	18 (2)	9 (2)
Age, years	30 ± 5	30 ± 5
Race, N (%)		
Black or African American/African Heritage	73 (6)	41 (7)
White	1004 (89)	504 (87)
Asian	23 (2)	22 (4)
Other	30 (3)	11 (2)
Ethnicity, N (%)		
Hispanic or Latino	101 (9)	54 (9)
Non-Hispanic or Latino	1029 (91)	524 (91)
Marital Status, N (%)		
Married or living with partner	1013 (90)	522 (90)
Never married	86 (8)	40 (7)
Divorced, widowed or separated	31 (3)	16 (3)
BMI before pregnancy	24.3 ± 7.1	24.7 ± 8.7
Years of education	13 ± 2	13 ± 2
Any substance use during pregnancy, N (%)	105 (9)	51 (9)
Smoking	92 (8)	40 (7)
Alcohol	23 (2)	18 (3)
Illicit drugs	15 (1)	8 (1)

Source: Applicant Analysis.

Table 8: Applicant's Summary of Neonatal Composite Index by Subgroups

	Trial 003		Trial 003 U.S. subset	
Neonatal Composite Index, Subgroup	Makena (N=1091)	Placebo (N=560)	Makena (n=252)	Placebo (n=126)
Region				
U.S.	18/252 (7.1)	12/126 (9.5)		
Non-U.S.	41/839 (4.9)	17/434 (3.9)		
GA at randomization (weeks)				
16^0-17^6	25/481 (5.2)	12/230 (5.2)	4/93 (4.3)	4/36 (11.1)
18^0-20^6	34/610 (5.6)	17/330 (5.2)	14/159 (8.8)	8/90 (8.9)
Overall	59/1091 (5.4)	29/560 (5.2)	18/252 (7.1)	12 /126 (9.5)
GA of qualifying delivery* (weeks)				
20^0 - <28^0	17/221 (7.7)	3/97 (3.1)	3/30 (10.0)	2/17 (11.8)
28^0 - <32^0	14/198 (7.1)	13/102 (12.7)	3/37 (8.1)	4/18 (22.2)
32^0 - <35^0	15/339 (4.4)	9/182 (4.9)	3/73 (4.1)	5/39 (12.8)
35^0 - <37^0	13/330 (3.9)	4/176 (2.3)	9/110 (8.2)	1/51 (2.0)
GA of earliest prior PTB** (weeks)				
0 - <20^0	24/445 (5.4)	11/228 (4.8)	5/75 (6.7)	3/35 (8.6)
20^0 - <28^0	13/153 (8.5)	2/71 (2.8)	4/27 (14.8)	1/18 (5.6)
28^0 - <32^0	9/112 (8.0)	7/59 (11.9)	2/29 (6.9)	3/13 (23.1)
32^0 - <35^0	7/198 (3.5)	6/99 (6.1)	2/59 (3.4)	4/29 (13.8)
35^0 - <37^0	6/183 (3.3)	3/102 (2.9)	5/62 (8.1)	1/31 (3.2)
Previous PTB, N (%)				
1	43/933 (4.6)	22/478 (4.6)	11/184 (6.0)	8/92 (8.7)
>1‡	16/158 (10.1)	7/80 (8.8)	7/78 (9.0)	4/34 (11.8)
2	14/125 (11.2)	5/66 (7.6)	6/52 (11.5)	4/28 (14.3)
≥3	2/33 (6.1)	2/14 (14.3)	1/16 (6.3)	0/6 (0.0)
Cervical length at randomization***, N (%)				
<25 mm	2/17 (11.8)	2/9 (22.2)	1/13 (7.7)	1/3 (33.3)
≥25 mm	44/890 (4.9)	23/444 (5.2)	11/110 (10.0)	10/63 (15.9)
BMI before pregnancy (kg/m^2)				
Underweight (<18.5)	4/80 (5.0)	3/37 (8.1)	0/11 (0)	0/2 (0)
Normal (18.5 - <25)	34/629 (5.4)	12/328 (3.7)	7/112 (6.3)	2/49 (4.1)
Overweight (25 - <30)	10/249 (4.0)	9/125 (7.2)	6/63 (9.5)	6/34 (17.6)
Obese (≥30)	11/133 (8.3)	5/69 (7.2)	5/66 (7.6)	4/41 (9.8)
Any substance use during pregnancy, N (%)				
Yes	8/101 (7.9)	5/49 (10.2)	5/67 (7.5)	4/38 (10.5)
No	51/990 (5.2)	24/511 (4.7)	13/185 (7.0)	8/88 (9.1)
Smoking				
Yes	8/89 (9.0)	4/39 (10.3)	5/57 (8.8)	3/29 (10.3)
No	51/1002 (5.1)	25/521 (4.8)	13/195 (6.7)	9/97 (9.3)
Alcohol				
Yes	0/23 (0)	4/17 (23.5)	0/19 (0)	3/15 (20.0)
No	59/1068 (5.5)	25/543 (4.6)	18/233 (7.7)	9/111 (8.1)
Illicit drugs				
Yes	1/14 (7.1)	1/7 (14.3)	1/13 (7.7)	1/7 (14.3)
No	58/1077 (5.4)	28/553 (5.1)	17/239 (7.1)	11/119 (9.2)
Race				
Non-Hispanic black	6/69 (8.7)	3/39 (7.7)	5/68 (7.4)	3/39 (7.7)
Non-Hispanic non-black	50/923 (5.4)	23/468 (4.9)	13/153 (8.5)	7/64 (10.9)
Ethnicity				
Hispanic	3/99 (3.0)	3/53 (5.7)	0/31 (0)	2/23 (8.7)
Non-Hispanic	56/992 (5.6)	26/507 (5.1)	18/221 (8.1)	10/103 (9.7)
Years of education				
≤12	28/458 (6.1)	18/249 (7.2)	9/116 (7.8)	9/69 (13.0)
>12	31/632 (4.9)	11/311 (3.5)	9/135 (6.7)	3/57 (5.3)

* If more than one prior delivery was sPTB, qualifying delivery was the most recent. ** The earliest PTB may be indicated or spontaneous. ***Cervical length measurement was not captured for all subjects in a treatment group.
GA = gestational age, NA = not available
Source: Applicant Analysis; ‡ Statistical Reviewer Analysis.

Table 9: Applicant's Summary of PTB <35⁰ Weeks by Subgroups

Stratification Groups, n/N (%)	Trial 003 Makena (N=1130)	Trial 003 Placebo (N=578)	Trial 003 U.S. Subset Makena (N=258)	Trial 003 U.S. Subset Placebo (N=133)
Region				
U.S.	40/256 (15.6)	23/131 (17.6)		
Non-U.S.	82/857 (9.6)	43/443 (9.7)		
GA at randomization (weeks)				
16^0-17^6	61/493 (12.4)	31/238 (13.0)	16/96 (16.7)	9/40 (22.5)
18^0-20^6	61/620 (9.8)	35/336 (10.4)	24/160 (15.0)	14/91 (15.4)
Overall	122/1113 (11.0)	66/574 (11.5)	40/256 (15.6)	23/131 (17.6)
GA of qualifying delivery* (weeks)				
20^0 - <28^0	29/229 (12.7)	9/101 (8.9)	7/31 (22.6)	3/18 (16.7)
28^0 - <32^0	24/201 (11.9)	20/104 (19.2)	9/37 (24.3)	4/18 (22.2)
32^0 - <35^0	36/344 (10.5)	24/186 (12.9)	9/75 (12.0)	10/40 (25.0)
35^0 - <37^0	32/336 (9.5)	13/180 (7.2)	14/111 (12.6)	6/54 (11.1)
GA of earliest prior PTB** (weeks)				
0 - <20^0	53/459 (11.5)	26/234 (11.1)	13/78 (16.7)	5/36 (13.9)
20^0 - <28^0	21/156 (13.5)	7/73 (9.6)	7/27 (25.9)	3/19 (15.8)
28^0 - <32^0	15/113 (13.3)	12/60 (20.0)	8/30 (26.7)	3/13 (23.1)
32^0 - <35^0	18/201 (9.0)	12/100 (12.0)	5/59 (8.5)	6/29 (20.7)
35^0 - <37^0	15/184 (8.2)	9/106 (8.5)	7/62 (11.3)	6/34 (17.6)
Previous PTD, N (%)				
1	80/949 (8.4)	51/491 (10.4)	22/185 (11.9)	17/96 (17.7)
>1‡	42/164 (25.6)	15/81 (18.5)	18/71 (25.3)	6/35 (17.1)
2	29/127 (22.8)	10/67 (14.9)	13/52 (25.0)	4/29 (13.8)
≥3	13/37 (35.1)	5/14 (35.7)	5/19 (16.3)	2/6 (33.3)
Cervical length at randomization***, N (%)				
<25 mm	4/18 (22.2)	4/9 (44.4)	2/13 (15.4)	1/3 (33.3)
≥25 mm	92/907 (10.1)	45/455 (9.9)	21/112 (18.8)	13/66 (19.7)
BMI before pregnancy				
Underweight (<18.5)	13/83 (15.7)	4/38 (10.5)	0/11 (0)	0/3 (0)
Normal (18.5 - <25)	59/637 (9.3)	33/335 (9.9)	20/112 (17.9)	10/51 (19.6)
Overweight (25 - <30)	29/255 (11.4)	16/127 (12.6)	9/66 (13.6)	6/34 (17.6)
Obese (≥30)	21/138 (15.2)	13/74 (17.6)	11/67 (16.4)	7/43 (16.3)
Any substance use during pregnancy, N (%)				
Yes	19/105 (18.1)	13/51 (25.5)	11/69 (15.9)	10/40 (25.0)
No	103/1008 (10.2)	53/523 (10.1)	29/187 (15.5)	13/91 (14.3)
Smoking				
Yes	18/92 (19.6)	11/40 (27.5)	10/58 (17.2)	8/30 (26.7)
No	104/1021 (10.2)	55/534 (10.3)	30/198 (15.2)	15/101 (14.9)
Alcohol				
Yes	1/23 (4.3)	5/18 (27.8)	1/19 (5.3)	4/16 (25.0)
No	121/1090 (11.1)	61/556 (11.0)	39/237 (16.5)	19/115 (16.5)
Illicit drugs	2/15 (13.3)	3/8 (37.5)	2/14 (14.3)	3/8 (37.5)
Yes				
No	120/1098 (10.9)	63/566 (11.1)	38/242 (15.7)	20/123(16.3)
Race				
Non-Hispanic black	17/72 (23.6)	8/40 (20.0)	16/71 (22.5)	8/40 (20.0)
Non-Hispanic non-black	92/940 (9.8)	50/480 (10.4)	19/154 (12.3)	10/68 (14.7)
Ethnicity				
Hispanic	13/101 (12.9)	8/54 (14.8)	5/31 (16.1)	5/23 (21.7)
Non-Hispanic	109/1012 (10.8)	58/520 (11.2)	35/225 (15.6)	18/108 (16.7)
Years of education				
≤12	64/474 (13.5)	40/256 (15.6)	24/120 (20.0)	18/74 (24.3)
>12	58/639 (9.1)	26/318 (8.2)	16/136 (11.8)	5/57 (8.8)

* If more than one prior delivery was sPTB, qualifying delivery was the most recent. ** The earliest PTB may be indicated or spontaneous. ***Cervical length measurement was not captured for all subjects in a treatment group.
GA = gestational age, NA = not available
Source: Applicant Analysis; ‡ Statistical Reviewer Analysis.

Table 10: CDER's Subgroup Analysis – By History of SPTB (Trial 003)

Endpoint Subgroup	Makena (N=1130)	Placebo (N=578)	Treatment Difference* (95%CI)	Treatment Difference** (95% CI)
Neonatal composite index				
1	4.6 (43/933)	4.6 (22/478)	0 (-2.3, 2.3)	0.1 (-2.1, 2.4)
>1	10.1 (16/158)	8.8 (7/80)	1.7 (-5.9, 9.4)	0.5 (-3.0, 5.6)
PTB <35^0 weeks gestation				
1	8.4 (80/949)	10.4 (51/491)	-2.0 (-5.2, 1.2)	-0.9 (-4.1, 2.5)
>1	25.6 (42/164)	18.5 (15/81)	7.3 (-3.3, 17.9)	0.2 (-5.1, 8.7)
PTB <32^0 weeks gestation				
1	3.9 (37/951)	5.1 (25/491)	-1.2 (-3.5, 1.1)	-1.1 (-3.3, 1.1)
>1	10.3 (12/165)	6.2 (5/81)	4.3 (-2.5, 11.2)	0.1 (-4.3, 9.2)
PTB <37^0 weeks gestation				
1	19.8 (188/948)	19.6 (96/489)	0.2 (-4.1, 4.5)	0.7 (-3.6, 4.8)
>1	42.1 (69/164)	35.8 (29/81)	7.3 (-5.4, 20.1)	2.2 (-4.1, 13.0)

* Cochran–Mantel–Haenszel method
**Shrinkage estimation method
Source: Statistical Reviewer analysis

Table 11: CDER's Subgroup Analysis – By Marital Status (Trial 003)

Endpoint Subgroup	Makena (N=1130)	Placebo (N=578)	Treatment Difference* (95%CI)	Treatment Difference** (95% CI)
Neonatal composite index				
Married/living with partner	5.3 (52/980)	5.1 (26/506)	0.2 (-2.2, 2.5)	0.3 (-1.9, 2.6)
Single or without a partner	6.3 (7/111)	5.6 (3/54)	1.0 (-6.3, 8.4)	0.4 (-3.5,4.7)
PTB <35^0 weeks gestation				
Married/living with partner	10.0 (100/996)	11.2 (58/518)	-1.2 (-4.5, 2.1)	-0.9 (-4.1,2.3)
Single or without a partner	18.8 (22/117)	14.3 (8/56)	3.7 (-7.6, 15.1)	0.1 (-5.1, 8.8)
PTB <32^0 weeks gestation				
Married/living with partner	4.4 (44/999)	5.0 (26/518)	-0.6 (-2.9, 1.6)	-0.5 (-2.6, 1.6)
Single or without a partner	8.6 (10/117)	7.1 (4/56)	0.9 (-7.3, 9.2)	-0.3 (-4.3, 4.8)
PTB <37^0 weeks gestation				
Married/living with partner	22.2 (221/995)	21.1 (109/516)	1.1 (-3.2, 5.5)	1.1 (-3.1, 5.4)
Single or without a partner	30.8 (36/117)	28.6 (16/56)	0.9 (-13.5, 15.2)	1.1 (-6.6, 8.5)

*Cochran–Mantel–Haenszel method
**Shrinkage estimation method
Source: Statistical Reviewer analysis

Table 12: CDER's Subgroup Analysis – By Substance Use (Trial 003)

Endpoint Subgroup	Makena (N=1130)	Placebo (N=578)	Treatment Difference* (95%CI)	Treatment Difference** (95% CI)
Neonatal composite index				
Yes	7.9 (8/101)	10.2 (5/49)	-2.2 (-12.1, 7.7)	-0.2 (-6.6, 4.2)
No	5.2 (51/990)	4.7 (24/511)	0.4 (-1.9, 2.7)	0.3 (-2.0,2.5)
PTB <35^0 weeks gestation				
Yes	19/105 (18.1)	13/51 (25.5)	-7.3 (-21.3, 6.7)	-1.8 (-13.7, 4.1)
No	103/1008 (10.2)	53/523 (10.1)	0 (-3.2, 3.2)	-0.3 (-3.5, 2.8)
PTB <32^0 weeks gestation				
Yes	6.7 (7/105)	13.7 (7/51)	-7.0 (-17.6, 3.5)	-1.9 (-12.3, 2.8)
No	4.7 (47/1011)	4.4 (23/523)	0.2 (-2.0, 2.4)	0 (-2.3, 2.2)
PTB <37^0 weeks gestation				
Yes	33.3 (35/105)	33.3(17/51)	-0.2 (-15.9, 15.5)	1.0 (-7.7, 8.6)
No	22.1 (222/1007)	20.7 (108/521)	1.3 (-3.0, 5.7)	1.3 (-2.7, 5.5)

*Cochran–Mantel–Haenszel method
**Shrinkage estimation method
Source: Statistical Reviewer analysis

Table 13: CDER's Subgroup Analysis – By Education Level (Trial 003)

Endpoint Subgroup	Makena (N=1130)	Placebo (N=578)	Treatment Difference* (95%CI)	Treatment Difference** (95% CI)
Neonatal composite index				
≤12 years	6.1 (28/459)	7.2 (18/249)	-1.1 (-5.0, 2.8)	0.1 (-3.3, 2.8)
>12 years	4.9 (31/632)	3.5(11/311)	1.3 (-1.3,4.0)	0.7 (-1.6, 3.2)
PTB <35^0 weeks gestation				
≤12 years	13.5 (64/475)	15.6 (40/256)	-2.1 (-7.5, 3.3)	-1.0 (-5.3, 2.7)
>12 years	9.1 (58/638)	8.2 (26/318)	0.8 (-3.0, 4.6)	-0.6 (-3.9, 2.9)
PTB <32^0 weeks gestation				
≤12 years	6.1 (29/476)	8.2 (21/256)	-2.1 (-6.1, 1.9)	-0.5 (-4.4, 2.2)
>12 years	3.9 (25/640)	2.8 (9/318)	1.1 (-1.3, 3.4)	0.5 (-1.6, 2.7)
PTB <37^0 weeks gestation				
≤12 years	26.3 (125/475)	27.3 (70/256)	-1.0 (-7.8, 5.7)	1.0 (-4.8, 5.7)
>12 years	20.7 (132/637)	17.4 (55/316)	3.4 (-1.8, 8.7)	2.1 (-2.6, 6.7)

* Cochran–Mantel–Haenszel method
**Shrinkage estimation method
Source: Statistical Reviewer analysis

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/s/

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Appendix 4

CDER's Decisional Memo NDA 021945 Makena 20221005

I. SUMMARY

The Division of Urology, Obstetrics, and Gynecology (DUOG) recommends withdrawing accelerated approval for Makena (hydroxyprogesterone caproate or HPC) injection.

On February 3, 2011, Makena received accelerated approval under section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for the reduction in the risk of recurrent preterm birth (PTB) in women with a history of a singleton spontaneous preterm birth (sPTB). For effectiveness, the new drug application (NDA) relied on data from the Maternal Fetal Medicine Unit (MFMU) Network Trial 17P-CT-002 (Trial 002), in which, compared to placebo, Makena reduced the proportion of women delivering prior to 37 weeks gestation, a surrogate endpoint reasonably likely to predict clinical benefit to neonates. As a condition of the accelerated approval, the Applicant conducted a confirmatory Trial 17-ES-003 (Trial 003) to verify and describe Makena's benefit on neonatal outcomes from reducing the risk of recurrent PTB.

Completed in 2018, Trial 003 failed to confirm the clinical benefit of decreased neonatal mortality and morbidity as measured by the neonatal composite index. Trial 003 also failed to substantiate Makena's treatment effect on the surrogate endpoint that supported the 2011 accelerated approval (gestational age at delivery). Based upon the failure of the trial to confirm clinical benefit or replicate the prior findings, there is insufficient evidence to support the efficacy of Makena. Therefore, the grounds for expedited withdrawal of approval under section 506(c)(3)(B) and (C) of the FD&C Act and 21 CFR 314.530(a)(1) and (6) are met. The lack of demonstrated effectiveness and other factors described in this memorandum weigh in favor of withdrawal of approval. The Division thus concludes that the accelerated approval should be withdrawn.

II. BACKGROUND

Background on sPTB

Of the approximately 4 million births per year in the U.S., about 10% deliver prematurely, defined as birth prior to 37 weeks gestation. The significance of preterm birth is the burden of neonatal mortality and morbidity on the affected children, families, and society. In 2015, PTB accounted for 17% of infant deaths,[1] and surviving children often suffer developmental delay or long-term neurologic impairment. In 2016, complications of PTB were the leading cause of death globally in children younger than 5 years of age, accounting for approximately 16% of all deaths in this age group, and 35% of deaths among neonates.[2]

Of all preterm births, approximately 20-30% are "indicated," where healthcare providers deliberately induce delivery prior to full term because maternal, fetal or obstetrical problems render continuation of pregnancy unsafe for either the mother or the baby. The remaining 70-

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[1] CDC – Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm

[2] UN Inter-Agency Group for Child Mortality Estimation. Levels and trends in child mortality: Report 2017. New York: United Nations Children's Fund, 2017.

80% are "spontaneous," where PTB occurs without an apparent trigger and is typically preceded by spontaneous preterm labor[3] or preterm premature rupture of membrane.

SPTB is a poorly understood syndrome. There are multiple risk factors and various pathways that could potentially lead to the common outcome of sPTB. Factors associated with sPTB include those related to prior obstetrical/gynecological history (e.g., prior PTB, uterine anomalies or previous uterine surgery), maternal demographics (e.g., short interpregnancy interval, extremes of maternal age), non-Hispanic Black race, nutritional status/physical activities, and current maternal/pregnancy characteristics (e.g., severe systemic infection, smoking). SPTB may be more readily attributable to certain circumstances, such as increased uterine stretch (multiple gestations, polyhydramnios) or prior surgical excision of portions of the cervix resulting in cervical insufficiency during pregnancy, and these at-risk pregnancies are managed according to their underlying risk for sPTB. For many risk factors, however, the causative role is uncertain. Further, two-thirds of sPTBs occur in women without any identifiable risk factors.

Background on progestogen treatment of sPTB
In clinical practice, there are two clinical factors considered to be major risks for sPTB in singleton pregnancies that are managed with progestogen therapy. The most important identifiable risk factor is a history of singleton sPTB. Such obstetrical history approximately doubles the risk of sPTB in the current pregnancy, and this risk increases with the number of prior singleton sPTBs. It is unclear how a prior sPTB increases the risk of recurrence in the current pregnancy. Since the early 2000s, a short cervical length in the current pregnancy, commonly defined as < 20-25 mm by ultrasound measurement at 18-24 weeks gestation, has become an accepted risk factor for sPTB. The cause(s) leading to a short cervix is unknown. Starting in the mid-2000s, based on published literature, the American College of Obstetricians and Gynecologists (ACOG) and the Society of Maternal Fetal Medicine (SMFM) have recommended treatment with progestogens, a drug class that acts on the progesterone receptor, to reduce the chance of sPTB in singleton pregnancies with either of these two risk factors. The mechanism of action of progestogens in potentially prolonging pregnancy under these two risk circumstances is unknown, although hypotheses include the drugs' possible anti-inflammatory and uterine quiescence effects. There is extensive published literature on the role of progestogens, especially vaginal progesterone, in reducing the risk of sPTB. However, for reasons explained later in this document, this literature has major limitations and is insufficient to support a conclusion that there is substantial evidence of effectiveness for Makena's approved use.

The two most commonly prescribed progestogens to reduce the risk of sPTB in singleton pregnancies are progesterone (e.g., gel, tablets) administered intravaginally daily and hydroxyprogesterone caproate (HPC) injection given weekly. The initial assessment for progestogen therapy is the women's obstetrical history. For pregnant women *without a prior sPTB* (this includes those with their first pregnancy because there is no prior delivery) and a *short cervix* in the current pregnancy, both ACOG and SMFM recommend vaginal progesterone

[3] Preterm labor refers to uterine contractions resulting in cervical change that occur prior to 37 weeks gestation. In most cases, however, preterm labor resolves and does not result in a preterm birth.

as treatment at the time of diagnosis of short cervix (typically 18-24 weeks gestation) to reduce the risk of sPTB, although such use is not FDA-approved. For pregnant women *with a prior singleton sPTB*, SMFM specifically recommends HPC intramuscular injection starting at 16-20 weeks as prophylaxis to reduce the risk of *recurrent* PTB, an FDA-approved use for Makena (see "Background on Makena" below). The SMFM statement published in 2017 stated that vaginal progesterone should not be considered a substitute for HPC injection because data are insufficient to support the efficacy of vaginal progesterone as prophylactic treatment in decreasing the risk of recurrent PTB in women with a prior singleton sPTB. According to the 2017 SMFM statement, women with a prior singleton sPTB who start HPC injection at 16-20 weeks gestation and then develop a short cervix during the current pregnancy may be candidates for a cervical cerclage, a surgical procedure where a suture is placed around the cervix to physically strengthen the cervix. These women are not treated additionally with vaginal progesterone. Although they both act at the progesterone receptors, progesterone (e.g. gels, tablets) and HPC injection are different drugs. Weekly intramuscular injection of HPC and daily intravaginal progesterone are expected to produce dissimilar systemic and local (e.g., cervix, uterine) progestogen exposure, precluding the ability to exchange one drug for the other. Furthermore, a prior sPTB and a short cervix diagnosed midtrimester are different risk scenarios treated differently. Nevertheless, published literature has, at times, conflated these two drugs and two clinical risk scenarios in evaluating the efficacy of progestogens for reducing the risk of preterm birth.

Although the goal of progestogen (HPC, progesterone) use in various studies has been to reduce the risk of delivering prematurely, the ultimate clinical outcome of interest is improvement in neonatal health. Related to degree of fetal development, gestational age at delivery is believed to be a proxy for neonatal developmental health. In general, the likelihood of adverse outcomes in the neonate born spontaneously prematurely increases with decreasing gestational age at delivery. However, the likelihood and severity of adverse neonatal oucomes do not correlate linearly with gestational age at delivery. For example, it is expected that prolonging pregnancy could result in improved neonatal morbidity/mortality in the extremely premature infants (those born at < 28 weeks gestation). It is less clear whether iatrogenically prolonging pregnancy could result in better neonatal morbidity/mortality in neonates born late preterm (those born 34 weeks to < 37 weeks gestation). Another factor adding to the uncertainty of the relationship between gestational age at delivery and neonatal outcomes is that the mechanism of action of preterm labor and of premature birth is poorly understood. It could be that preterm labor leading to preterm birth may be triggered by an unrecognized toxic uterine environment, and iatrogenically prolonging the pregnancy with pharmacotherapy may render a worse outcome to the neonate than if spontaneous birth were allowed to occur. Thus, there is a certain degree of uncertainty regarding the impact prolonging pregnancy has on improving neonatal outcomes.

Background on Makena

Granted accelerated approval in 2011, Makena (HPC injection) is the only pharmacotherapy approved to reduce the risk of *recurrent* sPTB (prophylaxis) in women with a prior singleton sPTB. Its approval is predicated on findings of a single adequate and well-controlled trial (Trial 002) demonstrating that, compared to placebo, a smaller proportion of Makena-treated women delivered prior to 37 weeks gestation, a surrogate endpoint FDA determined reasonably likely to predict clinical benefit to neonates, the outcome of interest.[4] As a condition of Makena's accelerated approval, the applicant conducted a postmarketing confirmatory trial to verify and describe Makena's clinical benefit on neonatal outcomes. The results from this confirmatory trial did not demonstrate a statistically significant nor clinically important treatment effect for either part of the co-primary efficacy endpoint of proportion of women delivering prior to 35 weeks (surrogate endpoint) and the neonatal composite index (clinical benefit of interest). Also, no differences between Makena and placebo were seen in the secondary outcomes of delivery < 32 or < 37 weeks (<37 weeks was the primary efficacy endpoint in Trial 002 that formed the basis for accelerated approval).

Background on HPC

FDA first approved a drug product with the active ingredient HPC under the tradename Delalutin (HPC, 250 mg/mL, injected intramuscularly) in 1956, for various obstetrical and gynecological indications. In the 1990s the application holder for the new drug applications (NDAs) for Delalutin, NDA 10–347 and NDA 16–911, discontinued marketing this product and, in September 1999, requested that FDA withdraw its approval. At the time of withdrawal, which was determined not to be for reasons of safety or effectiveness, Delalutin was indicated for several gynecological uses in non-pregnant women but had no approved obstetrical indications.[5] In 2003, Trial 002 was published in the New England Journal of Medicine reporting that HPC 250 mg/mL intramuscularly once weekly reduced the risk of preterm delivery in women with a prior sPTB.[6] Because no approved HPC-containing product was available in 2003, compounded HPC injection was the only option available for those choosing to use this treatment to reduce the risk of recurrent PTB. With ACOG's and SMFM's endorsement of progestogens (including HPC) to reduce the risk of recurrent PTB starting in the mid-2000's, the use of compounded HPC injection increased significantly until Makena was approved in 2011. Since 2015, FDA has

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[4] We note that a 2014 CDER/CBER guidance described "delay in delivery" for a treatment for preterm labor as an intermediate clinical endpoint (ICE) – rather than a surrogate endpoint – that is reasonably likely to predict clinical benefit for the purpose of accelerated approval. *See Guidance for Industry: Expedited Programs for Serious Conditions* (May 2014) at 19. However, we consider gestional age of delivery prior to 37 weeks to be a surrogate endpoint, as we did in Makena's approval, because it does not directly measure clinical benefit, which is improved neonatal health outcomes. This is consistent with the definition of "surrogate endpoint" in section 507 of the FD&C Act, added in 2016 by the 21st Century Cures Act and reflected in FDA's Table of Surrogate Endpoints that Formed the Basis of Drug Approval or Licensure, available at https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure. We further note that if gestational age of delivery were to be characterized as an ICE rather than a surrogate endpoint, this would have no impact on our analysis, or on our conclusion and recommendation that Makena's approval should be withdrawn.

[5] *See* Determination That DELALUTIN (hydroxyprogesterone caproate) Injection, 125 Milligrams/Milliliter and 250 Milligrams/Milliliter, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 75 FR 36419 (June 25, 2010). The approved gynecological indications at the time of withdrawal were: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; as a test for endogenous estrogen production ("Medical D and C"); and for the production of secretory endometrium and desquamation. FDA withdrew approval of Delalutin's obstetrical indications after evaluating the efficacy of Delalutin under the Drug Efficacy Study Implementation (DESI) program. *See id.* at 36420.

[6] Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, et al. Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate. N Engl J Med 2003; 348:2379-85.

approved generics of Delalutin. Therefore, currently there are two categories of approved HPC products, both at a dosage strength of 250 mg/mL (and the same dosage form to be injected intramuscularly, one of which is approved only for an obstetrical indication (Makena and its generics) and the other of which is approved only for gynecological conditions (generics of Delalutin).

III. EVIDENCE REGARDING MAKENA'S EFFICACY

CDER approved Makena in 2011 under the accelerated approval pathway. The accelerated approval pathway may be used where a product intended to treat a serious or life-threatening disease or condition has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. After approval under the accelerated approval pathway, FDA requires at least one postmarketing confirmatory trial to verify and describe the anticipated clinical benefit.[7]

A. ACCELERATED APPROVAL (TRIAL 002):

The accelerated approval for Makena was supported by data from a single clinical trial (Trial 002). This trial was designed and conducted without FDA's input. The results were published in the New England Journal of Medicine in 2003 before the original applicant first sought marketing approval in 2006. Initiated in 1999 and completed in 2002, Trial 002 enrolled 463 women with a singleton pregnancy and at least one prior singleton sPTB from 19 university-based clinical centers in the United States in the MFMU Network. The primary efficacy endpoint was the proportion of pregnant women delivering < 37 weeks gestation, with those delivering < 35 or < 32 weeks as secondary endpoints. The trial showed that HPC 250 mg injection administered intramuscularly once weekly starting at 16 weeks 0 days to 20 weeks 6 days gestation and used through 36 weeks 6 days gestation or birth reduced the proportion of women who delivered <37 weeks gestation. This treatment effect appeared independent of race, number of prior preterm deliveries, and gestational age of the prior PTB. The treatment effect was sufficiently persuasive to support accelerated approval based on the findings of a single adequate and well-controlled trial. The proportions of women delivering at <35 and <32 weeks gestation were also statistically lower among women randomized to Makena compared to placebo; however, the treatment differences were smaller relative to the treatment difference for < 37 weeks, and the upper bound of the 95% confidence interval (CI) for the treatment differences for these two timepoints were near zero. See table 1.

Table 1: Efficacy – Proportion of subjects with Efficacy Outcome (Trial 002)

Efficacy Outcome	HPC (Makena) (N=310)	Placebo (N=153)	Treatment difference (95% CI)
Birth <37 weeks	37%	55%	-18% (-28, -7)
Birth <35 weeks	21%	31%	-9% (-19, -0.4)
Birth <32 weeks	12%	20%	-8% (-16, -0.3)

[7] See section 506(c)(2)(A) of the FD&C Act, 21 CFR part 314 subpart H, and FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014), available at https://www.fda.gov/media/86377/download.

Source: adapted from Table 5 in Makena's prescribing information

Approximately 60% of the study population were Black. Black Americans generally have a higher rate of PTB compared to other racial/ethnic groups in the U.S. In Trial 002, the rate of PTB in the vehicle (placebo) group was 52% in Black women and 59% in non-Black women (See Table 2). An exploratory analysis evaluating the effect of race on efficacy did not show that race affected the treatment effect. The extent by which HPC reduced the percentage of women with a birth < 37 weeks, compared to vehicle (placebo), was similar between Black and non-Black women in Trial 002. See Table 2.

Table 2: Preterm Births < 37 weeks by Race and Treatment Group (Trial 002)

Race	HPC Group n/N (%) [A]	Vehicle Group n/N (%)
Black	66/183 (36.1%)	47/90 (52.%)
Non-Black	49/127 (38.6%)	37/63 (58.7%)

n = number of patients in a specific category who delivered < 37 weeks gestation
N = number of patients overall in a specific category
Source: Division Director Memo dated February 3, 2011, Table 8

Prior to approving Makena in 2011, we recognized the challenges of the feasibility of conducting a confirmatory efficacy and safety trial in the United States, given the endorsement of professional practice guidelines and accepted clinical practice of using progestogens for preterm birth. Prior to approval, we required that the Applicant provide evidence that it could successfully complete the confirmatory trial, which was to be ongoing at the time of approval, and that at least 10% of subjects be enrolled from the U.S. and Canada.

B. CONFIRMATORY TRIAL (TRIAL 003)

Initiated in 2009 and completed in 2018, the confirmatory trial (Trial 003) was an international, randomized, double-blind, placebo-controlled study that enrolled women with eligibility criteria like those of Trial 002. The trial's co-primary efficacy endpoint was (a) delivery < 35 weeks gestation and (b) a neonatal morbidity/mortality composite index (neonatal composite index).[8,9] The inclusion of a clinical endpoint (the neonatal composite index) was intended to verify clinical benefit and resolve uncertainty about the relationship between the surrogate endpoint used in Trial 002 (delivery < 37 weeks) and clinical benefit, consistent with 21 CFR 314.510 and section 506(c)(2) of the FD&C Act. Trial 003 randomized a total of 1,708 women from nine countries, with Russia, Ukraine, and the United States enrolling 36%, 25%, and 23% of women, respectively. Of note, the number of U.S. women enrolled in Trial 003 (N=391, Trial 003 U.S. subgroup) was close to that in Trial 002 (N=463). Data were available for 1651 liveborn neonates. The trial did not demonstrate a statistically significant treatment effect for the co-primary endpoint, or for either of its individual components (proportion of women delivering prior to 35 weeks and neonatal composite index). Also, no differences between Makena and placebo were seen in the secondary outcomes of delivery < 32 or < 37 weeks (<37 weeks was the primary efficacy endpoint in Trial 002 that formed the basis for accelerated approval). See Table 3.

Table 3: Efficacy – Proportion of subjects with Efficacy Outcome (Trial 003)

Efficacy Outcome	HPC (Makena) (N=1130)	Placebo (N=578)	Treatment Difference (95% CI)	P-value
Neonatal composite index*	5.4%	5.2%	0.2% (-2.0, 2.5)	0.84
Birth < 35 weeks	11%	12%	-0.6% (-3.8, 2.6)	0.72
Birth < 32 weeks	5%	5%	-0.4% (-2.8, 1.7)	
Birth < 37 weeks**	23%	22%	1.3% (-3.0, 5.4)	

*Proportion of neonates experiencing at least one event of the composite index
**Primary surrogate efficacy endpoint of Trial 002
Source: FDA 2019 AC Briefing Book

[8] The differences in the threshold of gestational age (GA) of delivery between Trial 002 (primary endpoint GA < 37 weeks) and Trial 003 (co-primary endpoint GA < 35 weeks) reflect the timing at which these thresholds were considered to be an adequate surrogate endpoint that reasonably likely predicts neonatal outcomes:

- Trial 002 was designed, conducted, completed and published in 2003 without any FDA input or concurrence.
- The original applicant submitted the NDA for Makena in 2006. The 2006 Advisory Committee members opined that GA of delivery < 37 weeks was not an adequate surrogate, but GA < 35 weeks could be adequate.
- The protocol for Trial 003 included the co-primary endpoint of GA of delivery < 35 weeks based on the 2006 advisory committee input. Trial 003 started in 2009 using the agreed upon co-primary surrogate endpoint of gestational age of delivery <35 weeks.
- By the time the NDA was resubmitted in the third review cycle in 2010, new data emerged that infants born late preterm (between 34 and < 37 weeks gestation) are at higher risk of adverse neonatal outcomes than term infants. This new evidence led FDA to determine, in 2011, that gestational age < 37 weeks could be an acceptable surrogate endpoint reasonably likely to predict clinical benefit. In this third review cycle, FDA then reconsidered data from Trial 002 and approved Makena in 2011 under accelerated approval based on the surrogate endpoint of gestational age < 37 weeks.

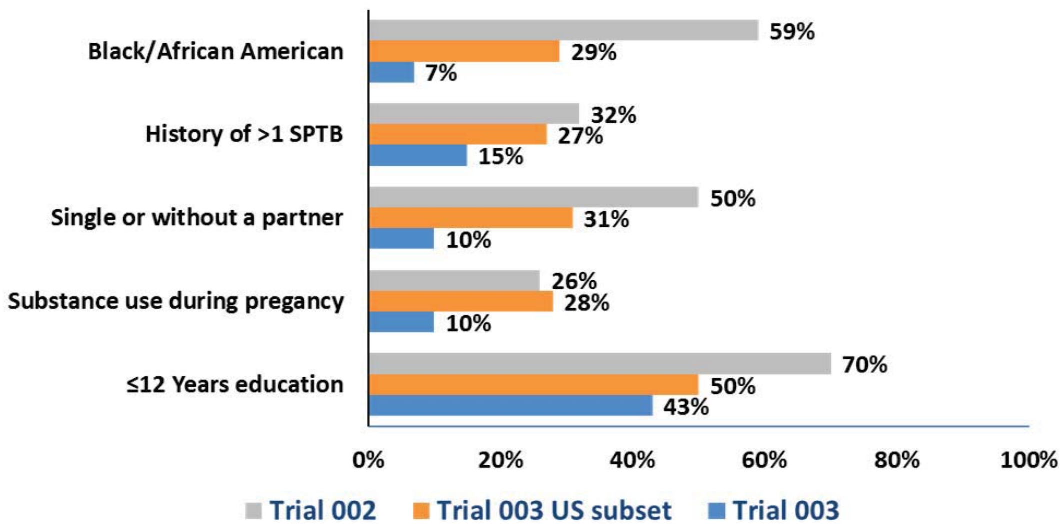
[9] The neonatal composite index consists of neonatal death, grade 3 or 4 intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), or proven sepsis. A neonate was considered to have a composite index event if s/he experienced any of the above 6 adverse outcomes at any time during childbirth hospitalization up through discharge from the neonatal intensive care unit.

After Trial 003 failed to demonstrate efficacy on the co-primary endpoint of neonatal index and gestational age of delivery < 35 weeks (these two components [neonatal index, gestational age < 35 weeks] together constitute the co-primary efficacy endpoint), the Applicant conducted a series of exploratory subgroup analyses[10] to understand the potential reasons for the negative findings in Trial 003. The Applicant analyzed the co-primary efficacy endpoint for these subgroups for the overall study population in Trial 003 and in the U.S. subgroup. In all, these analyses did not uncover a subgroup in which Makena provided evidence of efficacy.

CDER Exploratory Subgroup Analyses

A comparison among the study populations in (a) Trial 003 overall, (b) Trial 003-U.S. subgroup, and (c) Trial 002 indicated that a greater proportion of patients in Trial 002 had certain risk factors for PTB, such as being Black or having > 1 prior sPTB, than in the Trial 003-U.S. subgroup or Trial 003 overall. Compared to Trial 003, Trial 002 also had a higher percentage of women who were single or without a partner, who used substances during pregnancy, and who had lower educational levels. The demographics for the U.S. sub-group of Trial 003 (orange bars) falls in between Trial 002 (gray bars) and Trial 003 (blue bars), except for substance use during pregnancy, which was reported in a comparable proportion of women in Trial 002 and the U.S. sub-group of Trial 003. See Figure 1.

Figure 1: Comparison of Maternal Demographics Between Trials 002 and 003



Source: FDA Statistical Review

To investigate whether these differences could explain the disparate findings between Trials 003 and 002, CDER conducted exploratory analyses of Trial 003 using logistic regression models for each co-primary efficacy endpoint with treatment, region, each of the 5 demographic factors in

[10] The Applicant analyzed the following subgroups: geographic region (U.S vs. non-U.S.), gestational age at randomization, gestational age at qualifying delivery, gestational age at earliest prior PTBs, number of previous PTBs, cervical length at randomization, BMI before pregnancy, substance use in pregnancy, smoking, alcohol, illicit drugs, race, ethnicity, and years of education.

Figure 1, and their interaction with treatment. These analyses do not provide evidence of efficacy of Makena over placebo in any subpopulation in Trial 003 and there was no statistically significant interaction between Makena and any of these demographic factors. Analogous analyses in the Trial 003-U.S. subgroup produced results similar to those for the overall Trial 003 population.

1. Subgroup analysis by single factors:

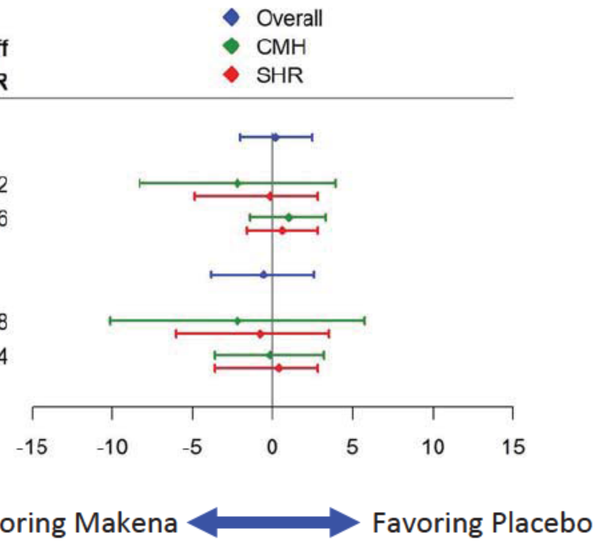
CDER conducted subgroup analyses of certain single factors that differed between Trials 002 and 003 that may play an important role in the different findings between Trial 002 and Trial 003. Subgroup analysis using the Cochran-Mantel-Haenszel (CMH) method evaluates a particular subgroup category independently from other subgroup categories and relies only on the data from the subjects in that particular category. Bayesian shrinkage estimation analysis (SHR) evaluates all subgroup categories jointly and borrows information across subgroups to reduce the variability of the estimates and prevent random highs and random lows. CDER conducted subgroup analyses using both the CMH and SHR methods.

Below we present subgroup analyses for Trial 003 of three of these factors.

a. Region (U.S. vs ex-U.S.): The Applicant posited the differences in efficacy findings between Trial 002 and Trial 003 may be attributable to the study population being U.S. women-only in Trial 002 compared to a multinational population in Trial 003. Therefore, we analyzed Trial 003's co-primary efficacy endpoint and two secondary endpoints of interest, one of which was the surrogate endpoint for Trial 002 (gestational age of delivery < 37 weeks), by region (U.S. vs. non-U.S. subgroups) using CMH and SHR analyses. The confidence intervals for treatment difference for these efficacy endpoints in both the overall Trial 003 population and in the regional subgroups of U.S. and non-U.S. include zero, indicating no evidence of Makena effect vs. placebo based on either analysis method (see Figures 2 and 3). Regarding the secondary endpoint of delivery < 37 weeks, the point estimate favors placebo in the U.S. subgroup of Trial 003 (Figure 3) and there was no numerical trend to suggest a potential treatment effect. In addition, there was no treatment by region interaction for each co-primary endpoint in Trial 003: whether a woman was from the U.S. or outside the U.S. did not have an effect on efficacy results.

Figure 2. Region Subgroup: No evidence of treatment effect on co-primary efficacy endpoint in either US vs. non-US Women (Trial 003)

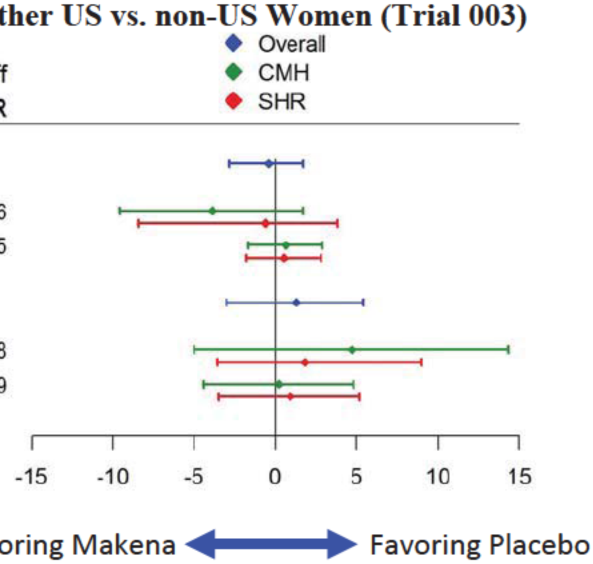
Endpoint / Subgroup	Makena	Placebo	Diff CMH	Diff SHR
Neonatal Index (%)	5.4	5.2	0.2	
US (252, 126)	7.1	9.5	-2.2	-0.2
Non_US (839, 434)	4.9	3.9	1.0	0.6
PTB<35 Weeks (%)	11.0	11.5	-0.6	
US (256, 131)	15.6	17.6	-2.2	-0.8
Non_US (857, 443)	9.6	9.7	-0.2	0.4



CMH: stratified Cochran-Mantel-Haenszel
SHR: shrinkage estimation

Figure 3. Region Subgroup: No evidence of treatment effect on secondary efficacy endpoints of gestational age at delivery in either US vs. non-US Women (Trial 003)

Endpoint / Subgroup	Makena	Placebo	Diff CMH	Diff SHR
PTB<32 Weeks (%)	4.8	5.2	-0.4	
US (256, 131)	5.5	9.2	-3.9	-0.6
Non_US (860, 443)	4.7	4.1	0.6	0.5
PTB<37 Weeks (%)	23.1	21.9	1.3	
US (256, 131)	33.2	28.2	4.7	1.8
Non_US (856, 441)	20.1	20.0	0.2	0.9



b. Race: Another factor postulated to play a role in the differences in the efficacy outcomes between Trial 002 (59% Black) and Trial 003 (7% Black) was race. In the U.S., Black race is associated with a higher risk of preterm birth. The treatment differences for the co-primary endpoint and secondary endpoints of interest for Trial 003 overall and subgroups by race (Blacks vs. non-Blacks) are close to 0 with all confidence intervals including 0 (Figures 4 and 5). This race subgroup analysis did not provide evidence that Makena had a treatment effect in Black or non-Black women. Of note, in the U.S. subgroup of Trial 003, 29% of the patients were Black. There was no evidence of a treatment effect of Makena in this U.S. Black subgroup or in the overall U.S. subgroup of Trial 003.

Figure 4. Race Subgroup: No evidence of treatment effect on <u>co-primary efficacy endpoint</u> in Blacks vs. non-Blacks (Trial 003)

Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
Neonatal Index (%)	5.4	5.2	0.2	
Black (69, 40)	8.7	7.5	0.8	0.4
Non-Black (1022, 520)	5.2	5.0	0.2	0.2
PTB<35 Weeks (%)	11.0	11.5	-0.6	
Black (72, 41)	23.6	19.5	3.0	-0.1
Non-Black (1041, 533)	10.1	10.9	-0.8	-0.7

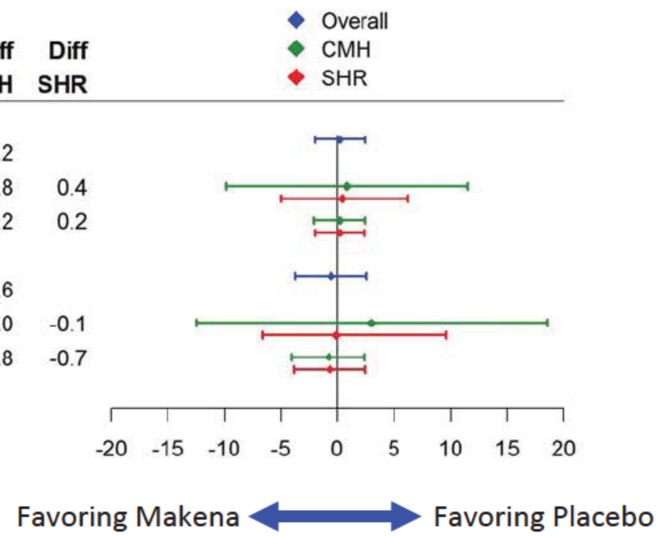
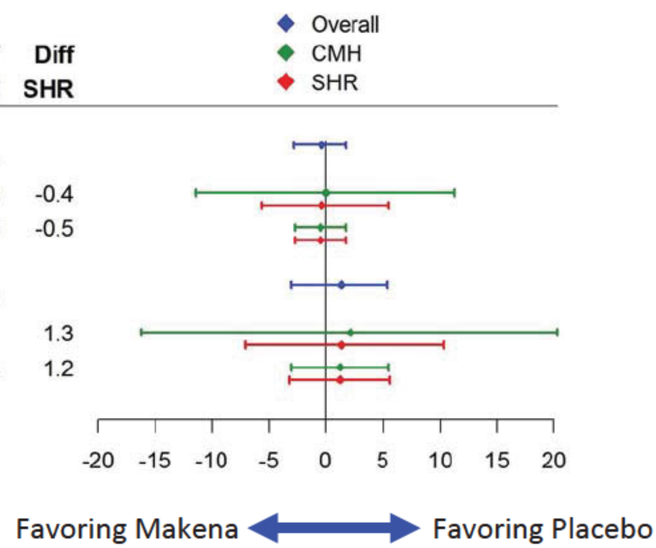


Figure 5. Race Subgroup: No evidence of treatment effect on <u>secondary efficacy endpoints of gestational age at delivery</u> in Blacks vs. non-Blacks (Trial 003)

Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
PTB<32 Weeks (%)	4.8	5.2	-0.4	
Black (72, 41)	11.1	9.8	0	-0.4
Non-Black (1044, 533)	4.4	4.9	-0.5	-0.5
PTB<37 Weeks (%)	23.1	21.9	1.3	
Black (72, 41)	37.4	34.2	2.1	1.3
Non-Black (1041, 533)	22.1	20.9	1.2	1.2



c. Number of Prior sPTB: The risk of recurrent singleton PTB increases with the number of prior singleton sPTBs. Trial 003 enrolled a smaller proportion of women with > 1 prior singleton sPTBs (15%) than Trial 002 (32%). Figures 6 and 7 below present the subgroup analysis results for this factor. The subgroups are categorized as one prior sPTB and more than one prior sPTB. This subgroup analysis did not provide evidence that Makena had a treatment effect on either co-primary efficacy endpoint in either subgroup. There was also no evidence of a treatment effect for Makena based on the results for the secondary endpoints of interest.

Figure 6. Number of prior singleton sPTBs subgroup: no evidence of treatment effect on <u>co-primary efficacy endpoint</u> in either subgroup of 1 vs. > 1 prior sPTBs (Trial 003)

Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
Neonatal Index (%)	5.4	5.2	0.2	
1 (933, 478)	4.6	4.6	0	0.1
>1 (158, 80)	10.1	8.8	1.7	0.5
PTB<35 Weeks (%)	11.0	11.5	-0.6	
1 (949, 491)	8.4	10.4	-2.0	-0.9
>1 (164, 81)	25.6	18.5	7.3	0.2

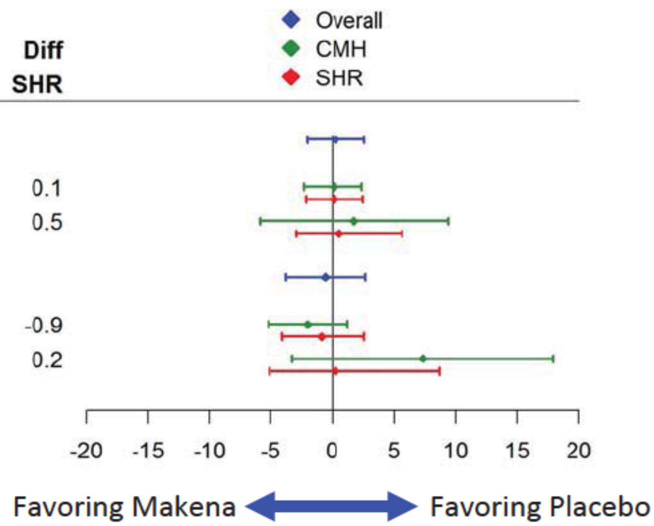
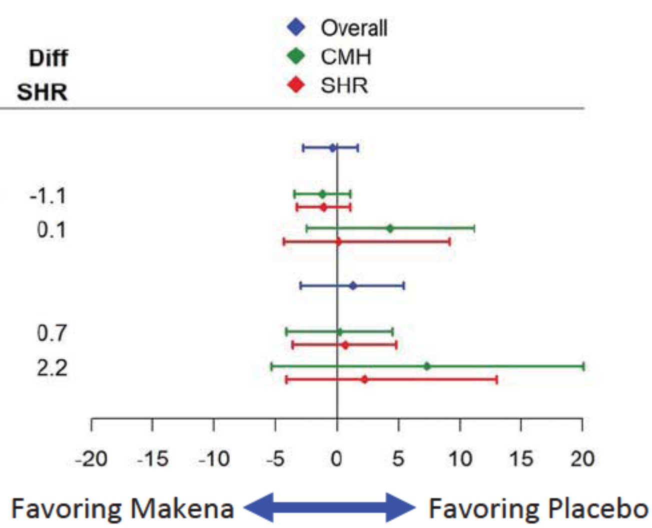


Figure 7. Number of prior singleton sPTBs subgroup: no evidence of treatment effect on <u>secondary efficacy endpoints of gestational age at delivery</u> in either subgroup of 1 vs. > 1 prior sPTBs (Trial 003)

Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
PTB<32 Weeks (%)	4.8	5.2	-0.4	
1 (951, 491)	3.9	5.1	-1.2	-1.1
>1 (165, 81)	10.3	6.2	4.3	0.1
PTB<37 Weeks (%)	23.1	21.9	1.3	
1 (948, 489)	19.8	19.6	0.2	0.7
>1 (164, 81)	42.1	35.8	7.3	2.2

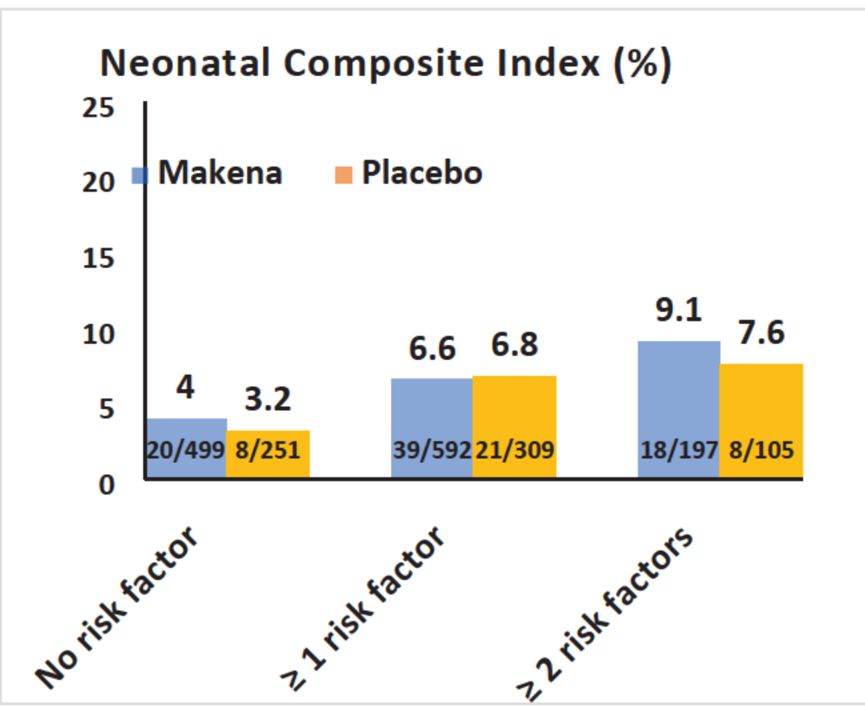


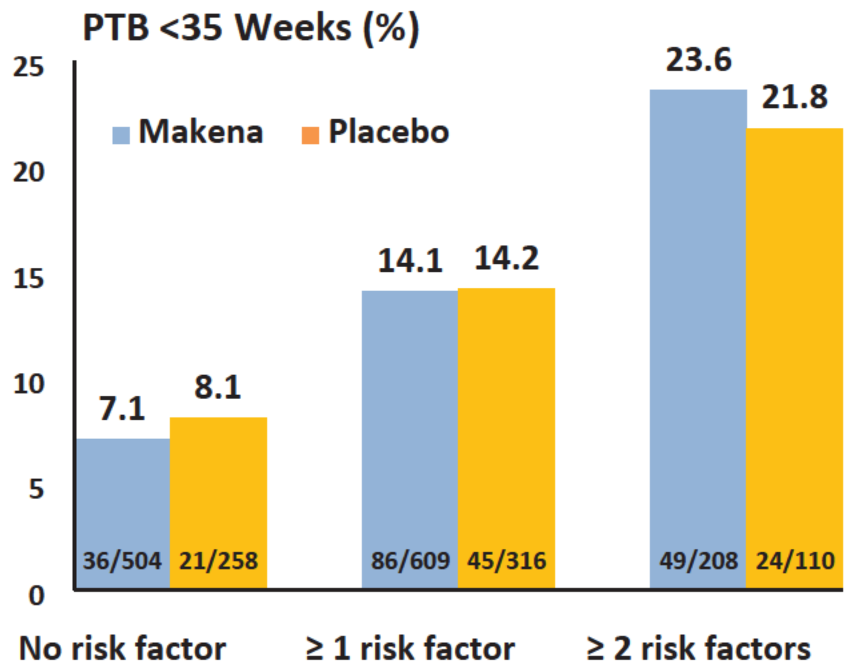
We also conducted subgroup analyses by substance use during pregnancy, marital status, and education level because the proportion of women with these factors, which have been purported to be associated with PTB risk, differed between Trial 002 and Trial 003 (see "Demographics" above). The results showed no evidence of a treatment effect for Makena vs. placebo in these subgroups.

2. "Composite" Risk Subgroup:

The Applicant identified 5 risk factors (history of > 1 prior sPTB, black race, substance use in current pregnancy, ≤ 12 years of education, unmarried with no partner) that were more prevalent in the study population of Trial 002, which therefore represented a higher risk population, compared to that of Trial 003. The Applicant hypothesized that Makena may be effective in a higher risk population and, perhaps, not in a lower risk population, such as that of Trial 003. CDER conducted post-hoc efficacy analyses exploring a potential relationship between efficacy and "composite" risk level based on these 5 factors. Our analyses by "composite" risk level of having (a) none of the aforementioned 5 factors, (2) at least one factor, and (3) at least 2 factors showed that the incidence of having a neonatal index event and preterm birth increases with increasing risk level. However, within each specific risk level, Makena did not confer effect over placebo. Although these risk factors may have an impact on the background incidence of PTB and/or neonatal composite index event, there was no evidence in Trial 003 that they impact the treatment effect of Makena (see Figure 8). That is, Makena did not have an effect for women at lower or higher risk of recurrent PTB.

Figure 8. "Composite" risk level subgroup: no evidence of treatment effect in any risk group defined using five risk factors selected by the Applicant (Trial 003)





Risk factors: Black race, history of more than one sPTB, single/without partner, substance use in pregnancy, ≤ 12 years education

In summary, Trial 003 did not demonstrate a treatment effect of Makena on reducing the rate of neonatal composite index or preterm birth prior to 35 weeks gestation, nor was there evidence of a treatment effect on the rate of preterm birth prior to 37 weeks or 32 weeks gestation. Exploratory subgroup analyses of Trial 003 did not provide evidence of a treatment effect in any identified subgroup, nor was there consistent evidence of treatment effect within a specific subpopulation across Trials 002 and 003 (e.g., by race, number of prior sPTB).

IV. OTHER EVIDENCE REGARDING HPC EFFECTIVENESS FOR sPTB

We are aware that there are published and unpublished studies that evaluated HPC for PTB under different conditions of use, such as various HPC doses, dosing regimens, formulations, or different patient populations. The differences limit the ability of these studiesto reliably inform Makena's effectiveness for its intended use.

For completeness, CDER evaluated the published literature, including an unpublished meta-analysis of some of the studies (which also includes Trial 002), and conducted our own meta-analysis (including both Trials 002 and 003) to assess whether these data inform on the effectiveness of HPC (the active ingredient in Makena) for sPTB. Our findings are summarized below:

- The Evaluating Progestogen for Prevention of Preterm birth International Collaborative (EPPPIC) study (unpublished): Attendees of the October 2019 Advisory Committee meeting made CDER aware of this study as they thought it may potentially inform Makena's treatment effect for sPTB. Funded by the Patient-Centered Outcomes Research

Institute (PCORI), this study was an individual participant data meta-analysis of studies that evaluated the efficacy of various progestogens (vaginal progesterone, oral progesterone, HPC) compared to control (placebo or non-intervention) or to each other administered during pregnancy to reduce PTB risk in at-risk asymptomatic women with singleton or multifetal gestations.[11] Most women with a singleton pregnancy in the EPPPIC meta-analysis study had a short cervix diagnosed in the midtrimester or a prior sPTB; these are the two risks most commonly associated with progestogen treatment. Using the study-level data obtained from the EPPPIC study, we conducted a CDER meta-analysis that includes only trials from EPPIC that could possibly inform Makena's progestagional effect on preterm birth in singleton pregnancies with either of these two risk factors.[12] We selected only trials that evaluated HPC in singleton pregnancies that were prospective, randomized, double-blind, and placebo-controlled because this study design can best inform the drug's efficacy.

Our meta-analysis includes four trials from the EPPPIC study that evaluated HPC (and not other progestogens, such as progesterone) compared to placebo in singleton pregnancies (Trial 002, PHENIX singleton, PROGFIRST and SCAN) and Trial 003. Trials 002 and 003 are appropriately designed, conducted and analyzed to inform Makena's effectiveness for its approved use. The PROGFIRST trial, submitted in 2006 in the original NDA of Makena, enrolled the same target population and investigated the same dose and dosing regimen as Makena's, but the investigational HPC product had product quality issues impacting the drug's potency that resulted in the trial being terminated prematurely (only 57% of subjects completed the trial) and precluded CDER accepting the trial as evidence of efficacy. There was no evidence of efficacy of HPC in the abbreviated PROGFIRST trial. SCAN, the largest trial of the four trials selected from the EPPPIC study, enrolled 657 pregnant women and evaluated the efficacy of HPC 250 mg IM once weekly (the same dose and dosing regimen as Makena) compared to placebo in a target population different from Makena's - nulliparous women (women who have not given birth before) with a short midtrimester cervical length. Compared to placebo,

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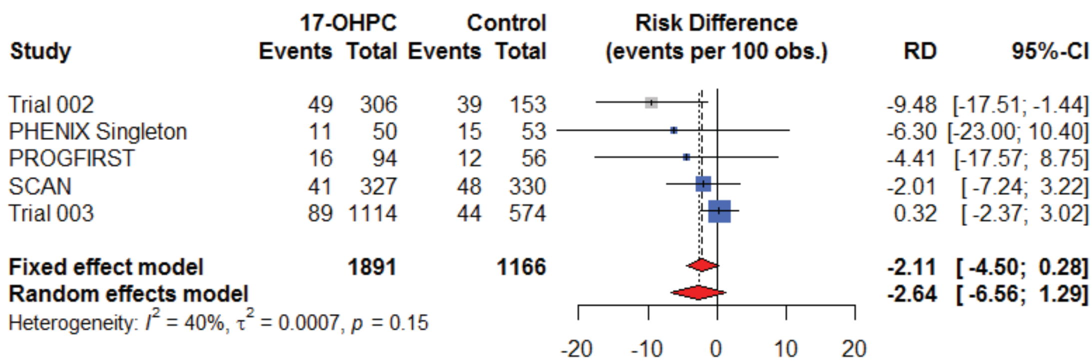
[11] The PCORI website states that "compared to no hormones, women with short cervix or previous preterm birth who received either 17-OHPC [HPC] or vaginal progesterone had a lower chance of their baby being born before 34 weeks, might have lower chance of their baby dying or having serious problems, might have more health problems" (https://www.pcori.org/research-results/2017/evaluating-hormone-treatments-women-increased-risk-preterm-birth-%E2%80%93-epppic, last accessed September 28, 2020). As discussed in section II of this memo, it is not appropriate to conflate the two clinical conditions (short cervix and history of prior sPTB) or the two progestogen products (vaginal progesterone and injectable HPC). Regarding Makena's approved use, the EPPPIC meta-analysis contains data from Trial 002 but not Trial 003 because Trial 003 results were not available when the analysis for EPPPIC was conducted. Trial 003 was almost four times larger than Trial 002 and was appropriately designed and conducted to assess Makena's approved use. PCORI's conclusions about HPC are thus based on a data set that, as compared to the one analyzed by CDER, is much smaller, includes very different results, and includes data, other than Trial 002, that is less relevant to Makena's effectivenss for its intended use.

[12] We obtained a draft manuscript of this study from the principal investigator through personal communication. We evaluated select information in the EPPPIC meta-analysis because it could potentially help to understand any effect of HPC, the active ingredient in Makena, on singleton pregnancy at risk for preterm birth and ensure a comprehensive assessment of the available evidence. We note that the information obtained from EPPPIC did not alter our conclusion about Makena's lack of treatment effect for its intended use. We would have arrived at our same recommendation to withdraw approval of Makena without the information from this unpublished meta-analysis.

HPC did not reduce the rate of preterm birth < 37 weeks gestation (25.1% HPC vs. 24.2% placebo). The PHENIX trial enrolled pregnant women with a risk factor for sPTB at baseline (prior sPTB, cervical surgery, uterine malformation, DES exposure) and a short midtrimester cervical length, and evaluated HPC 500 mg IM weekly (Makena's approved dose is 250 mg) compared to placebo. This higher HPC dose did not reduce the proportion of women delivering prior to 37 weeks (45% HPC vs. 44% placebo).

Because the EPPPIC study used PTB < 34 weeks as the primary endpoint, our meta-analysis also compared PTB < 34 weeks in the HPC and placebo arms. We used absolute risk difference (RD) to be consistent with Trials 002 and 003. The number of patients included in our meta-analysis was 1,369 from the four selected EPPPIC trials, and 1,688 from Trial 003 (see Figure 9 below). Our meta-analysis of the five trials using a random effects model did not demonstrate efficacy of HPC over placebo in reducing the risk of PTB < 34 weeks (RD = -2.64%; 95% CI: -6.56, 1.29).

Figure 9: CDER's Meta-analysis of four trials from EPPPIC study and Trial 003



The negative findings from the meta-analysis do not support a treatment effect of HPC, the active ingredient in Makena, on PTB in populations that are typically treated with progestogens (history of sPTB or short cervix in the current pregnancy without a prior sPTB).

- We identified two observational studies that provided exploratory evidence about HPC's effect for its approved use. These studies were conducted at two large urban institutions that served an obstetrical population with risk factors generally similar to that in Trial 002. They compared the institutions' sPTB rate when HPC was standard of care to the institutions' sPTB rate prior to HPC becoming the standard of care (historical controls). Neither study showed that HPC had an effect in reducing the PTB rate in women with a prior singleton sPTB.
    - Bastek et al. performed a retrospective, cross-sectional study to assess the sPTB rate and gestational age at delivery at the Hospital of the University of Pennsylvania (HUP) over two 2-year periods (all deliveries occurring "pre-HPC during calendar years 2004 to 2005 vs. all deliveries occurring "post-HPC" during

calendar years 2008 to 2009).[13] In 2006, it became the standard of care at HUP to offer HPC to all eligible patients, defined as women with a singleton pregnancy and a history of sPTB of a single infant between 20 and 36[6] weeks gestational age (per Makena labeling).

To study the effect of HPC in women who are within the approved population of Makena, the investigators conducted the analysis in a subgroup that excluded women without a history of sPTB, those with multiple gestations, delivery prior to 21 weeks, fetuses with anomalies, and women who delivered preterm due to preeclampsia. The subgroup included 2,141 singleton pregnancies (965 pre-HPC and 1,176 post-HPC). The mean maternal age was higher in the pre-HPC (29 years) compared to the post-HPC (27 years) cohorts. There were significantly fewer Black women in the pre-HPC group (68%) than in the post-HPC group (82%). There was no difference in the prevalence of women without insurance between the pre-HPC group (1.14%) and post-HPC group (1.19%), although more post-HPC women (91%) received Medicaid/financial assistance compared to pre-HPC women (83%). It did not appear that the investigators adjusted for these imbalances in their analyses. There was no difference in the institution's rate of sPTB prior to 37 weeks of gestation (17% vs. 17%, $p = 0.79$) or the mean gestational age at delivery (38 weeks vs. 38 weeks, $p = 0.21$) between the pre-HPC and post-HPC study periods.

- Nelson et al. conducted a prospective cohort study to assess the effectiveness of HPC to prevent recurrent PTB ≤ 35 weeks in pregnant women compared to similar births in the obstetrics population prior to the implementation of HPC at Parkland Hospital, a large institution serving medically indigent women in Dallas, Texas.[14] The primary outcome was the recurrence of birth ≤ 35 weeks for the study cohort compared to a historical reference rate of 16.8% of recurrent sPTB in their population. A sample size of 413 women was estimated for 90% power to detect a one-third reduction in recurrent preterm birth (from 16.8% to 11.2%). We note that this estimated one-third reduction approximates the relative risk reduction for recurrent PTB < 35 weeks gestation in Trial 002 (31% placebo vs. 21% Makena). From 2012 to 2016, 456 consecutive women with prior sPTB ≤ 35 weeks enrolled between 16 and 20 weeks and were treated with HPC. A total of 1290 women who gave birth before HPC became available at the hospital (1988 to 2011) were matched to 430 HPC-treated women with regard to maternal race, BMI, and specific history of prior preterm birth. The women were predominantly Hispanic (80%) and Black (17%), with 89% having completed a highest level of education of 12th grade or less, and nearly half had a BMI ≥ 30 kg/m^2. After

[13] Bastek JA, Adamczak JE, Hoffman S, Elovitz MA, Srinivas SK. Trends in prematurity: What do changes at an urban institution suggest about the public health impact of 17-alpha hydroxyprogesterone caproate? Matern Child Health J. 2012;16:564-568.
[14] Nelson DB, McIntire DD, McDonald J, Gard J, Turrichi P, Leveno KJ. 17-alpha hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. Am J Obstet Gynecol. 2017;216:600.e1-9.

controlling for the maternal demographic factors and obstetrical history, treatment with HPC did not reduce the rate of recurrent preterm birth ≤ 35 weeks (recurrence rate 25% vs. 23%, HPC treated vs. control, respectively, p = 0.45). Regarding the 3 secondary outcomes:

- HPC did not reduce the rates of recurrent sPTB when analyzed according to the specific sequence of prior preterm and term births. In general, a higher number of prior sPTB increases the risk of recurrent sPTB, and a higher number of intervening term deliveries decreases the risk of recurrent sPTB.
- Recurrent sPTB was not associated with HPC plasma concentrations. Plasma HPC concentrations were available for 116 and 101 of the HPC-treated women at 24 weeks and 32 weeks gestation, respectively. The mean plasma concentration of HPC was 10.2 ± 5.2 ng/mL and 12 ± 5.9 ng/mL at 24 weeks and 32 weeks, respectively. When analyzed at either blood draw time point, HPC plasma concentrations of HPC were not different between women delivering ≤ 35 weeks and those delivering later in pregnancy.
- HPC was not associated with prolonging the duration of the current pregnancy compared to that of the prior preterm birth. There was no statistical difference in the change in gestational weeks at delivery in women treated with HPC compared to the historical comparison women (0.4 ± 5.3 weeks vs. 0.1 ± 4.7 weeks, respectively, p = 0.63).

A side effect of HPC treatment was a significantly increased rate of gestational diabetes compared to case-matched historical controls, 13.4% vs. 8%, for HPC treated vs. untreated women, respectively.

The strengths of these two studies are that they evaluated U.S. women with general baseline risk factors similar to those in Trial 002 and who are within the approved population for Makena. The studies also evaluated intramuscular 250 mg HPC injection with the same dosing regimen as Makena. However, both studies are non-randomized observational studies and residual confounding cannot be excluded. Overall, the findings of these observational studies do not support an effect of HPC, the active ingredient in Makena, on reducing the risk of recurrent PTB in women with a prior sPTB.

ADVISORY COMMITTEE MEETING

On October 29, 2019, a panel of experts from the Bone, Reproductive, and Urologic Drugs Advisory Committee met to discuss the findings of Trials 002 and 003 and the implications of Makena's approval.[15] Please refer to Appendix 1 for summary minutes. There were 3 voting questions and the voting results follow:

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[15] Meeting Information and Materials for the October 29, 2019 Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee Meeting, at https://www.fda.gov/advisory-committees/advisory-committee-

- **VOTE 1:** Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal outcomes? **Yes -** 0; **No** – 16; **Abstain -** 0

- **VOTE 2**: Based on the findings from Trial 002 and Trial 003, is there substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth?
  Yes - 3; **No** - 13; **Abstain** - 0

- **VOTE 3**: Should FDA-
  A. Pursue withdrawal of approval for Makena – **9 votes**
  B. Leave Makena on the market under accelerated approval and require a new confirmatory trial – **7 votes**
  C. Leave Makena on the market without requiring a new confirmatory trial – **0 votes**

The advisory committee members unanimously voted that Trial 003 did not verify the clinical benefit of Makena, an overwhelming majority voted that there was not substantial evidence that Makena reduces the risk of preterm birth, and a small majority favored removing Makena from the market. However, a sizable minority of the members recommended that FDA leave Makena on the market and require a new confirmatory trial. Many of those who voted to leave Makena on the market under accelerated approval (Option B in Vote 3) acknowledged the efficacy data for reducing the risk of recurrent preterm birth are conflicting and not particularly persuasive. They also asserted that more data are necessary to characterize the effect of Makena, especially to identify subpopulations that might benefit from Makena. However, these members did not believe another randomized, placebo-controlled trial would be feasible, including after withdrawal of Makena's approval. They were primarily concerned that certain healthcare providers would recommend and that certain patients would insist on receiving treatment, regardless of the evidence of efficacy. They opined that prescribers and their patients would resort to compounded HPC injection as they believed this would be the only option if Makena were to be removed. They believed that compounding would pose a worse scenario from a safety and drug quality perspective than leaving Makena, an FDA-approved product, on the market despite uncertain efficacy.[16] Some members indicated that withdrawal of Makena would be warranted only if the drug was unsafe.

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calendar/october-29-2019-meeting-bone-reproductive-and-urologic-drugs-advisory-committee-meeting-announcement

[16] We note that generic Delalutin (HPC 250 mg/mL injection) products, which have the same active ingredient, concentration, and route of administration as Makena, continue to be approved and marketed. Delalutin generics are approved for certain gynecological conditions and are not approved to reduce the risk of recurrent PTB. Although CDER would not suppcort the use of HPC to reduce the risk of recurrent PTB, we acknowledge that some health care providers/patients might use the approved generic Delalutin off-label for this unapproved use. In general, once a drug has been approved for marketing, a health care practitioner may prescribe it for a particular patient for a use other than the approved indication when the practitioner determines that it is medically appropriate for that patient.

CONCLUSION AND RECOMMENDATION

The FD&C Act and its regulations provide that the Agency may withdraw a drug's accelerated approval when, among other things, post-approval trials fail to verify the drug's clinical benefit or the drug is not shown to be safe or effective,[17] both of which are the case here.

Failure to verify Makena's clinical benefit:

CDER approved Makena under the accelerated approval pathway based on the results of a single adequate and well-controlled clinical trial, Trial 002, in which the drug showed a treatment effect on the surrogate endpoint of the proportion of women delivering at < 37 weeks gestational age. As a condition of approval, CDER required the applicant to conduct an appropriate postapproval study to verify and describe Makena's predicted effect on neonate morbidity/mortality. The Applicant conducted such a study (Trial 003), an adequate and well-controlled trial evaluating the efficacy of Makena. Trial 003 failed to verify a clinical benefit of Makena to neonates born to mothers receiving Makena compared to placebo, and the advisory committee panel unaminously agreed with this conclusion.

Makena not shown to be effective:

Trial 003 failed to show that Makena has a treatment effect on the clinical outcome of interest, the neonatal morbidity/mortality composite index. CDER's various subgroup analyses did not identify a population for whom Makena provided benefit. This is the only trial that has been conducted that is appropriately designed to evaluate Makena's effect on neonatal outcomes.

Trial 003 also failed to substantiate an effect on the surrogate endpoint of the proportion of women delivering preterm. Given the divergent findings on the surrogate endpoint between Trial 002 and Trial 003, most of the advisory committee members concluded that there was not substantial evidence of Makena's effect on reducing the risk of preterm birth. Although the populations of Trials 002 and 003 differed in certain risk factors for PTB (e.g., demographics and socioeconomic factors), CDER determined these risk factors were not effect modifiers and did not explain the differences in the efficacy findings between the two trials.

For reasons discussed previously, we determined that there was substantial evidence of Makena's effect on the surrogate endpoint of delivery prior to 37 weeks gestation at the time of its approval in 2011, based on the single, adequate and well-controlled trial that was available at that time. However, based on currently available evidence, including another adequate and well-controlled trial (Trial 003), CDER has concluded there is not substantial evidence of effectiveness of Makena for its intended use.

At present, data are available from two adequate and well-controlled clinical trials (Trials 002 and 003). These are the most robust data informing the efficacy of Makena for its intended use. Trial 002 met its primary efficacy endpoint, a surrogate endpoint reasonably likely to predict clinical benefit. However, Trial 003, a larger, well-designed, well-conducted trial, unequivocally

[17] See section 506(c)(3)(B) and (C); 21 CFR 314.530(a)(1) and (6).

failed to demonstrate Makena reduced the risk of recurrent PTB prior to 35 weeks gestation, prior to 37 weeks (the primary efficacy endpoint for Trial 002), or prior to 32 weeks. Subgroup analyses of Trial 003 did not identify a population in whom Makena reduced the risk of preterm birth. If these conflicting findings of Trials 002 and 003 had been submitted at the same time in an NDA seeking approval for Makena, we would conclude that there is not substantial evidence of effectiveness of Makena for reducing the risk of recurrent PTB.

The Applicant asserts that Trial 002 should carry more weight than Trial 003. The Applicant states that data obtained from Trial 003 are not generalizable to U.S. women because Trial 003 evaluated an international population with fewer risk factors (e.g., race, number of prior sPTB, certain socioeconomic factors) for PTB. We do not agree.

- Exploratory subgroup analyses of Trial 003 by region (U.S. vs. non-U.S.) did not show that Makena reduced the proportion of women delivering < 35 weeks, < 32 weeks, or < 37 weeks gestation in either subgroup. There was no evidence of a treatment effect on PTB in U.S. or non-U.S. women (Figures 2 and 3).

- Trial 002 enrolled approximately 60% Black women compared to 7% in Trial 003. Overall, Black people comprise approximately 13% of the U.S. population. In Trial 002, an effect of Makena was observed in Black and non-Black women. In Trial 003, Makena did not have an effect in Black or non-Black women. We conclude that race did not impact Makena's effect, or lack thereof, in either trial. Of note, 29% of the U.S. subgroup in Trial 003 was Black, and there was no evidence of Makena's effect in the U.S. subgroup or in the U.S. Black subgroup.

- Other risk factors in addition to region and race differed between Trials 002 and 003 (e.g., number of prior sPTBs, level of education, with/without partner). Analyses did not show that these factors impacted the effectiveness of Makena. The differences in these factors between these two trials did not explain the lack of Makena's effect on reducing the risk of recurrent preterm birth in Trial 003. Subgroup analysis of Trial 003 by a "composite" of risk factors that serve as proxy for risk level indicated that Makena did not have an effect for women at lower or higher risk for recurrent PTB.

Our assessment included other available data on the effect of HPC (the active ingredient in Makena) on the recurrence of singleton sPTB. These data included CDER's meta-analysis of select studies from the EPPPI meta-analysis and observational studies with HPC, none of which showed an effect of HPC on reducing recurrent PTB. Although less robust and less relevant than Trials 002 and 003, these data provide additional support for our determination that there is not substantial evidence of Makena's effectiveness in reducing the risk of recurrent PTB.

Therefore, the grounds for expedited withdrawal of approval of Makena under section 506(c)(3)(B) and (C) of the FD&C Act and 21 CFR 314.530(a)(1) and (6) are met.

Beyond the fact that the statutory standard for withdrawal of approval has been satisfied, we recommend that Makena's accelerated approval should be withdrawn based on the following additional considerations:

1. An approved drug product should only be permitted to remain on the market if its benefits continue to outweigh its risks. Makena's medical risks include thromboembolic disorders, allergic reactions, decreased glucose tolerance, fluid retention that may worsen maternal conditions such as pre-eclampsia, depression, and injection site adverse reactions. The risk of exposing treated women to these harms, in addition to false hopes, costs, and additional healthcare utilization, outweighs Makena's unsubstantiated benefit.

2. Withdrawing Makena's approval upholds the regulatory integrity of accelerated approvals. Accelerated approval is a pathway for promising new therapies for serious and life-threatening diseases to be approved in an expedited manner, based on an effect on a surrogate or intermediate clinical endpoint, where clinical benefit is verified after approval. However, it does not change the approval standard for drugs; it is rooted in the fundamental regulatory requirement that a new drug product must be shown to be safe and effective to be marketed in the United States. In order for the accelerated approval program to serve its purposes and not operate as a lower approval standard, CDER must be able to withdraw approvals when it determines, based on careful analysis of the data, that the confirmatory trial(s) failed to confirm clinical benefit, or that, in consideration of all of the available data, the product is not shown to be effective for its approved indication.

3. Given the conflicting findings of Trials 002 and 003, both of which were adequate and well-controlled trials, new evidence of Makena's effect on reducing the risk of recurrent PTB and improving neonatal outcomes would need to come from adequate and well-controlled trial(s). It is unlikely such a trial could be performed in the U.S. at this time as long as Makena remains approved to reduce the risk of recurrent preterm birth and it is recommended for this use by current professional society guidelines, despite findings from Trial 003.[18]

4. Withdrawal of Makena from marketing would send a strong signal that there is not substantial evidence of effectiveness for its currently approved use, which may change the current standard of care and facilitate recruitment in an adequate and well-controlled trial.

AMAG's MEETING REQUEST and STUDY PROPOSAL

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[18] SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. https://els-jbs-prod-cdn.literatumonline.com/pb/assets/raw/Health%20Advance/journals/ymob/SMFM_Statement_PROLONG-1572023839767.pdf

On February 19, 2020, the Applicant submitted a meeting request to discuss proposals for providing evidence of effectiveness for Makena. FDA denied that request on March 11, 2020, as the request was premature because CDER's review of Makena, taking into account the discussion at the October 2019 Advisory Committee meeting, was still ongoing. The Applicant also submitted a briefing package on May 20, 2020, in which they included greater detail regarding their proposals for two observational studies: (1) a retrospective study to assess the comparability of patients treated with Makena and those not treated with Makena (Aim 1) and the effectiveness of Makena (and generics of Makena) in reducing the risk of recurrent sPTB in women with a singleton pregnancy who had a prior PTB (Aim 2) and (2) a prospective, real-world, observational study to assess the effectiveness of Makena (and its generics).

The retrospective study would use real-world U.S. data from electronic health record databases and claims databases. The proposed study population would include pregnant U.S. women who meet the criteria for treatment with Makena, and women who received Makena (and its generics) would be compared to those who did not receive Makena.

The Applicant included feasibility assessment results for the proposed retrospective study in the Optum© Insight dataset. They acknowledged that the dataset is limited in differentiating between spontaneous versus medically indicated preterm birth and proposed to determine the type of preterm birth through a claims-based algorithm. This algorithm is yet to be developed and validated. In addition, the Applicant proposed to include propensity score matched Makena-treated and untreated women as an approach to control for baseline risk imbalances to increase comparability between the two groups. They acknowledged that residual confounding may still be present as physicians are likely to prescribe Makena to women at high-risk for recurrent PTB, as it is the only FDA-approved drug for that indication.

The Applicant also provided information on potential baseline covariates, including demographics (e.g., age, race/ethnicity, marriage status, education level), medical history (e.g., number and type of prior PTB, substance abuse status/history), comorbidities (e.g., sexually transmitted disease, diabetes) and treatment received (e.g., cerclage placement, vaginal progesterone use). Depending on data availability, they will also consider adjusting for geographic regions or urban/rural location to address confounding by socioeconomic status on the risk of sPTB. The Applicant stated that they would not pursue the Makena effectiveness component of the retrospective study (Aim 2) if they could not create comparable groups through propensity-score matching (Aim 1).

The prospective, real-world, observational study would assess the effectiveness of Makena (and its generics) in reducing the risk of recurrent sPTB in women with a singleton pregnancy who had a previous history of singleton sPTB. Individual subject data, including demographics, detailed medical, social and obstetrical histories, race and ethnicity, age, weight and body mass index would be collected prospectively, including data from claims databases. The proposal included limited information and the timing of conducting this prospective observational study would depend on the results from the retrospective study.

After considering the existing clinical data for Makena, including the conflicting results of the two randomized controlled clinical trials and the proposed study designs, and taking into account the views expressed at the October 29, 2019 advisory committee meeting, we conclud that a randomized clinical trial is needed to establish substantial evidence of effectiveness of Makena, primarily because in nonrandomized, observational settings, users and non-users of Makena are likely to be inherently different in baseline risks for PTB, and risk factors for PTB are not well characterized. Major limitations with the proposed observational study designs preclude the ability to reliably conclude whether any treatment effect, if one is seen, could be attributed to Makena or to other confounding factors such as baseline risk differences between Makena users compared to non-users. Three major limitations follow:

- Difficulty in accurately identifying the intended population: Accurately identifying the indicated study population from data sources of observational studies would be extremely difficult. Due to the absence of specific ICD-9 or ICD-10 diagnosis codes for "history of sPTB," women who receive Makena for unapproved uses could not be reliably excluded from the proposed observational studies. Therefore, we cannot be certain that Makena is being administered only to the indicated population, especially for the retrospective study.

  The Applicant's proposed plan to use a claims-based algorithm to distinguish between prior sPTB and medically indicated PTB does not resolve this concern. This algorithm has not been created and validated to ensure the accuracy of ascertainment of PTB types. Misclassification of PTB types may result in inclusion of pregnant women who do not fall within Makena's indication.

- Limitation in comparability between Makena-users and non-users: So long as Makena is considered the standard of care in the U.S., identifying an appropriate non-user comparator group of women at a comparable baseline risk for recurrent PTB as Makena users would be highly unlikely. Because Makena is the only drug approved for reducing the risk of recurrent preterm birth and is currently the standard of care, Makena users would almost certainly be dissimilar from the control group of non-users in risk factors for preterm birth. Thus, it would not be possible to decipher whether any differences in the efficacy seen in the Makena users compared to non-users is because of the drug or the inherent differences in baseline risks between these two groups.

  The Applicant's proposal acknowledged the presence of differential recurrent sPTB risk factors at baseline between treated and untreated groups. Their reliance on data from the descriptive analysis (Aim 1) to determine feasibility of their evaluation on effectiveness of Makena in their proposed observational study (Aim 2) fails to resolve this problem for the aforementioned reasons. Therefore, the Agency does not consider the proposed observational study design suitable or sufficient to address the question of Makena's effectiveness.

- Limitation in controlling known and unknown confounding: There are factors (known as "confounding factors") that can influence both the choice to use Makena and the outcome of interest. If not controlled for, these confounding factors can result in spurious causal associations between the intervention and outcome of interest. Therefore, it is paramount to ensure adequate control of confounding factors to determine that any improvement in condition/disease outcomes is due to the drug and not due to other differences between the test and control groups. In a randomized trial, the process of randomization is expected to balance the confounding factors (both known and unknown) between the treatment and control groups. In an observational study, subjects are not randomized and therefore ensuring that confounding factors are balanced between the groups is more challenging. Adequate control for these confounders in an observational design requires (1) a solid understanding of pathophysiology of the condition/disease of interest to identify what confounders may impact disease outcomes and (2) the ability to reliably and accurately obtain information about these confounders in the database. Completely controlling confounding factors for PTB, both measured and unmeasured, in an observational setting is not possible given the following:
    - SPTB represents a syndrome and its causes are multifactorial. Risk factors for PTB include uterine distension, dysfunction of the cervix, infection of the lower genital tract, and other factors (such as cigarette smoking, inadequate maternal weight, and illicit drug use). The contribution of these factors to PTB, however, is not well-characterized. In fact, two-thirds of PTBs occur among women with no identifiable risk factors. Furthermore, most women with a prior sPTB do not experience a recurrence with the subsequent pregnancy without treatment. Therefore, it remains challenging to measure and control for confounders to ensure unbiased risk estimates.
    - Some risk factors, such as smoking and substance use, may not be reliably captured in an observational setting. For instance, among women indicated for treatment with Makena, if women receiving Makena are less likely to smoke compared to those who did not receive Makena, the improvement in gestational age of delivery in Makena users could be due to less smoking and not due to Makena. Without capturing substance use information on all study subjects, we would not be able to accurately interpret the study's findings.

The Applicant's proposal does not ensure adequate control of confounders. Though the Applicant considered several baseline covariates in their protocol, some covariates listed are unavailable in claims data or incomplete in electronic health records, such as substance abuse status or history and educational level. The proposed plan to address confounding by socioeconomic status on the risk of recurrent sPTB by adjusting for geographic regions is inadequate. Although the Applicant proposed to prospectively collect covariate information based on results from the retrospective study, the measurement and control of baseline risk factors for sPTB is likely to remain insufficient, and residual confounding remains a concern for addressing the effectiveness of Makena in a prospective observational study.

Based on these considerations and the need for a randomized controlled trial, the proposed studies would not alter our recommendation to withdraw approval of Makena.

APPENDIX 1. Summary Minutes from the October 29, 2019 advisory committee.

AC minutes

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTINE P NGUYEN
10/05/2020 09:08:56 AM
In addition to myself, I am also signing on behalf of Barbara Wesley and Christina Chang.

Appendix 5

Addendum to CDER Decisional Memorandum,
NDA 021945 Makena

Food and Drug Administration
Center for Drug Evaluation and Research
Memorandum to the File

NDA 021945 Makena (hydroxyprogesterone caproate)

Date:	January 14, 2022
To:	Patrizia Cavazzoni, MD Director Center for Drug Evaluation and Research (CDER)
From:	Barbara Wesley, MD, MPH Medical Officer Division of Urology, Obstetrics, and Gynecology (DUOG)
	Christina Chang, MD, MPH Clinical Team Leader, DUOG
	Christine Nguyen, MD Director, DUOG
	Tae Hyun Jung, PhD Statistical Reviewer Division of Biometrics VII (DB VII)
	Clara Kim, PhD Statistical Team Leader DB VII
	Huei-Ting Tsai, PhD Epidemiology Reviewer Division of Epidemiology II (DEPI II)
	Wei Liu, PhD Team Leader (Acting) DEPI II
Through:	Mark Levenson, PhD Director DB VII
	David Moeny, R.Ph, MPH Director DEPI II

Judy Zander, MD
Director
Office of Pharmacovigilance and Epidemiology

Janet Maynard, MD, MHS
Acting Director
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

Gerald Pan, MD, MHS
Director
Office of Surveillance and Epidemiology (OSE)

Peter Stein, MD
Director
Office of New Drugs (OND)

Subject: Addendum to the October 5, 2020, Decision Memorandum concerning the recently published EPPPIC meta-analysis

I. INTRODUCTION

This is an addendum to the October 5, 2020, memorandum wherein the Division of Urology, Obstetrics, and Gynecology (DUOG) provided the reasoning for recommending that CDER pursue withdrawal of approval for Makena (hydroxyprogesterone caproate or HPC) injection. On October 5, 2020, CDER issued a Notice of Opportunity of Hearing (NOOH), proposing to withdraw approval of Makena. Prior to issuance of the NOOH, CDER was made aware that a meta-analysis, funded by the Patient-Centered Outcomes Research Institute (PCORI), was being conducted to evaluate the efficacy of various progestogens (vaginal progesterone, oral progesterone, injectable hydroxyprogesterone caproate [HPC]) compared to control (placebo or non-intervention) or to each other administered during pregnancy to reduce the risk of preterm birth (PTB) in at-risk asymptomatic women with singleton or multifetal gestations. CDER's decision to issue the NOOH took into consideration preliminary data from this meta-analysis.

This meta-analysis, entitled "Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC) individual participant data meta-analysis of randomized controlled trials," has since been published in the Lancet.[1] CDER previously conducted a meta-analysis of the five placebo-controlled HPC trials in singleton pregnancies included in the then-unpublished EPPPIC meta-analysis, three of which evaluated HPC in the indicated population for Makena, as part of its review of the available evidence on Makena's efficacy prior to proposing withdrawing Makena's accelerated approval. After reviewing the scientific information from the published EPPPIC study, CDER has determined the results do not change CDER's proposal to withdraw Makena's approval; our rationale is described below.

II. CDER's REVIEW OF HPC SINGLETON TRIALS IN THE EPPPIC META-ANALYSIS

A. The EPPPIC meta-analysis and its placebo-controlled trials evaluating HPC in singleton pregnancies

EPPPIC is an individual participant data (IPD) meta-analysis of randomized controlled trials (RCTs) that evaluated the effect of various progestogens (vaginal progesterone, oral progesterone, and injectable HPC) compared to control (placebo or no-intervention) or to each other administered during pregnancy in preventing PTB (first occurrence or recurrent PTB). EPPPIC included a total of 31 RCTs, consisting of 11,644 women with singleton or multifetal gestations, with or without a history of prior PTB, and with or without a short midtrimester cervical length. Main outcomes included prenatal death, PTB (<37 weeks, <34 weeks and <28

[1] The EPPPIC Group. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. The Lancet 2021;397 (10280):1183-1194.

weeks gestation at delivery), serious neonatal complications (SNC),[2] and adverse maternal outcomes.[3] SNC and adverse maternal outcomes were each evaluated as a composite outcome. The meta-analysis also assessed individual neonatal and maternal complications included within the composite outcomes of SNC and adverse maternal outcomes and other pregnancy-related complications for a total of an additional 22 outcomes other than the main outcomes.

In general, the study methods reported in the EPPPIC publication appear reasonable, although there are important limitations with the study analysis and questionable data interpretation for the five relevant trials comparing the efficacy of HPC to placebo in singleton pregnancies. The EPPPIC meta-analysis had a published, prespecified study protocol and an unpublished statistical analysis plan. The authors conducted a systematic search to identify potential trials, published and unpublished, that completed primary data collection before July 2016 for inclusion and requested IPD data from trial investigators. In 2020, they included data from Trial 003 (PROLONG) in a targeted update of their initial analyses, following the publication of results from Trial 003.[4] The authors harmonized variable definitions to create uniform definitions across studies before combining data from individual trials for analysis. When data allowed, the authors examined patterns of treatment allocation in the individual trials to check whether the included trials conducted the randomization step appropriately. The IPD meta-analysis (primary analysis) used generalized linear mixed models with individual participant data, which incorporated random effects to allow for heterogeneity across trials. For trials not supplying individual-participant level data, the authors conducted a study-level meta-analysis as a sensitivity analysis. For the random-effect meta-analysis model, the DerSimonian-Laird method was used to account for the heterogeneity across the trials. The authors conducted subgroup analyses by the risk factors of a prior spontaneous PTB or a short cervix. The EPPPIC meta-analysis included most preferred items for reporting a systematic review and meta-analyses of IPD[5] in their manuscript, although the authors did not describe how they handled missing data within IPD and whether they found any important issues when checking the integrity of the IPD data.

Among the 31 trials included in the EPPPIC meta-analysis, five trials (Meis, or Trial 002; PROLONG, or Trial 003; PHENIX [singleton]; PROGFIRST; and SCAN) compared the efficacy of HPC to placebo in singleton pregnancies (Table 1). As Makena (HPC injection) is indicated for women with a singleton pregnancy who have a history of spontaneous PTB,

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[2] Serious neonatal complications (SNC) includes severe necrotizing enterocolitis stage II/III, intraventricular hemorrhage grade 3/4, retinopathy of prematurity stage 3 or worse, bronchopulmonary dysplasia, confirmed sepsis, patent ductus arteriosus, and neonatal infection.
[3] Adverse maternal outcome includes gestational hypertension, preeclampsia, gestational diabetes, and maternal infection.
[4] Blackwell SC, et al. 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial. Am J Perinatol 2020;37:127–136 (first published online on October 25, 2019).
[5] Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF; PRISMA-IPD Development Group. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA. 2015;313(16):1657-1665.

CDER's assessment focused on these five HPC singleton trials. Because the EPPPIC meta-analysis reported their findings mostly from assessing PTB < 34 weeks, CDER's assessment also focused on the results for PTB < 34 weeks. To account for the small number of HPC trials included in the meta-analysis, CDER conducted a sensitivity analysis using the Hartung-Knapp method, which typically provides conservative variance estimates. We previously discussed these five trials in our October 5, 2020, memorandum, and summarize them below.

Trial 002 and Trial 003: Trials 002 and 003 assessed Makena's efficacy using the approved dose and dosing regimen (250 mg HPC weekly injection, starting at 16-20 weeks gestation) to reduce the risk of recurrent PTB in women with a singleton pregnancy and a history of spontaneous PTB (sPTB), which is Makena's indicated patient population. Makena's accelerated approval in 2011 was based on the results of Trial 002, a randomized, double-blinded, placebo-controlled trial that enrolled 463 women with a singleton pregnancy and a prior sPTB. In Trial 002, Makena reduced the proportion of women delivering before 37 weeks gestation. This trial was not designed or powered to assess whether Makena showed an improvement on neonatal outcomes. FDA concluded that the effect on delivery before 37 weeks gestation was reasonably likely to predict clinical benefit to neonates, and approved Makena under accelerated approval with a postmarketing requirement to perfom a clinical trial to confirm neonatal benefit. This postmarketing requirement trial, Trial 003, was a multicenter, randomized, double-blinded placebo-controlled trial very similar in design as Trial 002, except that the primary objective was to confirm clinical benefit to neonates, with neonatal outcomes (neonatal composite index) being a co-primary efficacy endpoint; the other co-primary endpoint was delivery prior to 35 weeks gestation. Results from Trial 003 did not demonstrate a statistically significant treatment effect for the co-primary endpoint, or for either of its individual components (proportion of women delivering prior to 35 weeks and neonatal composite index). Also, no differences between Makena and placebo were seen in the secondary outcomes of delivery <32 weeks or <37 weeks (<37 weeks was the primary efficacy endpoint in Trial 002 that formed the basis for accelerated approval). Exploratory subgroup analyses for the overall study population in Trial 003 and in the U.S.-only subgroup also did not identify any subgroup for which evidence demonstrated Makena's efficacy. A brief summary of key design features and findings of Trials 002 and 003 can be found in CDER's Decision Memorandum dated October 5, 2020. Both trials were adequate and well-controlled to evaluate the efficacy and safety of Makena for its intended use.

PHENIX [singleton], PROGFIRST, and SCAN trials: Below, we describe the remaining three placebo-controlled HPC trials in singleton pregnancies included in the EPPPIC meta-analysis.

> The PROGFIRST trial, submitted and reviewed in 2006 in the original NDA for Makena, enrolled the same target population and investigated the same dose and dosing regimen as Makena's. However, the trial was terminated prematurely because the investigational

HPC product had product quality issues impacting the drug's potency. CDER determined that data from PROGFIRST were not acceptable as evidence of efficacy.[6]

- The SCAN trial, conducted in the U.S., evaluated efficacy of weekly 250 mg HPC to prevent PTB < 37 weeks in 657 nulliparous women (women without a prior birth) with a mid-trimester cervical length shorter than 30 mm. Although the SCAN trial evaluated the same Makena dose as Trials 002 and 003, its study population (women with a short cervix in the current pregnancy and no prior PTB) was different from Makena's indicated population (women with a prior sPTB unselected for cervical length in the current pregnancy). The SCAN study evaluated the efficacy of HPC in reducing incident/first-time PTB (i.e., for primary prevention of PTB) while Makena is approved for reducing recurrent PTB (i.e., for secondary prevention of PTB). The SCAN trial found numerically similar rates of PTB in the HPC and placebo arms (25.1% vs. 24.2%, respectively; relative risk, RR=1.03, 95% confidence interval (CI) = [0.79,1.35]), showing that HPC did not reduce the risk of PTB < 37 weeks gestation in women diagnosed with a short mid-trimester cervical length and who have not had a prior birth.

- The PHENIX (singleton) trial was conducted in France, assessing the efficacy of weekly HPC 500 injection in reducing the PTB rate among 105 pregnant women with a midtrimester cervical length shorter than 25 mm and with at least one other risk factor for PTB (prior PTB, cervical surgery, uterine anomalies, or prenatal diethylstilbestrol exposure). The study population in PHENIX (singleton) is not comparable to Trials 002 and 003 because only 55% and 57% of pregnancies in the HPC arm and placebo arm, respectively, in PHENIX (singleton) had a prior PTB. Also, while all patients in PHENIX (singleton) had short cervical length, patients in Trials 002 and 003 were unselected for cervical length. In addition, the PHENIX (singleton) study assessed an HPC dose (500 mg) double that of Makena (HPC 250 mg) and treatment was started between 20 and 31 weeks gestation (compared to Makena's treatment starting between 16 and 20 weeks gestation). The PHENIX (singleton) trial found no difference in the time from randomization to delivery between HPC and placebo (the primary endpoint) and the authors concluded HPC did not prolong pregnancy in women with singleton gestation and a short cervix and other risk factors for PTB. The trial also found that HPC did not reduce the rates of PTB at several gestational ages assessed as a secondary endpoints. The rates of PTB at < 37 weeks (45% in HPC group versus 44% in placebo group, p>0.99), at < 34 weeks (24% in HPC group versus 30% in placebo group, p=0.51), and at < 32 weeks (14% in HPC group versus 20% in placebo group, p=0.44) were similar between treatment groups.

[6] Per the 2006 clinical reviews, the PROGFIRST trial was terminated after about one year when the study drug was recalled by its manufacturer at the request of the FDA due to violations of manufacturing processes that potentially affected drug potency. At the time of trial termination, only 150 of 500 planned women had been randomized, and only 86 women (57 HPC; 29 vehicle) had completed treatment. In CDER's October 5, 2020 Decision Memorandum, we stated that 57% of subjects had completed PROGFIRST, which was incorrect.

In summary, the five placebo-controlled HPC trials in singleton pregnancies in the EPPPIC meta-analysis included Trials 002 and 003, as well as three other studies. Two of these other three studies (PHENIX, SCAN) were conducted in a study population dissimilar to Makena's indicated population. In particular, while all participants in Trials 002 and 003 had a prior spontaneous PTB, SCAN enrolled no patients with a prior PTB and PHENIX enrolled only some patients with a prior PTB. Further, PHENIX and SCAN both studied women with a short cervix at midtrimester while Trials 002 and 003 did not specify cervical length in the eligibility criteria and only 1.9% of women in Trial 003 with cervical length data had cervical length < 25 mm.[7] PHENIX also evaluated a dose and treatment time different from that of Makena. PROGFIRST was stopped prematurely because of significant manufacturing problems prompting the FDA to ask the sponsor to recall the investigational HPC product, which precluded use of these limited data from this trial as evidence of efficacy when it was reviewed by CDER in the original Makena NDA. We conclude the additional trials (SCAN, PHENIX, and PROGFIRST) included in the EPPPIC meta-analysis to assess HPC's effect in singleton pregnancies were either not comparable to Trials 002 and 003 (SCAN and PHENIX) or had other important limitations (PROGFIRST) and that these important issues limit the use of these trials to help inform Makena's efficacy for its approved use. Additionally, the two completed trials (SCAN, PHENIX) failed to show a treatment effect of HPC on PTB on populations distinct from Makena's indicated population.

[7] Trial 002 did not have information on cervical length. Because Trial 003 was almost identical in design to Trial 002, Trial 003 did not specify cervical length in the eligibility criteria or require its measurement in the study conduct. In Trial 003, which evaluated Makena in its target population based on prior obstetrical history and not cervical length, a total of 1405 of 1708 women (939/1130 Makena; 466/578 placebo) had cervical length information at randomization. Of those 1405 women, 1.9% in each study arm (18 Makena; 9 placebo) had cervical length < 25 mm at randomization. In the U.S. women subgroup in Trial 003, 194 of the 393 women (125 Makena; 69 placebo) had cervical length information at randomization. Of these 194 women, 8% (16) had cervical length < 25 mm (13/125 Makena [10%], 3/69 placebo [4%]).

Table 1. Summary of the five HPC singleton trials included in the EPPPIC meta-analysis

HPC Trial Year/Region	Sample Size (HPC/Placebo)	HPC Dose Timing of Initiation	History of PTB	Cervical Length
Meis trial 2003/ US	310/ 153	250 mg 16 0/7- 20 6/7 weeks	HPC: 100% Placebo:100%	No restriction (not measured)
PROGFIRST Unpublished/ US	94/ 56	250 mg 16 0/7- 20 6/7 weeks	HPC: 100% Placebo:100%	No restriction (not measured)
SCAN 2012/ US	327/ 330	250 mg 16 0/7- 20 3/7 weeks	Nulliparous, or no prior pregnancy that progressed to 20 weeks	All < 30 mm
PHENIX (Singleton) 2015/ France	51/ 54	500 mg 20 0/7- 31 6/7 weeks	HPC: 55% Placebo:57%	All < 25 mm
PROLONG 2019/ Int'l	1,130/ 578	250 mg 16 0/7- 20 6/7 weeks	HPC: 100% Placebo:100%	No restriction (<2% is <25mm)

Of the five HPC singleton trials in Table 1, four (PROGFIRST, SCAN, PHENIX (singleton), PROLONG) did not indicate a treatment effect of HPC for reducing the risk of preterm birth.

B. Results and interpretation of the meta-analysis of the five HPC singleton trials

The EPPPIC authors evaluated the same five HPC singleton trials (for a total sample size of 3083) as those discussed above in their meta-analysis and reported the following relative risk (RR) comparing the risk of PTB < 34 weeks among HPC-exposed women to those who received placebo:

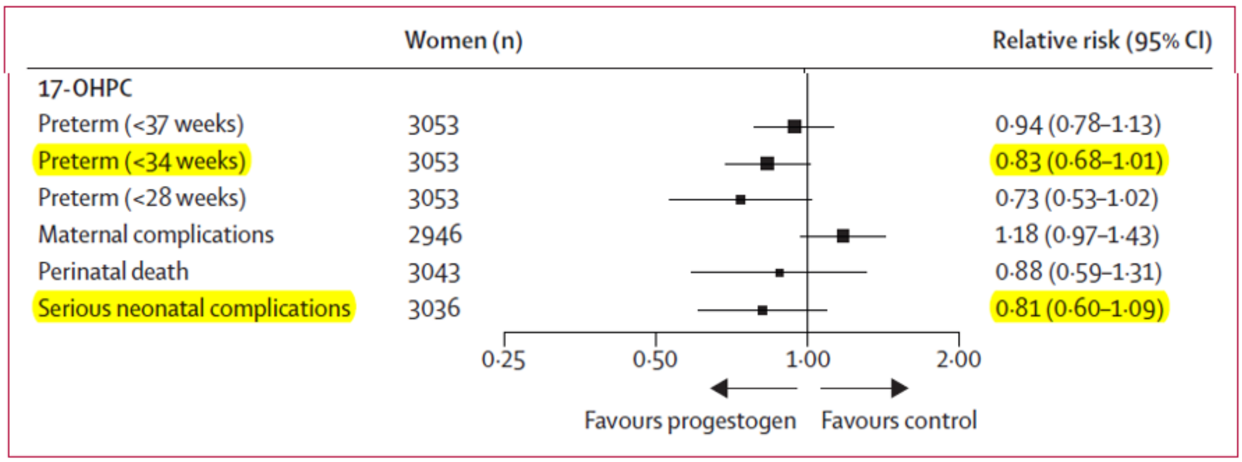
- IPD meta-analysis (Figure 1 below): RR = 0.83 (95% CI: 0.68, 1.01)
- Study-level meta-analysis: RR of random effect model = 0.83 (95% CI: 0.68, 1.00); RR of fixed effect model = 0.83 (95% CI: 0.68, 1.00)[8]

The EPPPIC authors also stated that their "analyses suggest a…possible reduced risk of composite serious neonatal complications for …17-OHPC,"[9] with an RR of 0.81 (95% CI: 0.60, 1.09) (Figure 1 below). It should be noted that the composite neonatal endpoint assessed in EPPPIC and the Makena trials[10] are different. Neonatal death, respiratory distress syndrome

[8] CDER confirmed the EPPPIC authors' estimate of the random effect model (0.83 (95% CI: 0.68, 1.00), but could not confirm their estimate using the fixed effect model (CDER obtained 0.84 (95% CI: 0.69, 1.02).
[9] The EPPPIC analysis assessed adverse neonatal sequelae associated with early births using a composite of serious neonatal complications (severe necrotising enterocolitis stages 2–3, intraventricular haemorrhage grades 3–4, retinopathy of prematurity stage 3 or worse, bronchopulmonary dysplasia, confirmed sepsis, patent ductus arteriosus, and neonatal infection) as well as individually. The authors also assessed respiratory distress syndrome, neonatal respiratory support, birthweight, and admission to neonatal intensive care individually. 17-OHPC is the abbreviation used in the EPPPIC study for indicating HPC.
[10] The neonatal composite index consists of neonatal death, grade 3 or 4 intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), or

(RDS), and stage 1 necrotizing enterocolitis, which were assessed as part of the neonatal composite endpoint in the Makena trials, were not included as part of composite serious neonatal complications in EPPPIC. Also, the composite neonatal endpoint in EPPPIC included retinopathy of any stage and patent ductus arteriosus, which were not among the neonatal complications evaluated in the composite endpoint in the Makena trials. Whether these differences substantially affect the generalization of EPPPIC findings for neonatal outcomes is unclear. However, it is important to note that EPPPIC's exclusion of crucial adverse neonatal events, such as neonatal deaths and RDS, in the neonatal composite endpoint could have resulted in an underestimation of the number of serious neonatal complications.

Figure 1. Results of main outcomes from the EPPPIC meta-analysis of five HPC singleton trials



Source: abbreviated from Figure 2 in the EPPPIC publication

The EPPPIC authors stated that their "results showed a consistently favourable direction of effect for birth and neonatal outcomes, with a clear reduction in the RR of early preterm birth before 34 weeks for ….17-OHPC, although CIs just crossed equivalence for 17-OHPC." The EPPPIC authors thus concluded that HPC "reduced birth before 34 weeks in high-risk singleton pregnancies" and that "given increased underlying risk, absolute risk reduction is greater for women with a short cervix, hence treatment might be most useful for these women."

We do not agree with the authors' conclusion that HPC reduced PTB before 34 weeks in "high-risk" singleton pregnancies, identified by the authors as a prior PTB or a short cervix in current pregnancy for the following reasons. First, the confidence interval for the reduced PTB before 34 weeks includes the possibility that HPC does not have a treatment effect. Second, multiple endpoints were analyzed, which increases the risk of false positive findings. Third, HPC did not reduce the risk of PTB < 37 weeks or < 28 weeks gestation.

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proven sepsis. A neonate was considered to have a composite index event if s/he experienced any of the above 6 adverse outcomes at any time during childbirth hospitalization up through discharge from the neonatal intensive care unit.

We also do not agree with the authors' conclusion that "[r]esults for other birth and neonatal outcomes were consistently favourable, but less certain." Several neonatal complication outcomes (i.e., fetal death or stillbirth, respiratory support, and severe intraventricular hemorrhage) results were unfavorable to HPC.

For the sensitivity analysis of PTB < 34 weeks, CDER conducted a random-effect meta-analysis using the Hartung-Knapp method, which has shown better properties when the number of studies is small or the studies are heterogeneous in the meta-analysis. The analysis resulted in the same RR point estimate, but with a wider confidence interval of [0.63, 1.08]. CDER's analysis based on the same five HPC singleton trials is already documented in the October 5, 2020, decision memorandum.

Evaluation of subgroup analyses by "high-risk" factors

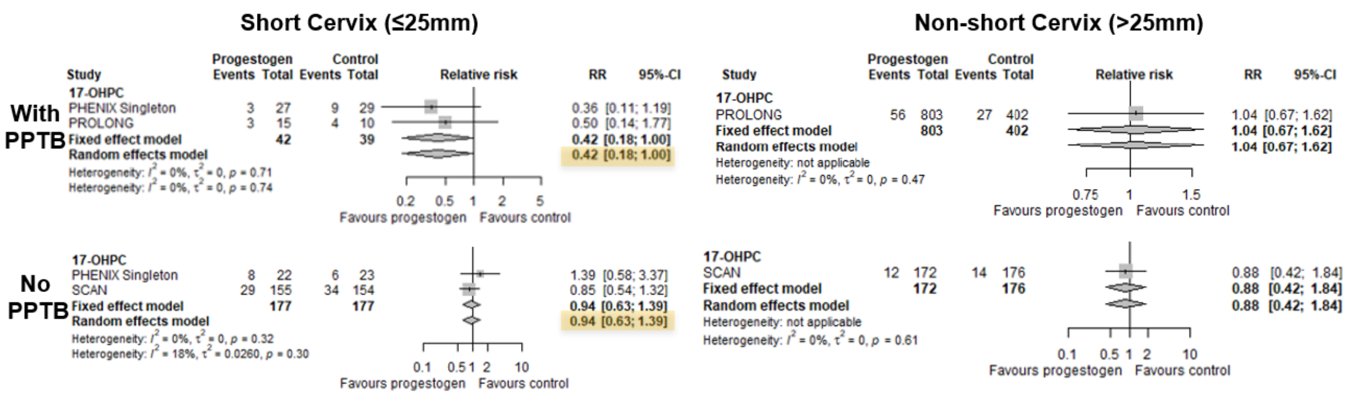
In their assessment of HPC efficacy for PTB < 34 weeks in "high-risk" singleton pregnancies, the authors included the following two subgroup analyses using the risk factors of cervix length and prior PTB status:

1. The first subgroup analysis was a study-level meta-analysis in four subpopulations defined by cervix length (≤ 25 mm and > 25 mm) and prior PTB status (Figure 2). Only study participants who had patient-level information on both cervix length <u>and</u> prior PTB information were included in this analysis. This analysis did not include Trial 002 and PROGFIRST because these earlier studies did not collect cervical length information. There was a suggestion of a treatment effect for HPC in only one of the 4 subpopulations (women with a prior PTB and a short cervix). There was no evidence of HPC's treatment effect in women without a prior PTB (regardless of short cervix status) or in women with a prior PTB and a non-short cervix.

   Using a significance level unadjusted for multiplicity, the RR was marginally significant only in the subgroup of women with <u>both</u> risk factors (short cervix ≤ 25 mm and with prior PTB); RR = 0.42; 95% CI = [0.18; 1.00] based on 19 PTB events (in the current pregnancy). However, this subgroup represents only a very small proportion (n = 81; 2.7%) of the women included in the HPC trials in the EPPPIC meta-analysis. Findings based on such small numbers of women and without consideration for multiplicity are tenuous and are exploratory. Furthermore, 56 of the 81 women (~70%) in this subgroup were from the PHENIX (singleton) trial that evaluated an HPC dose twice that of Makena and administered later in pregnancy than Makena. The remaining 25 women were from Trial 003. It is notable that, in Trial 003, which enrolled Makena's indicated population – women with a prior PTB and unselected for cervical length – a very small proportion of women with cervical length data had a short cervical length (27/1405 or ~2%). Thus, there is not evidence that Makena's intended population is reflected in this small subgroup of women with a prior PTB <u>and</u> a short cervix. Further, findings based on combining a dissimilar dose and dosing regimen are not interpretable for the purpose of characterizing the effect of Makena for its approved conditions of use.

In the subgroup of women with a short cervix but no prior PTB (n = 354; 11.5%) (lower left forest plot in Figure 2), the authors' own analysis showed that HPC was not effective. For women who did not have a short cervix (n = 1553; 50.4%) (the two forest plots on the right in Figure 2), the authors' own analysis again showed that HPC was not effective regardless of whether they had prior PTB.

Figure 2. Analysis of subpopulations defined according to categorized cervical length and prior PTB status < 34 weeks



Source: EPPPIC Publication, Supplementary Appendix Figure 9 (17-OHPC only) (p.9)
Note: We note a discrepancy in the numbers of women in the top right forest plot in this figure (women with non-short cervix and prior PTB) between the manuscript reviewed by CDER and the final publication. In the EPPPIC manuscript reviewed by CDER prior to the publication, the numbers of women who received HPC and control were 731 and 361, respectively. In the final publication, these numbers were changed to 803 and 402, respectively, without explanation.

2. The second subgroup analysis included five analyses - three univariate logistic regression models that included cervix length as either a categorical variable (≤ 25 mm vs. > 25 mm) or as a continuous variable and prior PTB-status, and two multivariable logistic regression models that included both risk factors (cervix length and prior PTB), one with cervix length as a categorical variable and the other with it as a continuous variable. Without adjusting the significance level for multiplicity, this subgroup analysis considered a p-value less than 0.1 to be statistically significant.

   Table 2 describes the results of the subgroup analysis that included both risk factors, using the endpoint of PTB < 34 weeks. The EPPPIC authors concluded that "[they] found some evidence suggesting a possible reduction in benefit of 17-OHPC with increasing cervix length (PTB < 34 weeks p = 0.06; PTB < 37 weeks p = 0.095)."

Table 2. Analyses examining the impact of short cervix and previous PTB on the effectiveness of progestogens

Outcome PTB < 34 weeks	Univariate regression models						Multivariable regression models			
Variable	CL only (categorical)		CL only (continuous)		PPTB only		Categorical CL		Continuous CL	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Cervix length	0.769 (0.419; 1.41)	0.396	1.02 (0.994; 1.06)	0.118			0.647 (0.309; 1.36)	0.249	1.04 (0.998; 1.08)	0.061
PPTB					0.869 (0.49; 1.54)	0.632	0.748 (0.36; 1.55)	0.437	0.65 (0.312; 1.36)	0.251

Source: EPPPIC Publication Supplementary Appendix Table 4 (p.31)
CL = cervical length; PPTB = prior preterm birth; OR = Odds Ratio; CI = confidence interval

These findings from the two subgroup analyses provided by the authors align with their statement (in the Discussion section in the published article) that “there was no apparent benefit in subpopulations of women with previous preterm birth and cervical length greater than 30 mm.” However, the authors concluded that treatment with HPC “might be most useful” for “women with a shorter cervix” (which the authors did not clearly define), despite the fact that their analysis of treatment covariate interactions found “no clear evidence that the relative effects of …17-OHPC differed by cervix length, or by history of previous preterm birth. (Table 2 above).” To support this conclusion, the authors referenced a previously reported observation,[11, 12] that the underlying risk of PTB is greater at shorter cervical lengths, suggesting that this subpopulation has the **potential** for the largest absolute risk reduction, even though their data did not confirm this.

The EPPPIC authors did not conclude that there was neonatal benefit based on their subgroup analyses.

The EPPPIC authors relied, in part, on their subgroup analyses, to support their conclusion that HPC was effective in reducing the risk of PTB < 34 weeks in women with a short cervix (in the current pregnancy) or a prior PTB. We do not agree these subgroup analyses support the authors’ conclusion for the following three main reasons:

1. The subgroup meta-analyses used considerably smaller sample sizes compared to the meta-analysis of the five placebo-controlled HPC trials. Particularly, the subpopulation

[11] Iams JDGR, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med 1996; 334: 567–72.
[12] Heath VCF, Southall TR, Souka AP, Elisseou A, Nicolaides KH. Cervical length at 23 weeks of gestation: prediction of spontaneous preterm delivery. Ultrasound Obstet Gynecol 1998; 12: 312–17.

for which the authors concluded HPC reduced PTB included only 81 women with both short cervix and prior PTB, which comprised only 2.7% of the population of the five HPC trials. Further, the majority of women in this subgroup (~70%) were treated with an HPC dose regimen twice that of the approved Makena dose. Although the prevalence of a short cervix in Trial 002 and PROGFIRST is unknown, in Trial 003, which enrolled Makena's indicated population (women with a prior PTB and unselected for cervical length) only a very small proportion of those with cervical length information (27/1405 or ~2%) had a short cervix. Therefore, there is not evidence the subgroup of women with a prior PTB and a short cervix represents Makena's approved population.

2. Similar to the subpopulation subgroup meta-analysis, the subgroup logistic regression analyses excluded study participants with missing cervical length information. The authors of EPPPIC reported that of all participants in the five HPC trials, 34.7% of the women did not have cervix length information. It is unclear how generalizable those with cervical length measurement are to the general population of women at risk for recurrent spontaneous PTB from having a prior sPTB.
3. The authors of EPPPIC conducted multiple hypothesis testing without controlling for type 1 error rate inflation. Further, the authors used a significance level of 0.1 in the subgroup logistic regression analysis without justification. This signifance level is larger than the typically used level of 0.05. Taken together, these methodological flaws contravene accepted statistical practice in establishing efficacy and raise the probability of falsely concluding that there was a treatment effect when there was none.

III. CONCLUSIONS AND RECOMMENDATION

We conclude that the findings of the EPPPIC HPC singleton meta-analysis do not support Makena's efficacy in reducing the risk of PTB or providing any clinical benefit.

First and most important, the meta-analysis failed to show a clinical benefit of HPC in reducing serious fetal/neonatal outcomes, such as fetal death/stillbirth, death after live birth, low and very-low birth weight, and seven severe neonatal complications[13] assessed as a composite or by individual condition. The most clinically important clinical outcome in any treatment for preterm birth is benefits to the neonates.

Second, the meta-analysis does not provide compelling evidence of efficacy of HPC in women with a singleton pregnancy at "high-risk" for PTB, defined by the authors as women with a short cervix in their current pregnancy or who have had a prior PTB. The confidence interval for the reduced PTB before 34 weeks includes the possibility that HPC does not have a treatment effect. Also, HPC did not reduce the risk of PTB < 37 weeks or < 28 weeks gestation.

The authors conducted subgroup analyses in women with individual patient data for both cervical length and a prior PTB. There was a suggestion of treatment effect in only one of the four subpopulations - the one where both risk factors exist (prior PTB and short cervix, see Figure 2); there was no evidence of a treatment effect of HPC in the other 3 subpopulations – those without a prior PTB with or without a short cervix and those with a prior PTB and a non-short cervix. However, the positive findings for the subpopulation of women with both risk factors were based on a very small proportion (2.7%, N = 81) of the women included in the five singleton HPC trials. The authors arrived at this small subpopulation after excluding women without cervical length information. This very small sample size increases the potential variability in the treatment effect estimates and calls into question the generalizability of the findings from this subpopulation. In fact, in Trial 003, which enrolled Makena's indicated population (a prior PTB unselected for cervical length), only ~2% of the women also had a short cervix in the current pregnancy; therefore, this small subpopulation does not represent Makena's approved population. This substantial exclusion also could have jeopardized the randomization between the HPC and control groups. Maintaining randomization is crucial for obtaining unbiased and unconfounded results. Further, the authors conducted subgroup analyses to test multiple hypotheses without lowering the threshold for a p-value to be considered statistically significant. The failure to implement p-value adjustment for multiple testing heightens the probability of obtaining false-positive findings. In addition, instead of using the conventional two-sided 0.05 threshold for a single statistical test, the EPPPIC authors chose 0.1, a less stringent threshold for claiming statistical significance, and they did so without explanation. The use of a less stringent p-value threshold by the authors further increased the likelihood of drawing a false positive conclusion of HPC efficacy in their "high-risk" population. Therefore, we do not find the subgroup analyses conducted by the EPPPIC authors adequate to support the use of HPC in the authors' defined "high risk population" (women with short cervix or a history of PTB). We do not agree with the Applicant's characterization that the "EPPPIC study reaffirms 17-OHPC for reducing early preterm birth in high-risk, singleton pregnancies."[14]

Third, we conclude that the EPPPIC meta-analysis does not add any evidence to support Makena's effectiveness for its intended use. Four of five placebo-controlled trials with HPC in singleton pregnancies included in the HPC meta-analysis (PROLONG [Trial 003], PHENIX singleton, SCAN, and PROGFIRST) failed to show a treatment effect for HPC on reducing PTB. Makena's approval in 2011 was based on the treatment effect seen in women with a prior sPTB, a major risk factor for PTB. However, the EPPPIC HPC singleton meta-analysis was conducted in mixed poplulations that combined those with history of PTB and those without history of PTB, including those who had never had a prior pregnancy. Further, the EPPPIC meta-analysis included a trial with dissimilar doses and timing for treatment initiation from the approved use (the PHENIX singleton trial assessed a dose that was double that of Makena and started anytime during week 20 to week 31, instead of starting anytime during week 16 to week 20). The EPPPIC meta-analysis also included data from PROGFIRST, which was terminated prematurely due to product quality issue and its limited results precluded CDER's accepting the trial as evidence of efficacy.

[14] The Applicant's Press Release, March 26, 2021. https://www.amagpharma.com/news/2512/.

In sum, the evidence from the EPPPIC HPC meta-analysis fails to show a clinical benefit of HPC in reducing serious fetal/neonatal outcomes and does not support HPC's efficacy in reducing the risk of recurrent spontaneous PTB in women with a singleton pregnancy and a prior sPTB. We also find the subgroup analyses conducted by the EPPPIC authors inadequate to support the efficacy of HPC in a "high risk population" (women with short cervix or a history of PTB) as defined by the authors. In our view, the evidence in the EPPPIC meta-analysis further strengthens CDER's previous conclusions that efficacy for Makena has not been shown. Therefore, we do not recommend changing CDER's proposal to withdraw Makena's approval.

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Appendix 6

Subgroup Figures Including Shrinkage Using 6M and 60K Iterations

Subgroup Figures Including Shrinkage Using 6,000,000 and 60,000 Iterations

The shrinkage analyses previously shown in FDA slides at the October 29, 2019, Meeting of the BRUDAC, CDER Statistical Review for NDA 021945-S023, and CDER Decisional Memo for NDA 021945 used 60,000 iterations (SHR1). Shrinkage analyses were re-run increasing the number of iterations to 6,000,000 (SHR2). CMH: stratified Cochran-Mantel-Haenszel.

Figure 8: Region Subgroup: No Evidence of Treatment Effect on the Neonatal Composite Index or the Proportion of Trial 003 Subjects Delivering < 35 Weeks Gestational Age

Endpoint / Subgroup	Makena	Placebo	Diff CMH	Diff SHR1	Diff SHR2
Neonatal Index (%)	5.4	5.2	0.2		
US (252, 126)	7.1	9.5	-2.2	-0.2	-0.1
Non_US (839, 434)	4.9	3.9	1.0	0.6	0.7
PTB<35 Weeks (%)	11.0	11.5	-0.6		
US (256, 131)	15.6	17.6	-2.2	-0.8	-0.8
Non_US (857, 443)	9.6	9.7	-0.2	0.4	-0.5

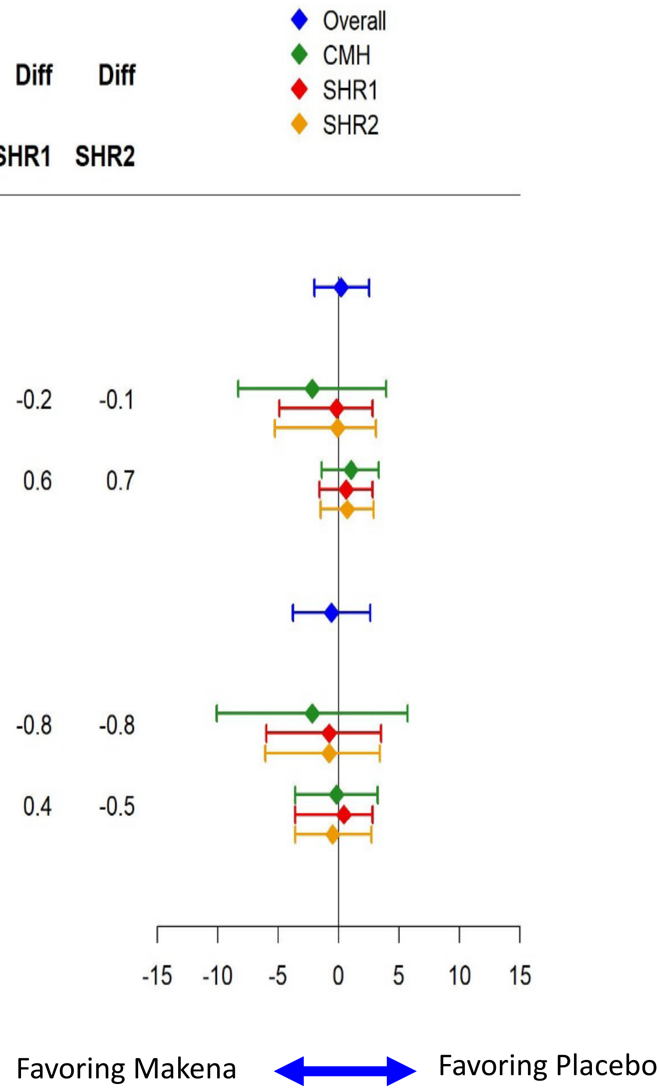


Figure 9: Region Subgroup: No Evidence of Treatment Effect on the Proportion of Trial 003 Subjects Delivering at < 32 and < 37 Weeks Gestational Age in Either US or non-US Subjects

Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR1	Diff SHR2
PTB<32 Weeks (%)	4.8	5.2	-0.4		
US (256, 131)	5.5	9.2	-3.9	-0.6	-1.3
Non_US (860, 443)	4.7	4.1	0.6	0.5	0.2
PTB<37 Weeks (%)	23.1	21.9	1.3		
US (256, 131)	33.2	28.2	4.7	1.8	1.8
Non_US (856, 441)	20.1	20.0	0.2	0.9	0.9

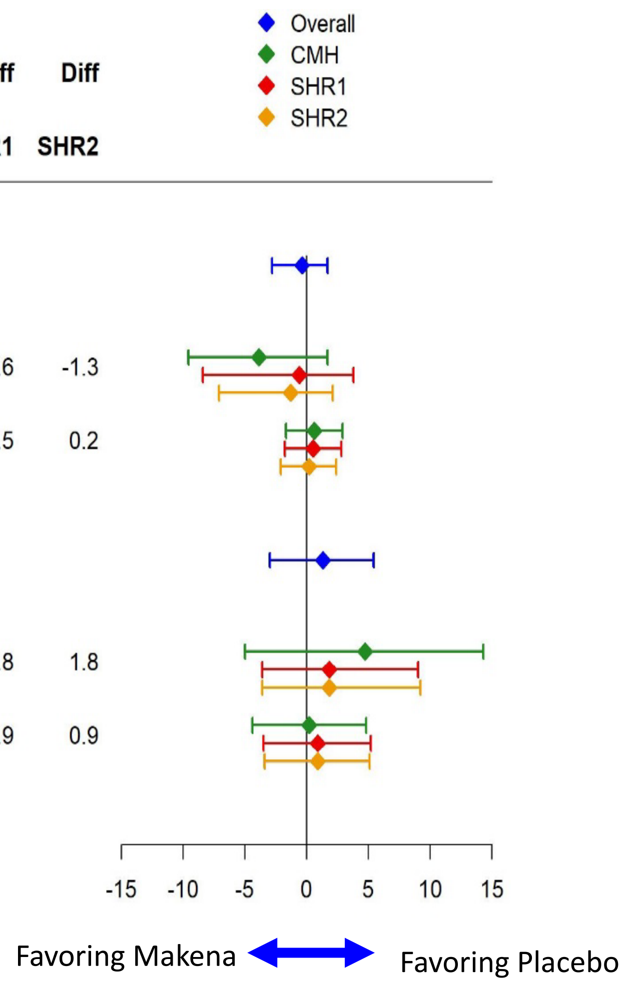


Figure 10: Race Subgroup: No Evidence of Treatment Effect on the Neonatal Composite Index or the Proportion of Trial 003 Subjects Delivering < 35 Weeks Gestational Age in Either Black or non-Black Subjects

Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR1	Diff SHR2
Neonatal Index (%)	5.4	5.2	0.2		
Black (69, 40)	8.7	7.5	0.8	0.4	0.3
Non-Black (1022, 520)	5.2	5.0	0.2	0.2	0.2
PTB<35 Weeks (%)	11.0	11.5	-0.6		
Black (72, 41)	23.6	19.5	3.0	-0.1	0.0
Non-Black (1041, 533)	10.1	10.9	-0.8	-0.7	-0.7

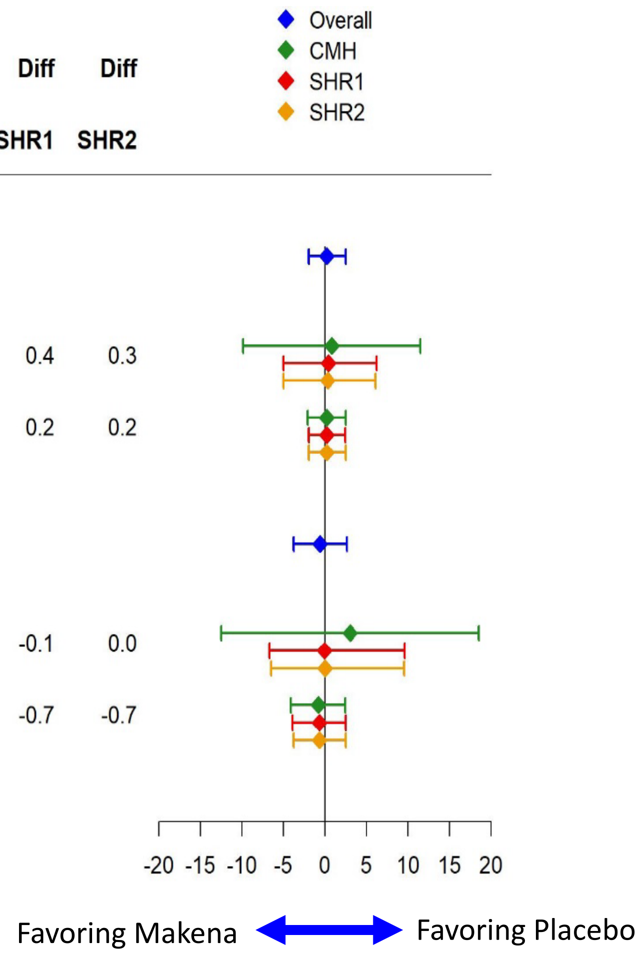


Figure 11: Race Subgroup: No Evidence of Treatment Effect on the Proportion of Trial 003 Subjects Delivering at < 32 and < 37 Weeks Gestational Age in Either Black or non-Black Subjects

Endpoint / Subgroup	Makena	Placebo	Diff CMH	Diff SHR1	Diff SHR2
PTB<32 Weeks (%)	4.8	5.2	-0.4		
Black (72, 41)	11.1	9.8	0	-0.4	-0.4
Non-Black (1044, 533)	4.4	4.9	-0.5	-0.5	-0.5
PTB<37 Weeks (%)	23.1	21.9	1.3		
Black (72, 41)	37.4	34.2	2.1	1.3	1.4
Non-Black (1041, 533)	22.1	20.9	1.2	1.2	1.2

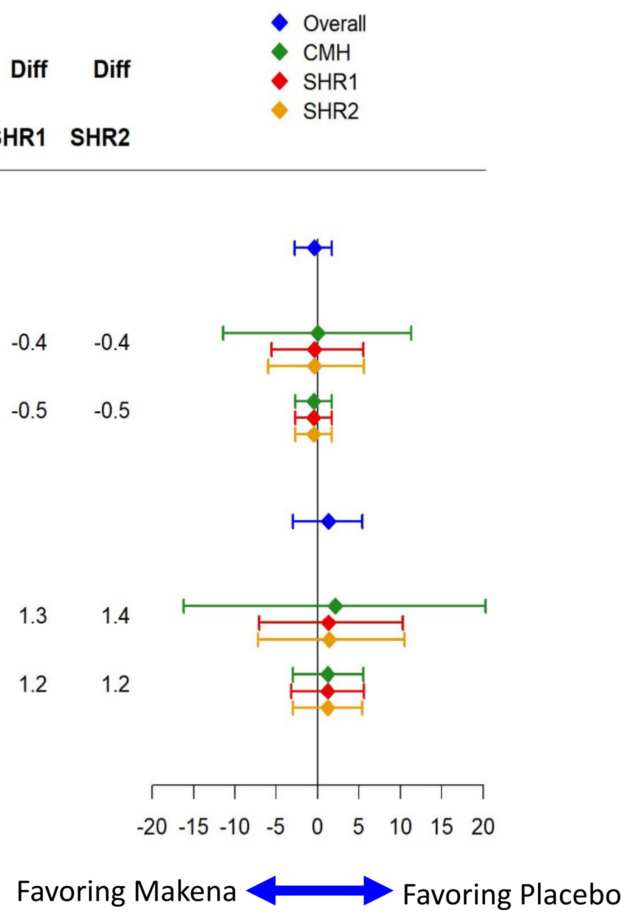


Figure 12: Number of Prior Singleton sPTBs Subgroup: No Evidence of Treatment Effect on the Neonatal Composite Index or the Proportion of Trial 003 Subjects Delivering <35 Weeks Gestational in Subjects With 1 or >1 Prior sPTBs

Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR1	Diff SHR2
Neonatal Index (%)	5.4	5.2	0.2		
1 (933, 478)	4.6	4.6	0	0.1	0.1
>1 (158, 80)	10.1	8.8	1.7	0.5	0.4
PTB<35 Weeks (%)	11.0	11.5	-0.6		
1 (949, 491)	8.4	10.4	-2.0	-0.9	-1.5
>1 (164, 81)	25.6	18.5	7.3	0.2	1.5

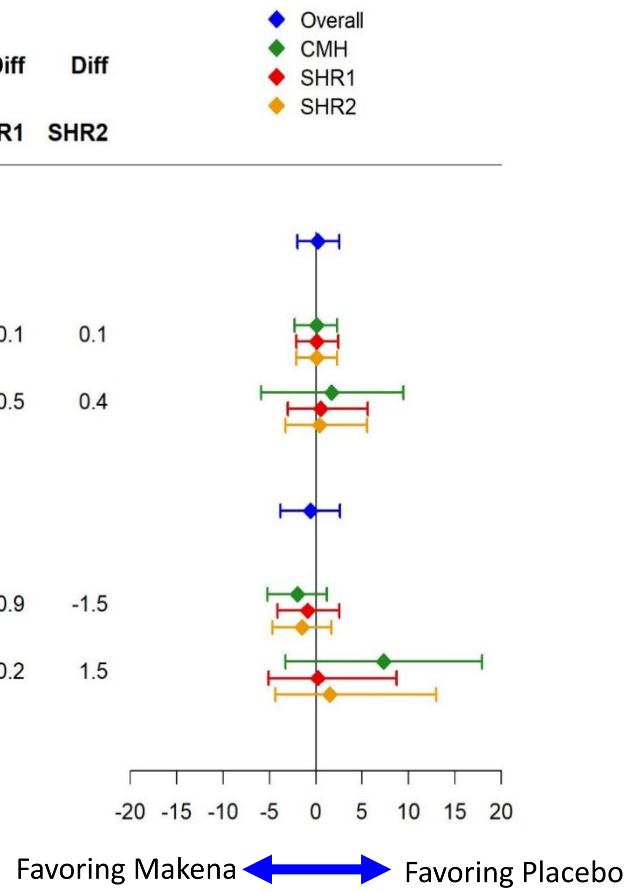
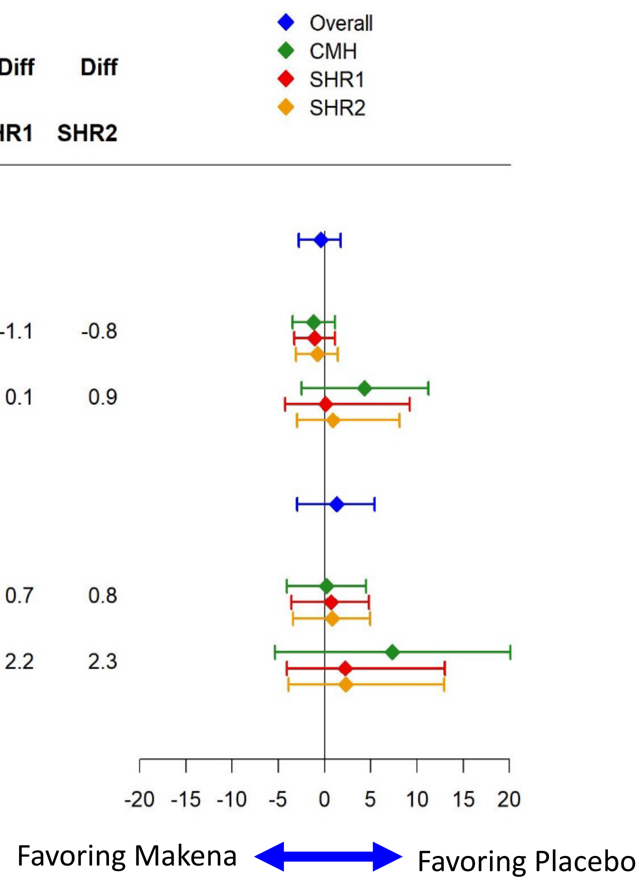


Figure 13: Number of Prior Singleton sPTBs Subgroup: No Evidence of Treatment Effect on the Proportion of Trial 003 Subjects Delivering at < 32 and < 37 Weeks Gestational Age in Subjects with 1 or > 1 Prior sPTBs

Endpoint / Subgroup	Makena	Placebo	Diff CMH	Diff SHR1	Diff SHR2
PTB<32 Weeks (%)	4.8	5.2	-0.4		
1 (951, 491)	3.9	5.1	-1.2	-1.1	-0.8
>1 (165, 81)	10.3	6.2	4.3	0.1	0.9
PTB<37 Weeks (%)	23.1	21.9	1.3		
1 (948, 489)	19.8	19.6	0.2	0.7	0.8
>1 (164, 81)	42.1	35.8	7.3	2.2	2.3



Appendix 7

Notification of Newly Identified Safety Signal to Covis Pharma Gmbh, June 9, 2022

NDA 021945

NOTIFICATION OF
NEWLY IDENTIFIED SAFETY SIGNAL

Covis Pharma GmbH
c/o Cardinal Health Regulatory Sciences
Attention: Lavonne M. Patton, Ph. D
Authorized U.S. Agent
7400 W 110th St., Ste 150
Overland Park, KS 66210

Dear Dr. Patton:

FDA staff in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) regularly conduct routine safety surveillance. When a safety signal for a marketed drug or biologic product is identified (from various sources, such as our FDA Adverse Event Reporting System (FAERS) database, literature, or regulatory submissions), a Newly Identified Safety Signal (NISS) is created in CDER's Lifecycle Signal Tracker (LiST) to facilitate timely evaluation and management.

We began evaluating a NISS on March 16, 2022, for Makena, hydroxyprogesterone caproate (HPC) injection, regarding the risk of cancer in offspring of women who took HPC during pregnancy. In accordance with the CDER Manual of Policies and Procedures (MAPP), *Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS)*,[1] we have classified this NISS as an Important Potential Risk.

As you may know, Title IX, Section 921 of the Food and Drug Administration Amendments Act 2007 (FDAAA) (121 Stat. 962) amends the Federal Food, Drug and Cosmetic Act (FDCA) to add a new subsection (k)(5) to section 505 (21 U.S.C. 355). This section in FDAAA, among other things, directs FDA to "post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by the Adverse Event Reporting System within the last quarter."

To comply with Section 921 of FDAAA, the Agency reviews the LiST database for all NISS that were identified for evaluation each quarter, and those that are based wholly or in part on FAERS data are posted in the corresponding quarter on the FAERS web

[1] We update CDER MAPP documents periodically. For the most recent version of a CDER MAPP, check following link: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp.

site. Therefore, if your safety issue is based wholly or in part on FAERS data, it will be included in the first quarter posting for 2022.

Additional information on Section 921 and the quarterly reports are available at FDA.gov.[2]

If you have questions, call me, at (301)-796-1218.

Sincerely,

{See appended electronic signature page}

Meredith Hillig, M.S.
Safety Regulatory Project Manager
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

[2] https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MEREDITH B HILLIG
06/08/2022 12:53:26 PM

Appendix 8

Commissioner Decision, Withdrawal of Breast Cancer Indication for AVASTIN 20111118

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Docket No. FDA-2010-N-0621

Proposal to Withdraw Approval for the Breast Cancer Indication for AVASTIN (Bevacizumab)

DECISION OF THE COMMISSIONER

November 18, 2011

COMMISSIONER'S DECISION

Avastin (bevacizumab) is a drug that has been approved by the Food and Drug Administration (FDA) for the treatment of several types of cancer. On February 22, 2008, FDA's Center for Drug Evaluation and Research (CDER) approved Avastin for use in combination with paclitaxel in the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer. This approval was under the rules for accelerated approval set forth in FDA regulations (21 C.F.R. § 601.40-46) and the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 506). Accelerated approval may be granted to drugs to treat life-threatening conditions for which there is unmet medical need in circumstances in which there are not sufficient data to justify a regular approval of a drug, but the evidence that is available provides a reason to hope that, once more testing has been completed, a the drug's safety and effectiveness will be confirmed. Accelerated approval is granted upon the condition that the drug's sponsor must diligently conduct additional studies to confirm and describe its benefit. Drugs that have been granted accelerated approval are subject to accelerated withdrawal of approval if the studies fail to verify clinical benefit or if the drug is not shown to be safe and effective.

CDER's decision to grant accelerated approval for Avastin's use in the treatment of breast cancer was not based on a showing that the drug helped patients live longer or improved their quality of life during the time during which they battled their cancer. There was not, at the time of approval, credible evidence of increased overall survival or increased quality of life, and there is no such evidence now. Instead, CDER based its accelerated approval on a different measure, referred to as "progression free survival" (PFS). PFS measures the interval between the time a patient is assigned to the control or investigational arm of a drug trial and either death or evidence, generally from radiological assessments, that the size of the tumor has increased. For a drug like Avastin, which has serious side effects, a small increase in PFS without a showing of improved survival or improvement in quality of life does not provide a clinical benefit that is meaningful to patients.[1] But at the time of the accelerated approval decision, there was evidence of a 5.5 month increase in median PFS, which was both statistically significant and of sufficient magnitude, based on one clinical trial. That increase was the basis for the approval.

On November 16, 2009, Avastin's sponsor, Genentech, Inc. submitted data from the trials that Genentech and FDA had agreed upon to confirm the benefit of the drug for this indication. The studies did not confirm that the increase in PFS was as substantial as the original study had suggested. On review, CDER concluded that these studies did not verify clinical benefit, and that the available evidence indicated that the drug was not shown to be safe and effective. It therefore proposed to withdraw the breast cancer indication, and, pursuant to FDA regulations (21 C.F.R. 601.43), in December 2010 CDER published a notice of opportunity for hearing to allow Genentech to respond.

Genentech requested a hearing, arguing that this approval should not be withdrawn.[2] Pursuant to the regulations, and as described more fully below, a hearing was held and CDER, Genentech, and the public were provided an opportunity to comment on CDER's proposal. On the basis of the administrative record of this hearing and the comments submitted to the public

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[1] Guidance for Industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*, 8 (May 2007), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.

[2] As discussed in more detail below, as the hearing process has gone forward, Genentech has placed increasing weight on the idea that the approval could be modified somewhat, and that it could be allowed to continue to sell this drug as approved by FDA for the treatment of metastatic breast cancer under certain conditions: an indication that it believes is narrower and would reflect the more recent data; additional cautions given to patients and prescribers; and marketing that would be limited and overseen by FDA.

docket, I conclude that the continued labeling of Avastin for the treatment of metastatic breast cancer is not justified and that the approval should be withdrawn.

The reasons for my decision are explained in detail in the remainder of this document. In section I of this document, I will speak directly to the concerns raised by patients and those who support them regarding the decision and its implications for them. I will then, in section II, provide background on Avastin and on metastatic breast cancer, and on the pivotal issue of what constitutes clinical benefit for this drug for this use. In section III of this decision, I will describe the legal standard that applies to decisions whether to withdraw approval under the accelerated approval authority applicable here.

I will then describe, in section IV, the process by which Avastin was approved for the metastatic breast cancer indication, the developments that led to the proposal to withdraw its approval, and the administrative hearing that we held on these issues. In section V, I will explain my reasons for concluding that, when the appropriate legal standards are applied to the facts presented here, withdrawal of approval is the appropriate action. In this section I will also address various arguments that Genentech has made in support of its request for a continued accelerated approval of its product for this use.

I. AN EXPLANATION FOR PATIENTS AND THOSE WHO SUPPORT THEM

This document, which lays out the basis for my decision, has several purposes. It is an explanation, for physicians, scientists, patients and the public in general, of the data available on the metastatic breast cancer indication for Avastin and of FDA's evaluation of those data. It also describes how FDA has applied the law and its regulations in making the decision to withdraw the approval for that indication.

I know I speak on behalf of the many physicians that have been involved with this issue here at the Food and Drug Administration and elsewhere in saying that we encourage patients, and those who support them, to ask hard questions and to demand explanations concerning the drugs that are recommended to treat serious illnesses. I will address here some of the questions that patients and their supporters may have about this decision.

Does the FDA decision mean that patients will not be able to use Avastin for the treatment of breast cancer? The short answer to this question is "No." FDA does not regulate the practice of medicine, and it is part of the practice of medicine for a physician to be able to prescribe a drug that is approved for one use (and Avastin continues to be approved for use in several cancers) for another, unapproved use. Thus, a physician can prescribe Avastin for the treatment of breast cancer if he or she chooses to do so, despite the withdrawal of approval of that use.

Does the FDA decision mean that patients will lose insurance coverage for the use of Avastin for the treatment of breast cancer? This is a more complicated question. FDA's decisions have no direct effect on insurance coverage. At this point, the Centers for Medicare and Medicaid Services (CMS) has said that it is continuing to reimburse for this use. While health insurance contracts with private providers obviously vary, it is our understanding that private insurers do cover the use of drugs for unapproved uses in those circumstances in which that use is considered appropriate medical practice. They may continue to reimburse for the use of Avastin for the breast cancer indication (use with paclitaxel), as many apparently now reimburse for use of Avastin with anti-cancer drugs other than paclitaxel even though use in combination with other drugs has never been approved by FDA. To be very clear, FDA's decisions on approval do not require any change in insurance coverage.

If I, as a patient, and my treating physician believe that Avastin is the right drug to treat my breast cancer, why shouldn't FDA approve the drug for that use? By law, FDA can only approve a drug for a particular use if there is credible, objective evidence that the drug is safe and effective for that use. This is, in effect, what FDA approval means; that the public and physicians can have confidence that claims made about a drug in its labeling have been carefully and impartially reviewed, and that they are supported by evidence. This requirement provides an essential protection to the public. When Congress first required FDA to begin evaluating the effectiveness of drugs in 1962, it required sponsors of drugs that had been on the market without proof of their effectiveness through adequate and well-controlled clinical trials to perform those trials and submit the evidence to FDA. Ultimately FDA found that many drugs that had been in common use prior to 1962, and that both doctors and patients had believed to be effective, were not shown by objective testing to be effective for the uses for which they were labeled.

There are many reasons why patients and physicians believe in drugs, whether based on personal experience or on their own evaluation of evidence. Over the years FDA's decisions with respect to particular drugs have often been questioned by those who preferred to rely on their own beliefs. In some cases, the disputes involved differing evaluations of carefully done clinical trials. In others, there was little or no scientific data to support those strongly held beliefs.

Ultimately, my responsibility, and the agency's responsibility, is to put aside any preconceived beliefs that I, or patients or physicians may hold, and take a hard look at the objective evidence. We may hope, as CDER scientists did when they granted the initial accelerated approval of Avastin for the breast cancer indication, that the additional studies conducted to support continued approval of a drug that has shown promise in an initial trial will confirm the effectiveness of the drug. But if the evidence does not show that, FDA cannot, and should not, continue to approve it.

Since FDA had already announced its decision to withdraw approval of Avastin for the breast cancer indication, did Avastin receive a fair hearing? As explained elsewhere in this decision, FDA has taken advantage of the way our agency is structured to assure that the hearing was fair. Within our agency, CDER is generally responsible for decisions with respect to the approval of this type of drug. That Center granted the accelerated approval of Avastin for the breast cancer indication in the first place, and then, based on new data, it made the determination that that approval needed to be withdrawn. I, as Commissioner, am not normally involved in drug approval decisions, and I was not involved in either the decision to approve this indication or CDER's initial decision to withdraw approval. When Genentech objected to the CDER decision to withdraw approval, it exercised its right to seek a hearing on that decision.

In conducting the hearing, FDA decided to utilize something called the "separation of functions" to protect the independence of the Commissioner's decision and make the process transparent. Under separation of functions, I as Commissioner (and those assisting me on this issue, such as Dr. Midthun, the Director of FDA's Center for Biologics Evaluation and Research who served as presiding officer at the hearing) communicated with CDER about the subject of this hearing only as part of the formal hearing record, in exactly the same way that we communicated with Genentech. CDER presented its views as a party in the hearing, as did Genentech. As the applicant, Genentech was a motivated, knowledgeable, and well represented proponent of its view. Both CDER and Genentech presented evidence at the hearing and challenged each others' presentations. In addition, members of the public submitted comments to the docket and testified at the hearing. That created the record that led to my own decision as Commissioner. I did not know, until review of that record and discussion of the issues with Dr. Midthun, how I would decide the issues presented. I have now made that decision based on the evidence.

How can FDA make a different decision than was made by the regulatory authorities in Europe? It is true that the European Medicines Agency has continued to approve Avastin for use with paclitaxel in the treatment of metastatic breast cancer, though the United Kingdom's National Institute for Health and Clinical Excellence (NICE) has not recommended Avastin's use with taxanes as a first-line treatment for people with metastatic breast cancer.[3] The regulatory standards for different government agencies may vary somewhat, and of course the decision-makers are different in different places. I can only apply the United States standards to the evidence that has been provided to FDA. That is what I have done in this decision.

Is it possible that Avastin might be approved, once again, for the treatment of certain patients suffering from metastatic breast cancer? Genentech has said that it will consider conducting a further adequate and well-controlled clinical trial that would be designed to show that the use of Avastin with paclitaxel would be safe and effective for patients, or for some subset of patients. If such a trial were completed and showed a clear benefit for this use, such as increased overall survival, better quality of life, or even a substantial increase in "progression free survival" of the type seen with the E2100 study that formed the basis for the initial accelerated approval, a new approval could be granted. In addition, Genentech has said that it would consider including in such a trial a mechanism to determine whether certain patients (those with high plasma levels of Vascular Endothelial Growth Factor-A (VEGF-A)) would

[3] http://www.nice.org.uk/newsroom/pressreleases/AvastinBevacizumabNotRecommended.jsp; http://guidance.nice.org.uk/TA214.

benefit most from use of Avastin. If such a therapeutic relationship could be demonstrated, that might represent a basis for Avastin to be approved for use by certain patients.

Ultimately, if Genentech does go forward with the new clinical trial that it has discussed, that will lead to more scientific evidence on the question of whether or not Avastin might provide a benefit for some patients in the treatment of metastatic breast cancer. At this stage, however, based on the evidence currently available, I have concluded that continued accelerated approval of Avastin for this use is not justified.

II. BACKGROUND

A. Avastin

Avastin (bevacizumab) is a recombinant, humanized monoclonal (IgG1) antibody that binds to and inhibits the biological activity of human vascular endothelial growth factor ("VEGF"), a protein that is important for the formation of blood vessels. Avastin has been tested in clinical trials in multiple tumor types, and it is thought that the drug may work by preventing the formation of new blood vessels that would otherwise maintain a tumor or allow it to grow.[4]

Avastin was approved by CDER on February 26, 2004 as a first-line treatment in combination with intravenous 5-fluororacil-based chemotherapy in patients with metastatic carcinoma of the colon and rectum. Since then, Avastin has been approved for non-squamous non-small-cell lung cancer in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease; glioblastoma, as a single agent for adult patients with progressive disease following prior therapy (accelerated approval); and metastatic renal cell carcinoma with interferon alfa. Joint Statement ¶ 2. None of these

[4] *See* "Joint Statement of Undisputed Facts and Select Issues in Dispute (Joint Statement), Docket No. FDA-2010-N-0621-0132.¶ 1,. *See also* FDA Briefing Document, ODAC Meeting of July 20, 2010, 5. This briefing document, and other documents pertaining to the 2010 ODAC meeting cited in this decision, are available in Docket No. FDA-2010-N-0621-0145, Appendix 18 unless otherwise noted.

indications has been at issue in this proceeding, and CDER has not proposed to withdraw or modify any of them. Joint Statement ¶ 3.

B. Metastatic breast cancer

Metastatic breast cancer is, at present, an incurable disease. According to the American Cancer Society, it is estimated that more than 40,000 women in the United States died from metastatic breast cancer in 2009, and that over 90% of patients diagnosed with metastatic breast cancer ultimately die from the disease. Joint Statement ¶ 5. The main goals of therapy are palliation of symptoms and prolongation of overall survival time without negatively impacting quality of life. Metastatic breast cancer is also a heterogeneous disease, for which no single therapeutic approach is appropriate for all patients. The appropriate treatment strategy for a particular patient depends on multiple individualized factors, including tumor burden and related symptoms, underlying tumor biology, age and medical co-morbidities, and prior treatment. Joint Statement ¶ 6.

Approximately 70-75% of primary breast cancers are HER2-negative. HER2 is an acronym for "human epidermal growth factor receptor 2," a protein that promotes tumor growth. Patients whose tumors over-express the HER2 protein or have more than two copies of the HER2 gene (gene-amplified) are considered to have HER2-positive metastatic breast cancer. Patients whose tumors do not over-express the HER2 protein or are not gene-amplified are considered to have HER2-negative metastatic breast cancer. Joint Statement ¶ 7.

Treatment options for patients with metastatic breast cancer include the use of single-agent or combination chemotherapy, hormonal therapy, and biological therapy. Joint Statement

¶ 8[5]. Nevertheless, these therapies provide limited benefit, and there is unmet medical need for additional safe and effective therapies for metastatic breast cancer. Joint Statement ¶ 4.[6]

C. Effectiveness for cancer treatments

In the context of oncology drugs, and particularly for diseases that are not curable like metastatic breast cancer, clinical benefit usually means a therapy that can prolong life or improve the quality of life by easing the burden of symptoms or restoring function. Above all, a demonstration that a therapy can prolong life has long been, and remains, the gold standard for approval. CDER has for that reason urged sponsors to design their trials to determine whether a candidate drug improves overall survival.[7]

Nevertheless, CDER has concluded, and I agree, that an improvement in PFS may constitute clinical benefit in appropriate circumstances.[8] CDER developed its policy on this

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[5] Other FDA-approved agents include: methotrexate, cyclophosphamide, thiotepa, vinblastine, 5-fluorouracil, and doxorubicin for metastatic breast cancer; paclitaxel, docetaxel, trastuzumab, capecitabine, capecitabine plus docetaxel, abraxane, lapatinib, and ixabepilone for 2nd and 3rd-line treatment; trastuzumab plus paclitaxel and gemcitabine plus paclitaxel for 1st line treatment. FDA Briefing Document for 2010 ODAC Meeting 5-6.

[6] Genentech points to a statement made by a CDER official during the hearing to suggest that CDER may not believe there is unmet need for first-line therapy for patients with metastatic breast cancer. Post-Hearing Submission of Genentech, Inc. In Support of Maintaining the Accelerated Approval of AVASTIN® (Bevacizumab) in Combination With Paclitaxel for the First-Line Treatment of HER2-Negative Metastatic Breast Cancer (Genentech Post-Hearing Submission), Docket No. FDA-2010-N-0621-0478, 13-14. However, CDER's position is that there is unmet need, as reflected in the parties' joint statement. *See also* Letter from Dr. Janet Woodcock to Breast Cancer Community, Dec. 16, 2010, available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237286.pdf ("[T]here are not enough effective treatments for this cancer."). The question of whether there is unmet need for additional safe and effective treatments for this cancer is not in dispute, and my decision is premised on the understanding that there is unmet need in this area.

7 Transcript of Public Hearing on Proposal to Withdraw Approval for the Breast Cancer Indication for Bevacizumab (Avastin), June 28, (hereafter, June 28 Tr.), 283:15-284:16; FDA Briefing Document for 2010 ODAC Meeting 5. The clinical endpoint by which survival is generally measured is referred to as "overall survival" (OS). It is defined as the time from randomization until death from any cause, and is measured in the intent-to-treat population. *Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (May 2007), 5.

[8] As Genentech points out, and as CDER also recognizes, it can be difficult to design a trial to measure OS for an oncology drug intended for first-line treatment. Patients may switch therapies during a trial if they find they cannot tolerate the investigational drug, and may even begin taking the control drug; many will take second- and third-line therapies after a trial concludes. These changes in therapy make it difficult to isolate the effect of the investigational drug. Mature OS data may also take years to develop. For these and other reasons, CDER, and the oncology community generally, have considered whether time to tumor progression, or other tumor-based effects that can be measured relatively quickly and more easily attributed to the first-line therapy, are appropriate to use as an alternative measure of clinical benefit.

matter over several years, after receiving input from the public, industry, and medical experts, ultimately concluding that PFS may serve as a basis for drug approval, with the important caveat that "[w]hether an improvement in PFS represents a direct clinical benefit … depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies." Guidance for Industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*, 8 (May 2007), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf. The limitation is essential because, as noted, PFS does not directly measure whether a treatment prolongs life or improves the quality of life. Small increases in PFS, even if they are demonstrated to be statistically significant by adequate studies, must be weighed against the drug's risk and may not represent meaningful benefit to patients. CDER has also approached PFS with care because measuring PFS raises substantial methodological problems. For example, tumor progression is typically measured at office visits, and cannot be recorded as precisely as survival time; radiographic measurement is technically difficult and requires the exercise of judgment; and many patients may be lost to a study before final PFS measurements are taken.[9]

The consideration of risks associated with a drug is a very significant issue with respect to Avastin and its use with respect to metastatic breast cancer. We know, from the clinical trials of Avastin, as well as our experience with this drug in the context of treatment of other cancers,

[9] CDER has long recognized these and other concerns with measurements that turn, in part, on tumor-based endpoints, *see, e.g.*, 2007 ODAC Meeting Tr. 14:4-17:10, available in FDA-2010-N-0621-0145, Appendix 10, and has sought input from experts and the public. In 1999, ODAC recommended that a related measure of tumor growth, time to progression (TTP), should not be considered clinical benefit in the context of first-line treatment of metastatic breast cancer, and since then, CDER has not used TTP as the basis of approval for a first-line agent for treatment of metastatic breast cancer. More recently, after further consideration of its general PFS policy and the specific context of treatments for first-line breast cancer such as Avastin, CDER concluded that PFS could constitute clinical benefit for a new first-line treatment, provided that there is also follow-up study to ensure that the drug did not undermine survival. Genentech has recognized that CDER's openness to the possibility that PFS benefit of a sufficient magnitude may constitute clinical benefit represents "progressive thinking" on the part of the agency. Transcript of Public Hearing on Proposal to Withdraw Approval for the Breast Cancer Indication for Bevacizumab (Avastin), June 29, 2011, (hereafter, June 29 Tr.), 7:15-21.

that it presents significant risks to patients. It may even cause death. This is a particularly important issue in light of the fact that patients may be diagnosed with metastatic breast cancer when they are still symptom-free, as were many patients in the E2100 trial. Exposure of such patients to significant adverse events, or even death, at a time when the patient, though facing an incurable and likely terminal disease, is otherwise capable of performing and enjoying life's functions can be justified only if the possibility that the patient will benefit is real.

This leads us to the essential question that FDA faces whenever it is asked to determine whether a drug has been shown to be safe and effective: does it offer a benefit that is meaningful to a patient in light of its risks, disease stage, and alternative therapies? No one would argue, for example, that a drug that had been shown to be effective in treating a common headache could be considered safe and effective if it frequently caused serious side effects in the patients using it. On the other hand, a drug that provides substantial benefit in the treatment of patients with otherwise incurable cancer might be found to be safe and effective even though it carries serious risks. Thus, FDA has found that Avastin is safe and effective for the treatment of several types of cancer despite the fact that the evidence shows that it may also subject patients to significant side effects, including, for some patients, death.

One question that has arisen during the hearings is whether there is a threshold improvement in median PFS that would have to be shown in the studies to establish a clinical benefit for Avastin for the treatment of metastatic breast cancer. There is not a simple answer to this question, because median PFS improvement, which has so far figured prominently in discussions of Avastin, is only one of several factors that must be considered. In addition, one must consider the PFS effect in terms of the hazard ratio; other evidence, if any, with respect to other measures of efficacy, such as overall survival and/or improvement in quality of life; the risks associated with use of the drug; and the level of confidence that the clinical study data accurately represent what will happen to patients in clinical use of the drug. The totality of the evidence must be considered in evaluating clinical benefit.

As discussed in detail in other parts of this decision, one of thc first studies that Genentech submitted for Avastin's breast-cancer indication, E2100, showed a PFS increase that CDER said would constitute clinical benefit if it could be confirmed in subsequent studies; this included an increase in median PFS of 5.5 months with hazard ratio of 0.48, no evidence of an effect on overall survival or improved symptoms, and a safety profile that included serious risks, but not risks that were unanticipated in light of previous experience with the drug. A threshold level has not been set that formally defines what lesser showing of PFS improvement, if any, would be sufficient for approval, and particularly what showing of improvement in median PFS would be necessary.

I understand why companies seeking to develop drugs, and advocates for this use of Avastin, would prefer to have more certainty about the threshold for approval. I, and the agency, are committed to working with the developers of new drugs to design useful trials that can definitively answer questions about drug approval. At this point, however, in light of the agency's limited experience in using PFS as a measure of effectiveness for first-line metastatic breast cancer therapies and the evidence that is available, and because of the multiple factors that an approval decision would require the agency to consider, it would not be appropriate to announce a bright-line cut off of median PFS improvement that would be necessary to establish safety and effectiveness.[10] Instead, I must focus on the particular circumstances presented here and determine whether the full body of available data justifies a conclusion that the use of

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[10] As discussed below, the multiple factors that must be considered with respect to each drug also make comparisons of FDA's approval decisions with respect to different drugs inappropriate in the context of the type of hearing involved here.

Avastin for the treatment of metastatic breast cancer has been shown to be safe and effective. The bases for my conclusions on that point are discussed in further detail below.

III. LEGAL STANDARD

In 1992, FDA issued regulations that provide a pathway for accelerated approval of new drugs and biologicals that are intended to treat serious and life-threatening illnesses for which there are limited treatment options, contingent on further study of the drugs' clinical effects after approval to confirm effectiveness. 21 C.F.R. § 601.40, Subpart E (§§ 601.40-46).[11] In 1997, Congress enacted section 506 of the FD&C Act, which essentially codifies in the statute FDA's accelerated approval regulations.[12]

The accelerated approval pathway represents a balanced approach. It recognizes, first, that patients with serious and life-threatening illnesses for which there are limited or no treatment options (i.e., unmet medical need) have an especially urgent need for the rapid development of new therapies, and that it may take many years to complete clinical trials that are able to provide substantial evidence of the kind of clinical benefit required for regular approval pursuant to FD&C Act section 505(d). The regulations therefore provide that new drugs being developed to treat such patients may be approved on the basis of different types of data, subject to a requirement to conduct confirmatory studies that will verify and describe their clinical benefit.

Specifically, accelerated approval may be based on (1) "an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit"; or, (2), as in the case of Avastin, "an effect on a clinical endpoint other than survival or irreversible morbidity." 21 C.F.R. § 601.41; *see also* FD&C Act

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[11] Proposed Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 13234 (April 15, 1992); Final Rule, 57 Fed. Reg. 58942 (December 11, 1992).
[12] This is reflected both in the text of section 506 and in the legislative history. *See, e.g.*, House of Representatives Report 105-310, 55 ("New FDCA subsection 741(b) [current section 506(b)] provides an alternative basis for approving fast track products that essentially codifies FDA's accelerated approval regulations.")

§ 506(a)(1), (b)(1). Such approvals are still contingent on a risk-benefit determination by the agency that in light of the expected clinical benefit and risk profile of the drug, approval is appropriate. Such approvals are also conditioned on a drug sponsor's agreement to conduct studies to verify and describe clinical benefit, 21 C.F.R. § 601.41; FD&C Act § 506(b)(2), and mechanisms for expedited withdrawal of approval are provided, 21 C.F.R. § 601.43, FD&C Act § 506(b)(3). Confirmatory studies and expedited withdrawal of approval are an essential element of the accelerated approval process, because in some cases the promise shown by early research will not be borne out. The agency must be able "to withdraw approval rapidly in the event it loses the assurances regarding demonstration of actual clinical benefit. ... Otherwise, the risk of continued exposure of patients with serious or life-threatening diseases to ineffective or unsafe drugs outweighs the potential benefits." 57 Fed. Reg. at 13239.[13]

Section 506(b)(3) of the FD&C Act sets out four bases for expedited withdrawal of approval of a product approved under the accelerated procedures. Section 601.43(a) sets out six bases. With respect to Avastin, there appears to be agreement that two of the bases are at issue, and these two bases appear in both the regulations and the statute.

The first of these, which is set out in nearly identical language in § 601.43(a)(1) and section 506(b)(3)(B) of the FD&C Act, is that FDA may withdraw approval if, in the words of the regulation: "A postmarketing clinical study fails to verify clinical benefit", or, in the words of the statute, if: "[A] post-approval study of the fast track product fails to verify clinical benefit of the product."

[13] *See also* 57 Fed. Reg. at 58954 ("Should well-designed postapproval studies fail to demonstrate the expected clinical benefit, the benefit expected at the time of approval (reasonably likely to exist) would no longer be expected and the totality of the data, showing no clinical benefit, would no longer support approval."); 57 Fed. Reg. at 13238 (If clinical benefit is not demonstrated in confirmatory studies, "the risk-benefit analysis changes significantly..." and continued marketing of the drug "is inappropriate and marketing approval should be rapidly withdrawn....")

In this case, the parties agree that "During CDER's review of [the sBLA], Genentech proposed and CDER agreed that the AVADO and RIBBON1 trials could serve as the required trial(s) to verify and describe the clinical benefit." Joint Statement ¶ 31. Thus, under the regulations (and the statute) FDA may withdraw the application if the AVADO and RIBBON1 trials fail to verify the clinical benefit of Avastin for the breast cancer indication for which it was approved.

CDER also argues that it would be appropriate to withdraw the metastatic breast cancer indication on a second, alternative, ground. This ground is also set forth in the regulation and in the statute. Section 601.43(a)(6) states that FDA may withdraw approval if: "Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use." Section 506(b)(3)(C) of the FD&C Act states that withdrawal is authorized if: "[O]ther evidence demonstrates that the fast track product is not safe or effective under the conditions of use."

In this case, the parties have agreed that the FDA-approved prescribing information for Avastin "is a fair and accurate description of the safety profile of Avastin," and that "[t]he safety data observed in the E2100, AVADO, and RIBBON1 studies were consistent with the safety profile of Avastin described in its approved prescribing information." Joint Statement, ¶¶ 22, 23. In light of this agreement, the dispute with respect to this issue centers on the effectiveness information for the breast cancer indication, and on the appropriate risk-benefit analysis to be made in light of that information as compared to the agreed risk of the product.

As noted, the safety profile of Avastin described in its approved prescribing information includes a black box warning concerning gastrointestinal perforation, surgery and wound healing complications, and severe or fatal hemorrhage. Genentech agrees that this warning is appropriate, and it does not state that the use of this drug in the treatment of breast cancer is safe in the abstract. Instead, it states that the drug should be found to be safe because its use provides benefits to patients that outweigh its risks. Applying the standard in the regulation and statute to the facts presented, therefore, FDA may withdraw the indication if: (a) the available evidence on Avastin demonstrates that the drug has not been shown to be effective for the breast cancer indication for which it was approved, or (b) if the available evidence on Avastin demonstrates that the drug has not been shown to be safe for the breast cancer indication for which it was approved, in that Avastin has not been shown to present a clinical benefit that justifies the risks associated with use of the product for this indication.

A third issue is presented by the fact that both section 506(b)(3) of the FD&C Act and section 601.43(a) do not by their terms require the withdrawal of an accelerated approval even if the bases for withdrawal they describe are present. Instead, in each case, the statute and regulation state that FDA "may" withdraw approval in those circumstances. This standard reflects the fact that decisions on withdrawals of approval of products necessarily reflect judgment on FDA's part as to what actions are appropriate to protect the public with respect to approved products, and what uses of those products should be stated on the labels of those products.[14] Accordingly, if either of the two grounds for withdrawal set out above are found, I must decide a third issue, which is whether FDA should nevertheless continue the approval of

[14] As FDA has stated elsewhere, "Failure to confirm clinical benefit in a completed trial ... may reflect, for example, unforeseen limitations in trial design, rather than clear evidence of lack of effectiveness," and when trials "do not appear to confirm clinical benefit, FDA must carefully assess each case, and consider the underlying reasons and the consequences of all regulatory options, including their potential impact on patients." U.S. Government Accountability Office, New Drug Approval: FDA Needs to Enhance Its Oversight of Drugs on the Basis of Surrogate Endpoints, GAO-09-866 (Sept. 2009), App. V, FDA Comments on GAO Report at 3.

the breast cancer indication while Genentech designs and conducts additional studies intended to verify clinical benefit.[15]

IV. PROCEDURAL HISTORY

A. Genentech's supplemental submission for the metastatic breast cancer indication

In a supplemental Biologics License Application (sBLA)[16] dated May 23, 2006 (sBLA 125085/91), Genentech requested that FDA approve Avastin, in combination with taxane-based chemotherapy,[17] for the treatment of patients who have not received chemotherapy (first-line) for their locally recurrent or metastatic breast cancer. Joint Statement ¶ 26. With this supplement, Genentech submitted data and analysis for two clinical studies, E2100 and AVF2119g.

The E2100 study was a randomized, open-label trial in the first-line treatment of metastatic breast cancer. This was a multicenter Phase III study led by the National Cancer Institute Therapy Evaluation Program and coordinated by the Eastern Cooperative Oncology Group ("ECOG"). Joint Statement ¶ 9. The study investigated the combination of paclitaxel and Avastin compared to paclitaxel alone. The study enrolled 722 patients, predominantly in the United States. Joint Statement ¶ 10. The primary endpoint studied in the E2100 study was PFS, which was defined as the length of time from the date on which a patient is randomized to a control or treatment arm of a clinical trial until disease progression or death occurs, whichever comes first. Joint Statement ¶ 11. In E2100, disease progression was considered to be tumor

[15] I have described the issues for decision as Dr. Midthun did when she wrote the parties on May 6, 2011 regarding the nature and conduct of these proceedings, which is also the way that the issues were presented in the Federal Register notice for the hearing. The proceedings before the hearing, the hearing itself, and the parties' post-hearing submissions have all gone forward on this basis. Neither CDER nor Genentech has indicated that it disagrees with this description of the issues. I do note that although Genentech does not challenge the safety information on Avastin's metastatic breast cancer labeling, it has presented arguments and information that bear on how that information should be understood. I have taken that into account in this discussion of the issues, and will also discuss Genentech's presentation with respect to this issue below.

[16] As noted, Avastin is approved for several different cancer indications. Because it is a biologic product, that approval has occurred through a biologics license application (BLA) submitted pursuant to section 351 of the Public Health Service Act. After the first approval, additional approvals may be sought, as here, through the submission of supplemental BLAs.

[17] "Taxanes" are a class of chemotherapies that includes paclitaxel and docetaxel.

growth, which was measured primarily by radiographic measurement. Secondary efficacy endpoints that were included in the trial were overall survival (OS) (which is the time from randomization until death from any cause) and objective response rate (ORR) (objective response is a complete or partial response to treatment determined by two consecutive investigators' assessments which are four or more weeks apart; objective response rate is the percentage of patients who have objective responses). Joint Statement ¶ 12. The parties agree that the following table accurately summarizes efficacy data from the E2100 study[18]:

Study Arm	**Median PFS** (months)	**Median OS*** (months)	**ORR**
E2100			
Paclitaxel + Avastin	11.3	26.5	48.9%
Paclitaxel	5.8	24.8	22.2%
Between-Arm Difference	5.5	1.7	26.7%
Hazard Ratio (95% CI)	0.48 (0.39, 0.61)	0.87 (0.72, 1.05)	(18.4%, 35%)
	p < 0.0001	p = 0.137	p < 0.0001

* Updated OS analysis where available. CI = confidence interval; NR = not reached.

[18] Joint Statement, ¶ 13, Attachment 2. "OS", as noted above, refers to overall survival, which is the time from randomization until death from any cause, and is measured in the intent-to-treat population. Note that the hazard ratio is reported with a 95% confidence interval. That means that in 95% of situations the true hazard ratio will fall between the two numbers in parentheses. The p value is a measure of statistical significance. Generally, a p value below .05 is considered to be significant and a value above that is considered not to be significant. Thus, in this chart, there is considerable confidence that the hazard ratio for PFS favors the Avastin-paclitaxel combination and that the difference in median length of PFS is statistically significant in the study. On the other hand, there is no compelling evidence of a favorable hazard ratio relating to overall survival or increase in median length of overall survival.

A survey instrument administered to patients did not demonstrate an improvement in quality of life.[19] As noted, Genentech and CDER agree that the prescribing information for Avastin represents a fair and accurate summary of the safety data in E2100.[20] The labeling notes that

[19] The survey instrument was the Functional Assessment of Cancer Therapy (FACT-B), which has scales for patient social/family well-being, emotional well-being, physical well-being, functional well-being, and a subscale specific to breast cancer. CDER and Genentech agree that the instrument did not demonstrate clinical benefit with Avastin. *See, e.g.*, FDA Briefing Document, 2007 ODAC meeting, 5; 2007 ODAC meeting Tr. 213:22-213:4 (statement by Genentech expert) (Dr. Winer: "[T]hat is why we're having this discussion about progression-free survival because we simply don't have the kind of quality of life data here that we can rely upon.") Unless otherwise noted, documents pertaining to the 2007 ODAC meeting cited in this decision are available in Docket No. FDA-2010-N-0621-0145, Appendix 10.

[20] Joint Statement ¶ 22. *See also id.* Attachment 1 (copy of Avastin prescribing information, as of the date of the June hearing, hereafter "Avastin Prescribing Information"). As reflected in the prescribing information, Avastin has serious toxicities, and is associated with serious and life-threatening adverse events. The prescribing information includes a boxed warning (commonly referred to as a "black-box warning") because of a risk of gastrointestinal perforation, surgery and wound-healing complications, and severe or fatal hemorrhage. Avastin Prescribing Information, 3. The boxed warning reads:

> **WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE**
> Gastrointestinal Perforations
> The incidence of gastrointestinal perforation, some fatal, in Avastin-treated patients ranges from 0.3 to 2.4%. Discontinue Avastin in patients with gastrointestinal perforation. [See Dosage and Administration (2.4), Warnings and Precautions (5.1).]
> Surgery and Wound Healing Complications
> The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Discontinue Avastin in patients with wound dehiscence. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. [See Dosage and Administration (2.4), Warnings and Precautions (5.2), and Adverse Reactions (6.1).]
> Hemorrhage
> Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis. [See Dosage and Administration (2.4), Warnings and Precautions (5.3), and Adverse Reactions (6.1).]

I note that Genentech, with CDER's approval, has revised the Avastin labeling further since the time of the hearing to highlight additional side effect information:

- a new Warning subsection describing the increased risk of ovarian failure in premenopausal patients receiving bevacizumab and chemotherapy and recommendation that females of reproductive potential be informed of the increased risk of ovarian failure prior to starting treatment with bevacizumab,
- identification of osteonecrosis of the jaw as an adverse reaction of bevacizumab, and
- new information regarding the risks of venous thromboembolic events [VTEs] and bleeding in patients receiving anti-coagulation therapy after first VTE event while receiving bevacizumab.

adding Avastin to paclitaxel in this study increased the rate of other serious adverse events, as follows:

> Grade 3–4[21] adverse events occurring at a higher incidence (≥ 2%) in 363 patients receiving paclitaxel plus Avastin compared with 348 patients receiving paclitaxel alone were sensory neuropathy (24% vs. 18%), hypertension (16% vs. 1%), fatigue (11% vs. 5%), infection without neutropenia (9% vs. 5%), neutrophils (6% vs. 3%), vomiting (6% vs. 2%), diarrhea (5% vs. 1%), bone pain (4% vs. 2%), headache (4% vs. 1%), nausea (4% vs. 1%), cerebrovascular ischemia (3% vs. 0%), dehydration (3% vs. 1%), infection with unknown ANC (3% vs. 0.3%), rash/desquamation (3% vs. 0.3%) and proteinuria (3% vs. 0%).
>
> Sensory neuropathy, hypertension, and fatigue were reported at a ≥ 5% higher absolute incidence in the paclitaxel plus Avastin arm compared with the paclitaxel alone arm.[22]

The AVF2119g study was an open-label, multicenter, randomized trial evaluating Avastin in combination with capecitabine compared with capecitabine alone in 462 patients who had previously been treated with a taxane and anthracycline for breast cancer. The primary endpoint studied was PFS as determined by an independent review committee. There was no statistically significant difference in PFS between the treatment arms [HR 0.98 (95% CI 0.77, 1.25), p=0.86]. The median PFS was 4.2 months in the capecitabine arm and 4.9 months in the capecitabine plus Avastin arm. There was also no statistically significant difference in overall

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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm274394.htm. Because this change occurred after the hearing, and Genentech did not have an opportunity to address the significance of this label change to the breast cancer indication for Avastin, I have not relied on this new information in making my decision in this proceeding.

[21] The severity of adverse events in the clinical trials submitted by Genentech was graded using the National Cancer Institute's ("NCI") Common Terminology Criteria for adverse events ("CTCAE"), v.2 and v.3.0 (Aug. 9, 2006), Docket No. FDA-2010-N-0621-0145, Appendix 14. "The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild AE; Grade 2 Moderate AE; Grade 3 Severe AE; Grade 4 Life-threatening or disabling AE; Grade 5 Death related to AE." CTCAE v.3.0 at 1.

[22] Avastin Prescribing Information, 3. More detailed information regarding these adverse events is available on pages 5-7 of the prescribing information. Only Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events were collected in E2100.

survival, which was a secondary endpoint [HR 1.05 (95% CI 0.86, 1.30), p=0.63, log-rank test]. The ORR was higher with Avastin plus chemotherapy as compared to chemotherapy alone.[23]

CDER decided to refer Genentech's sBLA for the metastatic breast cancer indication to the Oncologic Drug Advisory Committee (ODAC) for advice on this supplemental application and the question whether PFS could constitute clinical benefit in the context of first-line treatments for metastatic breast cancer. The results of the E2100 and AVF2119g trials were presented to ODAC on December 5, 2007. Joint Statement ¶ 27.[24] After a thorough discussion of the evidence and the issues, ODAC members voted as follows at the December 5, 2007 meeting:

- Are the data provided sufficient to establish a favorable risk/benefit analysis for the use of bevacizumab plus paclitaxel for first-line treatment of patients with metastatic breast cancer? (Voting Question)

  Vote: Yes = 4 No = 5 Abstain = 0

Joint Statement ¶ 28.

B. Accelerated approval for Avastin's metastatic breast cancer indication

In a letter dated February 20, 2008, Genentech requested accelerated approval for use of Avastin in combination with paclitaxel for the first-line treatment of HER2-negative metastatic breast cancer. Joint Statement ¶ 29. As previously discussed, accelerated approval is available when FDA concludes there is some evidence that a drug will provide a clinical benefit that justifies its risk but there is not sufficient evidence to support a traditional approval. To verify clinical benefit for Avastin with metastatic breast cancer, Genentech proposed two clinical trials

[23] FDA Briefing Document for 2007 ODAC Meeting 23-24.
[24] Genentech and CDER agree that the transcript and summary minutes for this meeting faithfully and accurately report on the meeting. Joint Statement ¶ 27.

that it had already begun - AVADO and RIBBON1.[25] On February 22, 2008, CDER granted accelerated approval for the following indication:

> Avastin is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer in combination with paclitaxel.
>
> The effectiveness of Avastin in MBC is based on an improvement in progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin.
>
> Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.

Joint Statement ¶ 30, Attachment 1. CDER's approval letter stated that regular approval for the metastatic breast cancer indication was contingent upon successful completion of and submission of efficacy supplements containing the final reports and revised labeling for these studies. Joint Statement ¶ 33.

C. Submission of AVADO and RIBBON1 studies, and Genentech's request for regular approval

The AVADO study (BO17708) compared Avastin at two doses, plus docetaxel, to docetaxel alone. The RIBBON1 study (AVF3694g) consisted of two independently powered comparisons under a single protocol: Avastin plus taxane/anthracycline compared with taxane/anthracycline alone (where the taxane was docetaxel or nab-paclitaxel), and Avastin plus capecitabine to capecitabine alone. Joint Statement ¶ 17. As in E2100, PFS was the primary efficacy endpoint in these studies, and OS and ORR were secondary endpoints. Joint Statement ¶ 18. These were placebo-controlled, double-blinded trials, which were adequate and well controlled.[26] Genentech and CDER agree that the following table accurately summarizes efficacy data from the AVADO and RIBBON1 studies[27]:

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[25] Joint Statement ¶ 31. Genentech agreed that "[s]atisfactory review of the results of" these trials would be "required for the conversion of this accelerated approval" to regular approval. Letter from Dr. Todd W. Rich to Dr. Patricia Keegan, February 20, 2008, 1-2, , Docket No. FDA-2010-N-0621-0145, Appendix 13.
[26] Summary of Questions presented to the ODAC at the July 20, 2010 meeting.
[27] Joint Statement ¶ 19, Attachment 2.

Study Arm	Median PFS (months)	Median OS* (months)	ORR
AVADO			
Docetaxel + Avastin 15 mg/kg	8.8	30.2	63.1%
Docetaxel + Placebo	7.9	31.9	44.4%
Between-Arm Difference	0.9	−1.7	18.7%
Hazard Ratio (95% CI)	0.62 (0.48, 0.79)	1.00 (0.76, 1.32)	(9.0%, 28.4%)
	p = 0.0003	p = 0.98	p = 0.0001
Docetaxel + Avastin 7.5 mg/kg	8.7	30.8	55.2%
Docetaxel + Placebo	7.9	31.9	44.4%
Between-Arm Difference	0.8	−1.1	10.8%
Hazard Ratio (95% CI)	0.70 (0.55, 0.90)	1.10 (0.84, 1.45)	(0.9%, 20.7%)
	p = 0.0054	p = 0.48	p = 0.0295
RIBBON1			
Taxane/Anthracycline + Avastin	9.2	27.5	51.3%
Taxane/Anthracycline + Placebo	8.0	NR	37.9%
Between-Arm Difference	1.2	NR	13.5%
Hazard Ratio (95% CI)	0.64 (0.52, 0.80)	1.11 (0.86, 1.43)	(4.6%, 22.3%)
	p < 0.0001	p = 0.44	p = 0.0054
Capecitabine + Avastin	8.6	25.7	35.4%
Capecitabine + Placebo	5.7	22.8	23.6%
Between-Arm Difference	2.9	2.9	11.8%
Hazard Ratio (95% CI)	0.69 (0.56, 0.84)	0.88 (0.69, 1.13)	(3.4%, 20.2%)
	p = 0.0002	p = 0.33	p = 0.0097

* Updated OS analysis where available. CI = confidence interval; NR = not reached.

Survey data on quality of life were collected in the AVADO study, and did not show an improvement in quality of life.[28] Genentech and CDER also agree that the safety data observed in the AVADO and RIBBON1 studies were consistent with the safety profile of Avastin described in its approved prescribing information, and that the prescribing information is a fair and accurate description of Avastin's safety profile. Joint Statement ¶ 22, 23.

[28] The FACT-B instrument was used. Summary Minutes of the Oncologic Drugs Advisory Committee, July 20, 2010, 4; 2010 ODAC Meeting Tr. 99:3-6, 17-20.

Genentech submitted the results of the AVADO and RIBBON1 trials on November 16, 2009 in sBLA 125085/191 and sBLA 125084/192, respectively. In its submission, Genentech requested expansion of Avastin's labeling to include an indication for use in combination with docetaxel chemotherapy and with taxane-based, anthracycline-based or capecitabine chemotherapy for the first-line treatment of HER2-negative metastatic breast cancer. Joint Statement ¶ 36.

On July 16, 2010, Genentech also submitted the results of another trial of Avastin, the RIBBON2 trial (also referred to as the AVF3693g trial). RIBBON2 was a double-blind, placebo controlled, international trial conducted by Genentech to evaluate the safety and efficacy of Avastin in combination with taxanes, capecitabine, or gemcitabine in patients who have received prior chemotherapy for metastatic HER2-negative breast cancer.[29] Genentech submitted these results, together with the results of AVF2119g, to support an efficacy supplement seeking approval of Avastin in combination with taxanes, capecitabine or gemcitabine for use in patients who have received prior chemotherapy for metastatic HER2-negative breast cancer, as well as to support removal of a limitations of use statement from the INDICATIONS AND USAGE section (1.3) of the Avastin label. RIBBON2 showed a difference in median PFS of 2.1 months [HR of 0.78 (95% CI: 0.64, 0.93), p=0.0072], and no overall survival benefit.[30]

The trials were presented to ODAC on July 20, 2010.[31] Joint Statement ¶ 37. Based on their review of these trials and presentations made by CDER and Genentech, ODAC members voted as follows:

[29] Note that this is a different class of patients than those in trials of patients that had not received prior chemotherapy for treatment of metastatic breast cancer.

[30] June 28 Tr. 168: 18-20; CDER Hearing Presentation Slide 78, Docket No. FDA-2010-N-0621-359.

[31] Genentech and CDER agree that the summary meeting minutes and transcript prepared for this meeting faithfully and accurately report on the meeting. Joint Statement ¶ 37.

- Does the addition of bevacizumab to docetaxel represent a favorable risk/benefit analysis for the initial treatment of patients with metastatic breast cancer?

  Vote: Yes = 0 No = 13 Abstain = 0

- Does the addition of bevacizumab to taxanes, anthracyclines, or capecitabine represent a favorable risk/benefit analysis for the initial treatment of patients with metastatic breast cancer?

  Vote: Yes = 1 No = 12 Abstain = 0

- Taking into consideration the totality of findings, and the responses to Questions 1 and 2 above, do the AVADO and RIBBON1 results provide confirmatory evidence of clinical benefit of bevacizumab in combination with paclitaxel for the initial treatment of metastatic breast cancer?

  Vote: Yes = 0 No = 13 Abstain = 0

- Should the indication for treatment of metastatic breast cancer be removed from the Avastin label?

  Vote: Yes = 12 No = 1 Abstain = 0.

Joint Statement ¶ 38.[32]

In response to feedback from the July 20, 2010 ODAC meeting, on August 16, 2010 Genentech submitted a summary of a proposed protocol for a study to characterize further the effect specifically of the combination of Avastin plus paclitaxel. The summary stated that the proposed study would include a prospective biomarker evaluation to try to identify patients who are more likely to derive a more substantial benefit from Avastin. Joint Statement ¶ 40.

D. Proposal to Withdraw Accelerated Approval

CDER scientists completed their review of the studies and Genentech's proposal, and determined that withdrawal of the accelerated approval was necessary. The final medical review leading to withdrawal was dated December 15, 2010. Consistent with the requirements of the

[32] Of the four ODAC members who voted that E2100 showed a positive risk-benefit profile based on the studies presented in 2007, two were still serving on the ODAC in 2010. Both of these ODAC members voted that AVADO and RIBBON1 failed to confirm benefit and that the metastatic breast cancer indication should be removed from the Avastin label. 2007 ODAC Meeting Tr. 278; 2010 ODAC Meeting Tr. 160.

accelerated approval regulations, 21 C.F.R. § 601.43(b), on December 16, 2010, the Director of CDER issued a Notice of Opportunity for a Hearing ("NOOH") on CDER's proposal to withdraw approval of Avastin's metastatic breast cancer indication. Joint Statement ¶ 42, 43.[33] The NOOH stated CDER's conclusion that AVADO and RIBBON1 failed to verify clinical benefit for Avastin in metastatic breast cancer and that Avastin is not safe or effective when used in accordance with its metastatic breast cancer indication. Joint Statement ¶ 44. On January 16, 2011, Genentech requested a hearing and submitted data analyses and information in support of its position that Avastin should "retain accelerated approval" for treatment of metastatic breast cancer in combination with paclitaxel, subject to Genentech's conduct of "a confirmatory study." Joint Statement ¶ 45.

E. The Hearing

The hearing procedures for the withdrawal of an accelerated approval for a biologic product are described in 21 C.F.R. § 601.43. This hearing was the first to be held pursuant to that provision.

FDA regulations provide a mechanism for the handling of hearings on matters such as withdrawals of regular drug approvals through a process that is referred to as "separation of functions," 21 C.F.R. § 10.55. This process is designed to assure that FDA hearings will provide a fair forum for discussion and resolution of the issues presented. The process takes advantage of the fact that FDA is organized with several Centers that are responsible for particular types of products, with a Commissioner's office that has responsibility for all regulated products. Thus, when separation of functions applies, the Commissioner's office acts in the role of a judge, while the product Center responsible for the decision being reviewed (here CDER) is one of the

[33] On August 27, 2010, at CDER's request, Genentech ceased affirmative marketing of Avastin for metastatic breast cancer. Joint Statement ¶ 41. On December 16, 2010, CDER issued two complete response letters on Genentech's November 16, 2009 sBLA submissions of the AVADO and RIBBON1 results. *Id.* at ¶ 42.

hearing participants, together with the applicant who is opposing that Center's action. Separation of functions requires that any communication between the Center that is a party in the hearing or the applicant and the Commissioner's office (including the presiding officer) concerning the subject of the hearing be on the record and not *ex parte*. Similarly, the Commissioner's office is not to communicate with others concerning the subject of the hearing in a manner that is not on the record.[34] While section 601.43(d) states the separation of functions does not apply to hearings on withdrawal of accelerated approvals, FDA decided to follow the separation of functions policy with respect to this hearing as a prudential matter given the significant public interest in the matter.[35]

Section 601.43(e)(1) requires an advisory committee be present at the hearing, review the issues involved, and provide advice and recommendations to the Commissioner. FDA interprets this regulation, consistent with the preamble to the proposal that became the regulation, 57 Fed. Reg. 13234 (Apr. 15, 1992), to require the participation of the standing advisory committee that advises the review division on the drug in question. In this case, that was the ODAC.[36] While FDA could have added consultants to the advisory committee for this proceeding, we faced the reality that many experts in this area have already expressed a view on this issue and/or might be considered as having conflicts because of their association with one of the parties to the hearing or with competitors to Genentech. Thus, we recognized the possibility that a decision to add

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[34] When separation of functions applies, all employees and officials of the Center that is a party in the hearing are considered to be on the Center's "team" unless the Commissioner specifically designates those persons on the public record as being available to assist her with respect to the hearing. In this case, one CDER physician was assigned to assist the Commissioner with respect to conflict of interest evaluation of advisory committee members, and several CDER employees whose job is to handle logistics and communication with respect to the CDER advisory committee were assigned to the Commissioner's team. These assignments were documented in the public record.

[35] I note that this does not necessarily create a precedent for other such hearings in the future.

[36] It is important to note that the role of the advisory committee in this hearing was to ask questions and then provide its advice and recommendations to me. Ultimately, it is my responsibility to decide the issues presented on the basis of the evidence. The vote of the advisory committee members, which as discussed below was unanimously in favor of withdrawal of approval, does not constrain me to agree with the position that they adopted.

consultants to the advisory committee would itself have been the subject of dispute between the parties. Accordingly, we concluded that the best way to obtain the advice of experts on these issues is for the parties to present those experts at the hearing itself and did not add consultants to the advisory committee. In fact, Genentech did present its preferred expert, Dr. Joyce O'Shaughnessy, at the hearing. The transcript reflects that Dr. O'Shaughnessy not only presented her views, but was consulted by members of the advisory committee during that committee's deliberations on the second day of the hearing.[37]

I appointed Dr. Karen Midthun, who serves as the Director of the Center for Biologics Evaluation and Research, and is an experienced medical product reviewer, to be the presiding officer at the hearing. By letter dated February 23, 2011, Dr. Midthun advised the parties that FDA was granting the hearing request. In order to focus the hearing on the issues requiring resolution, Dr. Midthun directed counsel for Genentech and CDER to consult together and to prepare a joint statement of those facts that were not in dispute and of those issues that were disputed. The joint statement, submitted on April 7, 2011, was useful in establishing the areas of factual agreement and is cited at various points in this decision. While the parties could not agree on the wording of the issues for decision and presented separate documents stating their different views on April 8, 2011, in general those statements reflected the standard set out in the regulation and statute and were not significantly different in substance from the issues identified in the notice of hearing. That notice was issued on May 6, 2011, and subsequently published in the Federal Register, 76 Fed. Reg. 27332 (May 11, 2011).

The notice of hearing specifically addressed one issue raised by the parties in their preliminary filings. Genentech had proposed to raise issues concerning the consistency of

[37] Genentech had originally identified an additional non-company expert, Dr. Howard Burris, as a witness at the hearing, but ultimately decided not to have Dr. Burris participate.

CDER's position with respect to Avastin with CDER's decisions with respect to other products for the treatment of metastatic breast cancer or of other products approved under the accelerated approval program. As the notice stated, issues with respect to FDA action on other products are not relevant to this proceeding. Each decision to withdraw or not to withdraw the approval of a product must be made on its own merits. If the decision with respect to another product is in error, that would not justify continuing that error with respect to the metastatic breast cancer indication for Avastin. *See Edison Pharm. Co., Inc. v. Food and Drug Admin.*, 600 F.2d 831, 843 (D.C. Cir. 1979). Moreover, the notice recognized that, as a practical matter, it would not be possible to evaluate the different circumstances associated with decisions with respect to other products[38] in the context of this or any hearing. Nevertheless, Genentech did make some arguments concerning other approvals and I will, for completeness, address those arguments later in this decision.

While Dr. Midthun had originally taken the position that interested persons other than the two parties to the hearing would be permitted to submit their views only in writing, she ultimately concluded, and I agreed, that it was appropriate to set aside time at the outset of the hearing to permit members of the public to provide oral testimony. That testimony, in many cases, expressed the strongly held belief that Avastin had helped particular individuals. In other cases, members of the public argued that the Avastin approval should be withdrawn.

On May 17, 2011, CDER and Genentech each submitted a summary of the evidence and arguments that they intended to present at the oral hearing. That hearing was held on June 28

[38] As previously noted, a decision on safety and effectiveness of a drug will depend on, among other considerations, the measure of effectiveness proposed, including, when PFS is used, hazard ratios and increase in median PFS, whether there is any evidence of effectiveness by other measures, such as overall survival or reduction in symptoms, levels of confidence in the clinical trials and their consistency, considerations of the toxicity of the drug compared to its potential benefit in the patient population for which it is intended.

and 29 at the FDA's White Oak facility. The hearing was open to the public and a webcast was made available to those who did not attend in person.

This is how the hearing was structured: First, the public presenters made their presentations. Thereafter, a panel of presenters from CDER was given two hours to explain CDER's reasons for the proposed withdrawal. There was then a one-hour opportunity for representatives of Genentech to ask questions of the CDER presenters. After that, there was a one-hour opportunity for Dr. Midthun and members of the advisory committee to ask questions of the CDER presenters. There was then an opportunity for CDER representatives to ask the CDER presenters any clarifying questions. This ended the first day of the hearing.

On the second day there was a two hour opportunity for Genentech witnesses to present the reasons they believed the approval should be continued. CDER representatives then had a one-hour opportunity to ask questions of the Genentech presenters, followed by a one-hour opportunity for Dr. Midthun and members of the advisory committee to ask questions of the Genentech presenters, followed by an opportunity for Genentech representatives to ask the Genentech presenters clarifying questions. There was then a discussion of the issues by members of the advisory committee, who ultimately voted on each of the issues.[39]

As noted, at the conclusion of the hearing, the advisory committee members were asked for their advice and recommendations, and they voted as follows:

- Question 1. Do the AVADO and Ribbon 1 trials fail to verify the clinical benefit of Avastin for the breast cancer indication for which it was approved?

  Vote: *Yes = 6* *No = 0* *Abstain = 0*

[39] There were seven members of the advisory committee, six of whom were voting members. The seventh was the industry representative. As noted, the advisory committee members included Dr. O'Shaughnessy in their discussion. They also asked some questions of representatives of Genentech and CDER.

- Question 2(a). Does the available evidence on Avastin demonstrate that the drug has not been shown to be effective for the breast cancer indication for which it was approved?

  Vote: *Yes = 6* *No = 0* *Abstain = 0*

- Question 2(b). Does the available evidence on Avastin demonstrate that the drug has not been shown to be safe for the breast cancer indication for which it was approved and that Avastin has not been shown to present a clinical benefit that justified the risks associated with use of the product for this indication?

  Vote: *Yes = 6* *No = 0* *Abstain = 0*

- Question 3. If the Commissioner agrees with the grounds for withdrawal, set out in Issue 1, Issue 2(a), or Issue 2(b), should FDA nevertheless continue the approval of the breast cancer indication while the sponsor designs and conducts additional studies intended to verify the drug's clinical benefit?

  Vote: *Yes = 0* *No = 6* *Abstain = 0*

After the hearing, CDER and Genentech were originally permitted until July 14, 2011 to submit a summary of their views as to what had been shown in the hearing. At the request of CDER and Genentech, this deadline was first extended to July 28, 2011 and then, at Genentech's request, it was extended again to August 4, 2011. FDA also decided to leave the docket open pending the submission of the parties' statements. The docket closed to CDER, Genentech, and the public on August 4, 2011, and at that point, the record for this proceeding closed. The record consists of the record made of the hearing (a video is available on the FDA website at http://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm255874.htm) and materials in the public docket, which includes submissions by the parties and the public, and correspondence with the Presiding Officer regarding this matter.

V. THE CONDITIONS FOR WITHDRAWING APPROVAL OF THE METASTATIC BREAST CANCER INDICATION HAVE BEEN MET

The first question that I addressed is whether either of the two grounds that CDER has proposed for withdrawing the application had been met. After careful review of the record, I conclude that both conditions have been met. The record reflects that when Avastin was submitted for approval of the metastatic breast cancer indication, there was evidence in E2100 suggesting an effect on PFS that might constitute clinical benefit, but this was only one study, and there were questions as to whether this study had accurately characterized Avastin's effect in the metastatic breast cancer context. Accordingly, and in light of well established safety risks associated with Avastin, CDER granted only accelerated approval, conditioned on confirmatory tests to verify a clinical benefit large enough to justify exposing patients to the drug. As results from these studies have come in, they have substantially changed the profile of this drug. AVADO and RIBBON1 have not verified the clinical benefit shown in E2100, and considering all the evidence, I cannot conclude that Avastin has been shown to be safe and effective for the metastatic breast cancer indication.

A. The confirmatory studies that Genentech submitted do not verify clinical benefit.

Clinical benefit refers to a benefit that is meaningful to a patient. It is different than a clinical endpoint, which is simply an outcome that is the subject of study, which may or may not be meaningful to the patient depending on the benefit conveyed and the risks of the therapy.

FDA's accelerated approval for Avastin's metastatic breast cancer indication was based on the results of the E2100 study, which did not demonstrate an overall survival benefit or improvement in quality of life for patients with metastatic breast cancer,[40] but did show an improvement in PFS in patients who were treated with the combination of Avastin plus paclitaxel as compared to paclitaxel alone. The increase in median PFS shown in this trial for patients in the Avastin plus paclitaxel arm was 5.5 months [hazard ratio 0.48 (95% CI (0.39-0.61)], which CDER concludes would represent clinical benefit for this indication if benefit of similar magnitude could be confirmed. However, in light of the known toxicities of Avastin and the risk of serious and life-threatening reactions to the drug, regular approval depended on confidence in the magnitude of PFS effect.

By itself, E2100 left a number of questions about whether the magnitude of treatment effect on PFS had been accurately described. It was only one study, and it did not show a gain in overall survival, as might be expected if its report of relatively substantial PFS gains was accurate. There were also methodological questions. A significant number of patients were lost to follow-up before the treatment effect on PFS could be confirmed, and so data were missing from the final analyses. Also, some disagreements were noted between initial measurements of tumor progression in this open-label trial and the independent review that was done later to confirm them. Although these methodological concerns were mitigated by independent review and careful analysis of the study data, which persuaded CDER that E2100 had shown an effect for Avastin on PFS, uncertainty about the magnitude of benefit remained. For example, although a sensitivity analysis conducted to estimate the effect of missing data on the reported PFS results showed a significant difference favoring the Avastin arm, estimates of the PFS difference varied

[40] Avastin Prescribing Information ("The effectiveness of Avastin in [metastatic breast cancer] is based on an improvement in progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin."). *See also* June 29 Tr. 171:9-12 (statement by Dr. Horning: "[W]e do not have quality of life data that meet CDER's standards from our first-line metastatic breast cancer trials").

according to assumptions about the nature of the missing data, ranging from a median PFS gain of 5.5 months (HR 0.48) to a median PFS gain of 2.4 months (HR 0.78).[41]

As previously discussed, as part of its sBLA, Genentech had submitted a study of Avastin plus capecitabine in metastatic breast cancer patients undergoing second-line treatment, AVF2119g, which did not show improvement in PFS, OS, or quality of life compared to capecitabine alone. Because AVF2119g had enrolled patients receiving second-line treatment, the results must be interpreted with care; such patients can be less responsive to treatment than patients receiving first-line treatment, and that may contribute to a less impressive result. After careful evaluation, CDER was unable to conclude that the difference with regard to Avastin's effect on PFS between E2100 and AVF2119g was due entirely to the difference in patient population. When the sBLA for the metastatic breast cancer indication was referred to the ODAC in 2007, its members split 5-4, with the majority voting that E2100 had not established a favorable risk-benefit analysis for use of Avastin with paclitaxel for first-line treatment of patients with metastatic breast cancer.[42]

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[41] CDER and Genentech dispute the significance of the methodological issues that CDER has raised regarding E2100. CDER has noted a number of issues, including missing scans in 10 percent of the patients; failure to follow 34 percent of the patients until an independent review determined a PFS event or end of study; lack of reliability in the determination of radiographic disease progression and the date of progression between the independent radiologist and study investigators…," and an "incomplete assessment of toxicities." June 28 Tr. 148:5-22; CDER Hearing Presentation Slides 26-27. Genentech argues that E2100 was well-designed and conducted, and points out that it took extensive steps to address the issues CDER raised- including multiple sensitivity analyses to determine the effect that missing data could have had; independent confirmation of scan interpretations, and assessment to test for possible bias; and assessment for possible bias from the fact that reported results of E2100 were based on an interim analysis. Genentech Post-Hearing Submission 15-19. Genentech argues that these additional evaluations found no bias, that E2100 was in line with other studies used to support approval, and that CDER had recognized E2100 demonstrated a robust effect and bias seemed unlikely. *Id.* I conclude that E2100 demonstrated an effect on PFS but did not conclusively establish its magnitude. The sensitivity analyses showed a range of effects on PFS and CDER concluded that there was definitely an effect on PFS, but was uncertain about the magnitude of the effect, especially in light of the failure to demonstrate an effect on PFS in AVF2119g. This uncertainty, particularly in light of the fact that an effect had been shown in only one trial, led to accelerated approval, requiring confirmatory studies.

[42] Joint Submission ¶ 37.

The Eastern Cooperative Oncology Group submitted a comment to the docket defending the quality and significance of E2100[43], and neither CDER nor I dismiss this study. It is undeniable, however, that this single study cannot be considered dispositive. Confirmation of the results that it reported was necessary, which is why Avastin was given accelerated rather than regular approval for the metastatic breast cancer indication.

As noted, to confirm the benefit of E2100, Genentech proposed two studies that were already underway, AVADO and RIBBON1. These studies tested combinations of Avastin with chemotherapy drugs other than paclitaxel, and were submitted not only to convert the Avastin-plus-paclitaxel approval into regular approval, but also to support a broad, taxane-based approval for Avastin, as well as approval for use in combination with docetaxel, taxane-based, anthracycline-based or capecitabine therapy.[44] The trials also showed that Avastin had a statistically significant effect on PFS, but the magnitude of this effect was much reduced. In AVADO, the improvement in median PFS at Avastin 7.5 mg/kg dosage, in combination with docetaxel, was 0.8 months [hazard ratio (HR) of 0.70 (95% confidence interval ("CI"): 0.55, 0.90), p=0.005], and the improvement at the Avastin 15 mg/kg dosage, in combination with docetaxel, was 0.9 months [HR 0.62 (95% CI: 0.48, 0.79), p<0.0003]. In RIBBON1, the improvement in median PFS in the Avastin plus anthracycline/taxane cohort was 1.2 months (HR 0.64 (95% CI: 0.52, 0.80), p<0.0001), and in the Avastin plus capecitabine cohort it was 2.9 months (HR 0.69 (95% CI: 0.56, 0.84), p <0.0002).[45] As in E2100, the studies also did not demonstrate that adding Avastin to chemotherapy provided a benefit to overall survival, and

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[43] Docket No. FDA-2010-N-0621-0468.

[44] Joint Statement, ¶ 36. Genentech suggested a broad taxane-based approval despite the fact that the best results in the confirmatory studies were when Avastin was used in combination with a non-taxane drug, capecitabine.

[45] Joint Statement, Attachment 2. As noted above, ORR differences were also substantially smaller than in E2100.

patient responses to questionnaires in the AVADO study did not demonstrate an improvement in quality of life.[46]

When these data were presented to the ODAC in 2010, the committee's view was that a favorable risk-benefit analysis had not been established for Avastin with any of the chemotherapy partners for which Genentech was seeking an approval (13-0 and 12-1); that the studies failed to verify clinical benefit for the Avastin plus paclitaxel indication (13-0); and that the metastatic breast cancer indication should be removed from product labeling (12-1).[47] Notably, of the four ODAC members in 2007 who voted that E2100 had established a favorable risk-benefit analysis, two were still serving on the ODAC in 2010; in light of the new studies, both changed their views and voted that clinical benefit was not verified and that the metastatic breast cancer indication should be removed from the Avastin labeling.[48] CDER, as noted, has also proposed to withdraw the indication on grounds that clinical benefit has not been confirmed.

I agree with CDER's position on this issue. Genentech's confirmatory trials failed to confirm the magnitude of effect on PFS that was shown in E2100, or show an improvement in OS benefit or quality of life. While the confirmatory studies did show a small effect on PFS, as seen from the hazard ratios reported, simply showing an effect cannot be considered to confirm

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[46] June 29 Tr. 143:21-144:3 ("Dr. Jenkins: So you would agree with the statement that there is no demonstrated overall survival advantage for Avastin in first-line metastatic breast cancer? Dr. Reimann: Yes."); June 29 Tr. 177 (Dr. Barron: "It's absolutely true that there was no statistically significant improvement in overall survival in E2100."). 2010 ODAC Meeting Tr. 99: 21-22 (Dr. Horning: "[W]e do not have any difference in patient-reported outcomes.").

[47] Joint Statement ¶ 38. *See also* 2010 ODAC Meeting Summary Minutes 4-7. The ODAC member who indicated that she supported leaving the indication on Avastin's labeling explained that this was only because the labeling stated that "There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin." 2010 ODAC Meeting Tr. 226:22-227:1.

[48] *See* 2007 ODAC Meeting Tr. 278; 2010 ODAC Meeting Tr. 160:4-13 (Dr. Mortimer: "I argued at [the 2007 ODAC meeting] that a doubling in response rate was an incredible improvement and that furthermore doubling the progression-free survival was also an amazing finding especially in the setting of a cooperative group trial, which, you know, if anything might be a little harder to prove. So I looked forward to this meeting to see what the advantages ultimately turned out. I have to say, I'm very disappointed that in fact it did not support the reasons that I argued so strongly in favor of the drug previously."); *id.* at 231:7-8 (Dr. Lyman: "[T]hese studies didn't fully live up to the E2100 data.").

clinical benefit for Avastin. Given the known toxicities of Avastin - which include risk of gastrointestinal perforation, wound-healing problems, serious hemorrhage, and other serious side effects (see prescribing information above at n.20, and discussion in section V.B.2.) - the diminished evidence of improvement of PFS combined with the demonstrated risk does not confirm the presence of clinical benefit. I conclude that the standard for withdrawal has been satisfied because clinical benefit has not been confirmed, and when this study is viewed in the light of the confirmatory trials, the evidence does not show that Avastin has had an effect on PFS large enough to constitute clinical benefit. The early promise suggested by E2100 has not been verified.

Genentech concedes that the magnitude of benefit shown in the confirmatory studies was less than in E2100, but argues that the confirmatory studies verify clinical benefit because they achieved their primary endpoint of showing a statistically significant effect on PFS, and that the benefit can be seen in the robust hazard ratios reported by the trials.[49] However, a statistically significant effect on a clinical endpoint does not, by itself, demonstrate meaningful benefit to a patient. The difference between treatment and control arms must be not only statistically significant (meaning, not likely owing to chance) but also large enough to be meaningful to a patient. And as noted above, the magnitude of effect on PFS shown in the confirmatory studies and RIBBON2 was disappointingly small. And, while hazard ratios are useful measurements, and are certainly part of risk-benefit analysis, it is not appropriate to assess a drug's magnitude of benefit by looking at hazard ratios alone. The reason is that a hazard ratio is a measure of relative risk: it compares the risk over a period of time that patients in the treatment arm will experience a negative event (tumor growth or death) against the risk that the same event will happen to patients in the control arm. To be interpreted correctly, it is generally necessary to

[49] *See, e.g.*, June 29 Tr. 8:18-21; 12:16-21.

also consider a measure of absolute difference. This is because the hazard ratio may be statistically significant, even if there is very little absolute difference between two groups. As CDER's statistician Dr. Sridhara explained, it would be possible to run two trials, each of which showed a hazard ratio of 0.5, when even though in one trial a drug was associated with a two-month increase in median PFS and in the other trial with a 12-month increase in median PFS.[50] Dr. Sridhara also explained: "we have had applications where the hazard ratio was .5 and, in fact, the difference in PFS was just two weeks. ... [T]he hazard ratio was small enough, but the difference in medians was too small to be clinically meaningful."[51] For example, in the case of Avastin, the hazard ratios were statistically significant not only with E2100, where the absolute gain in median PFS was notable, but also with AVADO, where Genentech concedes the magnitude of the PFS gain was much smaller.

It is for this reason that FDA-approved labeling informs prescribers of both absolute and relative differences in treatment effects, and of course, why the approved labeling for Avastin's metastatic breast cancer indication has also included both the absolute difference in median PFS as well as the relative risk reduction, expressed as the hazard ratio.[52] Even Genentech agrees, as a general matter, that it is necessary to look at both hazard ratio and absolute magnitude of effect

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[50] June 28 Tr. 242:12-16 ("[A] change in two months to four months [an improvement of 2 months] versus a change in 12 months to 24 months [an improvement of 12 months], under certain assumptions, you can say that the hazard ratio is .5 in both cases.") Generally, when the risk of an event is the same in both the treatment and control arm, the hazard ratio will be expressed as 1; when the risk in the treatment arm is lower than in the control arm, the hazard ratio will be less than 1.

[51] June 28 Tr. 243:17-19.

[52] Avastin Prescribing Information 14; Guidance for Industry: *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products -- Content and Format* 8 (January 2006), available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127534.pdf ("When presenting differences between study group and comparator, it is important to present the absolute difference between treatment groups for the endpoint measured, as well as the relative difference (e.g., relative risk reduction or hazard ratio). ... In most cases, the treatment effect is presented as a mean or median result accompanied by a measure of uncertainty or distribution of results for the treated groups.)

to evaluate Avastin's effect,[53] and of course, it has on several occasions recognized impact on median PFS as an appropriate measure of magnitude of effect. For example, Genentech's experts underscored the importance of improvement in median PFS in making their presentation to the ODAC in 2007, and the company prominently featured the median PFS difference shown by E2100 in its advertising materials for Avastin.[54] I note that Genentech agrees that the magnitude of benefit shown in AVADO (median PFS gain 0.8 or 0.9 months, HR 0.62 or 0.70) is less than the benefit shown in the capecitabine arm of RIBBON1 (median PFS gain 2.9 months, HR 0.69) even though the hazard ratios are in a similar range. Although Genentech argues that CDER has focused "solely" on the difference in median PFS, it is clear that CDER has considered both hazard ratio and measures of absolute magnitude in making its determination, and Genentech has not identified any other measure of absolute benefit that would lead to a materially different view of the efficacy data.

I conclude that the confirmatory studies did not in fact confirm the clinical benefit that appeared in the E2100 trial. Genentech's argument, ultimately, is that some lesser benefit than that seen in the E2100 trial should be considered to confirm the clinical benefit. Whether or not some benefit less than suggested by E2100 would be adequate, I conclude that the lesser benefit shown in the confirmatory trials presented by Genentech does not justify the risks associated with this drug in this patient population.

Genentech has made several other arguments, discussed in more detail below, that could be considered relevant to the question of whether clinical benefit has been confirmed, as well as

[53] *See, e.g.*, June 29 Tr. 140:16-20 (Dr. Jenkins asked: "[H]ow can I put a hazard ratio into perspective without looking at the magnitude of the median difference in progression-free survival?" Dr. Reimann answered: "You can't. You need to look both at hazard ratio and absolute benefits.").

[54] CDER Hearing Presentation Slide 97 (reproducing Genentech advertising materials); 2007 ODAC Meeting Tr. 89:5-8, 16-21 (statement of Genentech's expert, Dr. Winer) ("[F]or progression-free survival to equal benefit, for it to be meaningful, this progression-free survival needs to be substantial in magnitude.... In terms of the magnitude of the benefit, as you've heard now multiple times, the improvement in outcome in terms of progression-free survival is substantial with a hazard ratio of. 48 and an absolute improvement of 5-1/2 months.").

to the questions discussed in the following sections of whether Avastin has been shown to be safe and effective for its metastatic breast cancer indication and whether I should, as a matter of discretion, continue accelerated approval. Because, for the reasons explained below, I ultimately do not find any of those arguments convincing, I do not find them to be a basis for a conclusion that the clinical benefit that had been suggested by the E2100 results has been confirmed.

B. The available evidence demonstrates neither that Avastin has been shown to be effective for the treatment of metastatic breast cancer, or that it has been shown to be safe for that use

1. Avastin has not been shown to be effective for its metastatic breast cancer indication

For similar reasons, when I turned to the second issue presented, I also find that the risk-benefit analysis for this drug, in light of all the evidence, is not positive. If the FDA had before it, at the time of the initial decision on accelerated approval, all of the data that now are available, we could not have found that this drug was shown to be effective for the metastatic breast cancer indication. The evidence that use of this drug for this purpose provides any meaningful benefit to patients is weak and the evidence that use of the drug by metastatic breast cancer patients will harm some of those patients is undeniable.

Genentech has made an argument concerning the significance of the confirmatory studies that goes to the effectiveness of Avastin for treatment of metastatic breast cancer.[55] It argues that the less robust results observed with respect to studies other than E2100 are explainable because there is some synergy between Avastin and paclitaxel. Genentech contends that the "most plausible" explanation for the discrepancy between E2100 and the other trials is that Avastin is

[55] I discuss this argument with respect to issue two, as it would not seem to support the position that the additional trials had confirmed the clinical benefit suggested by the E2100 trial. At most, it would be a reason why those results could be considered not to disprove the results of the E2100 trial. Nevertheless, I have also considered whether this preferred-partner hypothesis would lead to the conclusion that the conditions for withdrawal are not satisfied; I conclude it does not.

more effective when paired with paclitaxel than with other chemotherapy agents. Specifically, Genentech hypothesizes that the Avastin-paclitaxel combination performed better because it was better tolerated by patients than the other combinations and administered on a more frequent and intense dosing schedule, which meant patients had "greater exposure to both a highly potent chemotherapy and the anti-angiogenic activity of Avastin." Genentech Post-Hearing Submission 21.

Genentech recognizes, however, that its hypothesis is far from proven. It has noted that "the scientific basis for the observed differential effect with paclitaxel is not yet understood," and that its hypothesis is only one of "multiple hypotheses [that] can be generated for why a differential effect would be observed with distinct chemotherapy partners."[56] There are clearly not data to establish this hypothesis, and some of the data that are available are not supportive. As CDER has pointed out, Genentech has not presented evidence of drug interactions or antagonism between Avastin and chemotherapy drugs other than paclitaxel to support this theory. Antagonism would be shown if the treatment effect of Avastin plus other chemotherapy agents, when they are given in combination, were smaller than the sum of the treatment effects when each drug is given alone. Synergism would be shown if the treatment effect of Avastin and paclitaxel taken together were greater than the effect when each is taken alone. Studies to test for these relationships are well known, and are commonly used to test hypotheses similar to the ones Genentech advances here. Genentech has not performed such studies, or if it has, it has not submitted them to FDA. The available evidence is to the contrary. CDER has conducted

[56] Submission of Genentech, Inc. in Response to the Food and Drug Administration's Notice of Opportunity for Hearing and Proposal to Withdraw Approval of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel for the First-Line Treatment of Patients with Metastatic Breast Cancer 3, 28, Docket No. FDA-2010-N-0621-0002.

exploratory analysis of the AVADO and RIBBON1 data to look for evidence of interactions between Avastin and the chemotherapeutic agents, and did not find them.[57]

Other studies with Avastin are also not consistent with the hypothesis that length of treatment correlates with treatment effect. In studies of Avastin with colorectal cancer, lung cancer, and renal cell cancer, Avastin showed improved survival or PFS even though treatment length was limited by protocol.[58] Genentech does not propose to design a study that could test its duration-of-treatment hypothesis.

In further support of its preferred-partner argument, Genentech notes that CDER approved Avastin only for use with paclitaxel, and argues that when CDER made this decision, it "implicitly recogniz[ed] that the chemotherapy partner affected the efficacy results observed in the different studies."[59] However, CDER indicates that this did not reflect a "general policy to consider each drug combination a distinct experiment that cannot be generalized," and does not indicate that CDER believed a differential effect among chemotherapy partners had been established.[60] Rather, these decisions reflected uncertainty about how to interpret the difference in the outcomes of the E2100 and AVF2119g trials.[61] A differential effect based on chemotherapy partners was one possible explanation, but this was by no means proven and to the extent a difference between partners might exist, the magnitude of any such difference was not defined. CDER's account seems entirely reasonable, and it is difficult to understand why CDER

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[57] June 28 Tr. 182:4-183:12. *See also* the four clinical pharmacology reviews submitted by CDER as exhibits 9-12 of its Post-Hearing Submission.

[58] June 28 Tr. 183:13-184:7. Genentech has put forth a hypothesis that longer duration of therapy leads to better outcome but, until that hypothesis is tested (i.e., a study is conducted to test it), it remains a hypothesis and does not provide the evidence that is necessary to support a decision to continue accelerated approval.

[59] Genentech Post-Hearing Submission 23. Genentech also quotes the minutes of the January 10, 2006 meeting with CDER, which indicate that one reason for the design of the RIBBON1 study was that "the treatment effect will vary according to the chemotherapy regimen used." Genentech Post-Hearing Submission 23.

[60] "Summary of Arguments Supporting CDER's Proposal to Withdraw Approval of Avastin's Indication for the Treatment of Metastatic Breast Cancer" (hereafter, CDER Summary of Arguments) 39, Docket No. FDA-2010-N-0621-0144.

[61] *Id.*; *see also* June 28 Tr., 254-55.

would have accepted AVADO and RIBBON1 as confirmatory studies (or why Genentech would have proposed them) if it was not thought that the results could be generalizable. Genentech, at the time that Avastin received accelerated approval, and up to the time CDER proposed to withdraw approval for the metastatic breast cancer indication, argued that the results of E2100 lent support to a broad, taxane-based indication for Avastin. For example, it stated in supplement STN BL 125085/91 section 2.5.1 at 8 that "all taxanes, at either of the two common schedules, are frequently used in the treatment of metastatic breast cancer because the literature supports considering taxanes as a class of cytotoxic agent based on their similar efficacy and safety in the treatment of metastatic breast cancer."[62]

Ultimately, I do not find that there is evidence of a preferred-partner relationship between Avastin and paclitaxel sufficient to overcome the negative results of AVADO and RIBBON1 and I do not find that the E2100 results alone, or together with the other data that have been submitted, demonstrate that Avastin is effective when utilized with paclitaxel.

Another argument raised in connection with the hearing that might be said to address the effectiveness of Avastin for its metastatic breast cancer indication[63] is the contention that, whatever its effect on most patients, Avastin is shown to be effective for a group of "super responders." A few women with metastatic breast cancer who have taken Avastin together with other chemotherapeutics have reported experiences that are much better than the norm, and some of them testified at the hearing about their improvement after they began on a combination Avastin-chemotherapy treatment.[64] Others gave testimony about family and friends, or

[62] STN BL 125085/91 section 2.5.1 at 8, quoted in CDER Summary of Arguments at 39.
[63] Again, this argument, even if accepted, would not seem to support the Genentech position that the clinical benefits suggested by E2100 have been confirmed. Those benefits, which were the basis for the accelerated approval, were shown for the test population as whole.
[64] In some cases, that therapy was apparently in combination with drugs other than paclitaxel, which is covered by the approval at issue here.

submitted comments to the docket. It is clear that many people feel strongly about this issue, or are convinced that some women are in fact "super-responders" to Avastin.

I have been moved by these stories. But I am also mindful of other complicating factors that make it difficult to draw conclusions from these stories alone. Patients who take Avastin are generally also taking a chemotherapy agent, as was true of all the patients in the trials, and their success may be attributable to the other agent. There is also often considerable variation in the natural history of this disease, from patient to patient, which we are not always able to predict or explain. And, of course, while some patients have better-than-average results on Avastin or chemotherapy, others have poor results or are even seriously harmed. It is often difficult to determine which of these factors is responsible for a particular outcome, and this is why applicants are required to run clinical trials to compare, as best they can, the effect that two different treatments will have. When we compare the survival and PFS curves of patients in the control arms and Avastin arms of the trials that Genentech has submitted, we do not find that Avastin has demonstrated a meaningful PFS or OS advantage, and it is not possible to determine if there is some subset of patients within the population as a whole that may have had a meaningful benefit.[65]

Genentech has proposed a new clinical trial that might identify a subset of patients for whom Avastin plus paclitaxel would present a positive benefit-risk calculation, and I will discuss that proposal below when I address the request that I extend the accelerated approval as a discretionary matter. At this point, however, there are simply not convincing data to show that Avastin plus paclitaxel is effective for all or even some patients who suffer from metastatic breast cancer.

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[65] *See*, *e.g.*, June 28 Tr. 228:8-11; 300:10-302:17.

I have discussed above the two confirmatory trials upon which Genentech principally relies. In addition to the confirmatory trials, Genentech submitted another trial of Avastin with capecitabine in second-line treatment of metastatic breast cancer - RIBBON2 - which showed a median PFS gain of only 2.1 months, [HR of 0.78 (95% CI: 0.64, 0.93), p=0.0072], and no overall survival benefit. Including RIBBON2, there have been five studies of Avastin submitted to FDA in support of the indication for metastatic breast cancer, involving more than 3,500 patients.[66] None of these studies has demonstrated an overall survival benefit or an improvement in quality of life, and none of the four studies, AVADO, RIBBON1, AVF2119g and RIBBON2, has come close to replicating the PFS gain shown in E2100.

Genentech has suggested that some observed differences in mortality, which do not reach the level of statistical significance, may nevertheless suggest a trend of OS benefit. I conclude that these do not change the risk-benefit determination or my judgment regarding clinical benefit.

First, Genentech pooled the safety data across E2100, AVADO, and RIBBON1, and noted that across these trials there were 3.8% fewer total deaths and 3.4% fewer deaths related to metastatic breast cancer, and deaths attributable to treatment were identical, at 1.8%.[67] However, even if the exploratory analysis of these pooled data is accepted, it does not offer evidence of OS benefit. The difference in median survival is one-third of a month (median survival of 26.7 months for the Avastin plus chemotherapy group vs. 26.4 months for the chemotherapy group), and this difference falls well short of statistical significance: the hazard ratio across the two

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[66] June 28 Tr. 207:2-6.
[67] Genentech Post-Hearing Submission 28-29; June 29 Tr. 20:2-10; Genentech Hearing Presentation Slides 21, 26, Docket No. FDA-2010-N-0621-0424.

groups is 0.97 (95% confidence interval of 0.86 - 1.08), and a p-value of 0.56.[68] In fact, the confidence interval includes the possibility that use of Avastin would reduce overall survival.

Moreover, CDER argues that using a pooled analysis in this context is inappropriate and misleading. Different studies followed patients for different lengths of time to collect mortality information, and made different allocations of patients to control arms and treatment arms. When the data are compared using a log-rank test, which is the appropriate test here, they do not demonstrate improvement in OS.[69]

Second, Genentech has also selected some OS data from E2100, and argued that although they do not demonstrate OS benefit, they "suggest that an improvement in survival is more likely than no improvement."[70] Specifically, Genentech notes a difference in the survival curves of patients in E2100 over the first 30 months, and a greater survival rate at the landmark dates of one year and two years.[71] However, a determination about survival benefit must be based upon all of the data, not an analysis of selected time points. Other points could be selected that would give a very different view, even in E2100, which is far the most favorable study for Avastin. For example, at three years, the data show a survival *dis*advantage with Avastin. When we do an appropriate analysis, based on all of the data, E2100 does not show a difference in OS that is statistically significant. And, as noted, other studies, which must also be considered, show less favorable or even negative results.[72] This is not to say that there is a survival disadvantage to

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[68] CDER Hearing Presentation Slide 125. *See also* June 29 Tr. 142-43 (Genentech agrees that it prepared this slide); June 29 Tr. 143:21-144:2 (Dr. Jenkins: So you would agree with the statement that there is no demonstrated overall survival advantage for Avastin in first-line metastatic breast cancer?" Dr. Reimann: Yes.")
[69] CDER Post-Hearing Submission 16.
[70] Genentech Post-Hearing Submission 29.
[71] June 29 Tr. 201:9-14; Genentech Post-Hearing Submission 29.
[72] In the AVADO trial, the difference in median OS favored the control arm (median OS of 30.8 months for the 7.5 mg/kg dose of Avastin plus docetaxel arm vs. 31.9 months for docetaxel control arm, HR 1.103; median OS of 30.2 months for the 15 mg/kg dose of Avastin plus docetaxel arm vs 31.9 months for docetaxel control arm, HR 1.003). Joint Statement, Attachment 2. In RIBBON1, median OS values for the taxane/anthracycline control arm are not

Avastin; the evidence does not demonstrate that. But it does underscore the importance of considering all the data. When that is done, as CDER and Genentech agree, no OS benefit with Avastin has been shown.

2. Avastin has not been shown to be safe for its metastatic breast cancer indication

Because no drug that is active is entirely safe, FDA interprets the concept of safety in relationship to a drug's effectiveness in the intended patient population. In other words, FDA determines whether the drug has been shown to provide a benefit that outweighs its risks. Here, those risks are considerable. As discussed above, CDER and Genentech agree that the safety profile of Avastin is accurately described by its prescribing information. Joint Statement ¶ 22, 23. This information includes a boxed warning, the most serious warning for prescription medication under FDA regulations, and Avastin's labeling warns of toxicities that include gastrointestinal perforations, wound healing complications, and hemorrhage.[73] Avastin's prescribing information also warns that it is associated with more common, serious toxicities, such as hypertension, proteinuria, and increased incidence of chemotherapy-related toxicities such as neutropenia, febrile neutropenia, sensory neuropathy, diarrhea, and hand-foot syndrome. The clinical trials that Genentech has submitted to FDA show that the addition of Avastin to chemotherapy leads to an increase in serious adverse events and grade 3-5 adverse events.[74] In

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available, but the hazard ratio favors the control arm: HR of 1.11 when Avastin plus taxane/anthracycline arm is compared to taxane/anthracycline arm. FDA Briefing Document for 2010 ODAC Meeting, 18, 21.

[73] Joint Statement, attachment 1, at 3. *See also* June 29 Tr. 141:20-142:9 ("Dr. Jenkins: [Y]ou agree that these are serious and potentially life-threatening risks associated with the use of this drug that warrant a boxed warning specifically for Avastin." Dr. Horning: Yes. ... Dr. Jenkins: And did Genentech agree to this boxed warning language, or did FDA order you to implement this language for the safety risk? Dr. Horning: We agreed.").

[74] A "serious adverse event" is an adverse drug experience that:

> (A) results in--(i) death; (ii) an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form); (iii) inpatient hospitalization or prolongation of existing hospitalization; (iv) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or (v) a congenital anomaly or birth defect; or (B) based on

the E2100 trial, there was a greater than 20% increase in grade 3-5 toxicities in the Avastin arm compared to the control arm.[75] Additional information is available in a pooled analysis of selected adverse events grade 3 and higher in the first-line trials (E2100, AVADO, and RIBBON1), prepared by Genentech, which shows that there was an increase in all of these adverse events, except for one, in those receiving Avastin plus chemotherapy[76]:

Selected Adverse Reactions	**Pooled Chemotherapy (n=982)**	**Pooled Avastin + Chemotherapy (n=1679)**
Any adverse event	23%	37%
Neutropenia	7.1%	10%
Sensory neuropathy	8.5%	9.5%
Hypertension	1.2%	9%
Febrile neutropenia	3.5%	6.5%
Venous thromboembolic event	3.8%	2.8%
Proteinuria	0	2.3%
Arterial thromboembolic event	0.3%	1.6%
Left ventricular systolic dysfunction	1.2%	1.5%
Hemorrhage	0.4%	1.5%
Abnormal Tissue Repair	0.8%	1.7%
Wound dehiscence	0.3%	0.8%
Fistula	0.3%	0.5%
GI perforation	0.3%	0.5%
RPLS	0	<0.1%

None of this is disputed, and because the evidence demonstrates only limited activity of Avastin in tumors, and no clear clinical benefit, the risk-benefit profile of Avastin cannot be considered positive.[77] Indeed, the above data may underestimate risks, because only two of the four studies

> appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A).

21 U.S.C. § 355-1(b)(4) (this is the definition for "serious adverse drug experience"; "serious adverse event" is a short-hand way of referring to this category of drug experience).

[75] CDER Summary of Arguments 27.

[76] Clinical Review of sBLA 125085\191, at 48 (reproducing Genentech Inc., Integrated Summary of Safety, Appendix B, Table 53, at 202.), available in FDA-2010-N-0621-0145, Appendix 15.

[77] As noted, when ODAC reviewed the data regarding Avastin in July 2010, its members concluded unanimously that the relatively small PFS differentials shown in AVADO did not establish a favorable risk-benefit analysis; 12 of

described here collected information on all adverse events. For example, in the E2100 trial, no data were collected on adverse events that resulted in discontinuation of therapy because of toxicity, and data were not collected that would allow characterization of the duration of toxicity or resolution of toxicity.[78]

Genentech does not dispute the safety information on Avastin's labeling or disavow its pooled analysis, and it acknowledges that the drug comes with serious risks, but it argues that the most common of adverse events, hypertension and proteinuria, are clinically manageable.[79] This does not change the result of the risk-benefit analysis, because substantial benefit has not been shown for Avastin and the risks that remain are serious. Even to the extent that grade 3-5 hypertension and proteinuria can be "managed", they are serious adverse events to which patients should not be subjected without adequate evidence of benefit. Patients are subjected to discomfort, anxiety, and risk of further complications, and are likely to require the administration of additional therapies, in some cases indefinitely. The long-term course of these adverse effects is not fully specified.[80] And, as noted above in the table, hypertension and proteinuria are *not* the only adverse events associated with Avastin. This toxicity profile could be tolerable in a drug

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13 ODAC members concluded that RIBBON1 did not show a favorable result for the combination of Avastin and taxane/anthracylcine or Avastin and capecitabine. Joint Statement ¶ 38.

[78] CDER Summary of Arguments 28.

[79] *See, e.g.*, Genentech Post-Hearing Submission 29-34.

[80] In its submissions and hearing presentation, Genentech has referred to preliminary results from an adjuvant colon cancer study that it agreed to conduct to study the safety profile of Avastin. Genentech argues that results reported for this study indicate that the additional hypertension and proteinuria caused by Avastin's toxicity may be reversible or controllable - for example, by suspending treatment with Avastin or reducing dosage, and by the administration of appropriate therapy. Genentech Post-Hearing Submission 31-32. While this may prove to be useful information for characterizing the long-term safety of Avastin, I note that data for this study have not been submitted to FDA, and the results remain preliminary. In addition, Genentech submitted only a few slides showing topline data five days before the hearing, which limited CDER's opportunity to review even this limited information. Docket No. FDA-2010-N-0621-0354. I also note that even on the most favorable reading for Avastin, the preliminary results indicate that the drug is linked to increases in hypertension and proteinuria at rates consistent with those described on the product's current labeling, and to other adverse events that have not resolved. Genentech Post-Hearing Submission 32.

for which substantial clinical benefit had been demonstrated, but it is not a tolerable set of adverse events in a drug for which clinical benefit has not been shown.

CDER and Genentech disagree about the number of deaths in the first-line trials that should be attributed to Avastin. CDER estimates that the deaths of between 0.8 and 1.7% of the enrolled patients are attributable to Avastin, and notes that Avastin's prescribing information, which Genentech has agreed is accurate, indicates that 1.7% of the patients in the E2100 trial had deaths attributable to Avastin.[81] Genentech argues that CDER has attributed too many deaths to Avastin, and that its drug has been unfairly portrayed as more dangerous than it really is.[82] Without seeking to diminish the importance of these disagreements, I find that for present purposes they are not dispositive. CDER and Genentech agree that Avastin has well established toxicities that increase the number of serious, and even life-threatening, adverse events. And, notwithstanding disagreement about the number of deaths attributable to Avastin, there does not appear to be disagreement that it is responsible for some deaths in the trials, which is further confirmation of its active toxicity.[83] Given this toxicity profile, and the lack of evidence to show substantial benefit, there cannot be a favorable risk-benefit analysis.

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[81] CDER Summary of Arguments 3, 16 (E2100 = 1.7%), 22-23 (AVADO = 0.8%), 24-25 (RIBBON1 = 1.2%). CDER believes this is a conservative estimate, and explains that it only attributed a death to Avastin if the death was caused by a severe toxicity known to be associated with Avastin, and then only after considering the available information in the case history for evidence that another cause could be responsible. *See* CDER Post-Hearing Submission 14-18 (noting, e.g., that "a patient who developed wound healing complications and fistula and died a few weeks later ... was attributed to causes other than Avastin," even though these complications are known to be associated with Avastin; and that "there were examples in which the same [adverse events] occurred in both the chemotherapy-only and Avastin arms of a trial, but ... CDER did not attribute the [adverse events] to Avastin because they could have been caused by chemotherapy.")

[82] Genentech claims that CDER attributed too many deaths to Avastin because it placed too much emphasis on whether a death had been caused by an adverse event known to be related to a toxicity of Avastin, and that CDER did not adequately consider whether there were deaths from similar causes in the chemotherapy-only arms, which would suggest Avastin was not responsible. Genentech Post-Hearing Summary 30-31. Genentech also asserts that the investigators in AVADO and RIBBON1 disagree with CDER regarding attribution of mortality and, although Genentech elsewhere repeatedly agrees that the labeling information for Avastin is accurate, it has raised questions regarding the methodology that produced CDER's mortality estimate for E2100. *Id.* Finally, as noted, Genentech has submitted its analyses of pooled survival data, which conclude that there were fewer deaths in the Avastin arms and equal numbers of treatment related deaths in the Avastin and non-Avastin arms.

[83] As noted, the data do not show an overall survival reduction from Avastin, or a survival benefit.

C. It would not be appropriate to exercise discretion to continue approval for the metastatic breast cancer indication

The final decision I must make is whether to exercise discretion to maintain the approval even though the legal conditions for withdrawal have been met. As noted, FDA may withdraw an accelerated approval when confirmatory trials fail to confirm clinical benefit, or when the evidence does not show that the drug is safe and effective. However, the agency also carefully considers the effect on current and future patients of such a decision, and there may be circumstances, in particular cases, that would lead the agency to conclude that it would be appropriate to exercise discretion and leave an approval in place pending further study. This is not such a case.

Accelerated approval was based on the results of E2100, which showed an effect on PFS that would be large enough to constitute clinical benefit, despite the known risks of Avastin, which are serious. However, we now have five trials[84], and they have substantially changed our view of this drug. The current evidence no longer supports a determination that it has a strong effect in metastatic breast cancer, and it appears likely that its effects are very weak, while the risks associated with this drug remain serious and potentially life-threatening. On this evidence, I cannot find a basis to exercise discretion to continue labeling that would describe this drug as safe and effective for the treatment of metastatic breast cancer. For the population of women with metastatic breast cancer, the evidence does not justify broad exposure to the risks of this drug.

[84] There have been five trials total: three in the first-line setting (E2100, AVADO, RIBBON1), and two in the second-line setting (AVF2119g, RIBBON2). There have, however, effectively been seven independently powered comparison arms, as two of the trials tested more than one chemotherapy partner or a different dose of Avastin.

Genentech has made several arguments about how FDA should proceed that appear to be directed to the exercise of discretion with respect to withdrawal of the accelerated approval[85], and I will address each of those here.

1. Genentech's argument that accelerated approval should be continued as long as there is uncertainty about clinical benefit

Genentech has proposed that FDA leave the metastatic breast cancer approval in place while it conducts additional studies that may confirm the magnitude of effect seen in the E2100 trial. This is in keeping with Genentech's view that approval should be continued for so long as there is uncertainty about whether Avastin may confer clinical benefit[86] -- or, as Genentech sometimes argues in a stronger formulation, that FDA should maintain an accelerated approval until "there is no reasonable likelihood of clinical benefit and no possibility that additional study might further characterize any existing benefit."[87] This is not what FDA or Congress intended in establishing the accelerated approval program, and it is not consistent with the protection of public health. Before FDA may grant accelerated approval, it must make a risk-benefit determination on the basis of evidence provided by the applicant. The labeling that is approved

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[85] Again, I recognize that in some cases these arguments could also be considered to be directed to issues one and two, discussed above. While, for organizational purposes, I discuss them here, they have also been considered in my analysis of the first two issues.

[86] While I reject this Genentech characterization of the standard for continued accelerated approval, I note that, even if I applied the standard that it proposes, the result would be the same. With the number of trials completed, there is not significant uncertainty about the clinical benefit of the use of Avastin with paclitaxel in the treatment of metastatic breast cancer. Genentech's stronger formulation appears simply to be an attempt to describe a standard that would never permit withdrawal of an accelerated approval once granted, as it can never be said that "there is no possibility that additional study might further characterize clinical benefit." In this case, even with the risks associated with Avastin's use, I believe CDER would permit a further clinical study of that use (i.e., CDER would not regard such a study as futile), and I do not see a basis to disagree with that judgment.

[87] "Pre-Hearing Summary of Evidence and Arguments of Genentech, Inc. In Support of Maintaining the Accelerated Approval of AVASTIN® (Bevacizumab) in Combination with Paclitaxel for the First-Line Treatment of HER2-Negative Metastatic Breast Cancer" (Genentech Summary of Arguments) 22, Docket No. FDA-2010-N-0621-0146. *See also* Genentech Post-Hearing Submission 13 ("The accelerated approval statute embodies Congress's intent that the agency accept uncertainty where there is potential benefit and significant unmet need."). It is not entirely clear whether Genentech is arguing that this standard should guide FDA's exercise of discretion, or whether it contends that this is the standard that must be met before FDA may withdraw an accelerated approval. I conclude, for reasons stated in the body of this opinion, that this is not an accurate characterization of the legal standard, and that the grounds for exercising discretion to continue the approval are not met with respect to this indication.

reflects what is known at the time, and it is conditioned on confirmatory studies to verify benefit. When those studies are received, FDA must review them and determine whether, in light of the new information they provide, the risk-benefit determination still favors approval. Where, as here, the studies do not verify the clinical benefit suggested by the initial data and the available evidence does not show the drug to be safe and effective, in the absence of unusual circumstances[88] the accelerated approval should not be continued.

I cannot accept Genentech's proposal that approval be continued until it has time to conduct an additional study of Avastin with paclitaxel that may or may not confirm the PFS gain shown in E2100. Genentech has already conducted additional studies that failed to verify the clinical benefit of Avastin for this use and that failure has altered the risk-benefit calculus for the drug. To grant Genentech's request, I would have to ignore the results of those studies and maintain an approval that is no longer supported by current data, to allow a substantial length of time for more studies on the chance they might confirm benefit. That would be inconsistent with the statute and protection of public health.[89]

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[88] The fact that the statute and regulations give FDA discretion on withdrawal demonstrate that there may be some circumstances in which FDA can decide to continue accelerated approval, while additional investigations are completed, despite disappointing results in the confirmatory studies. It is for this reason that I have carefully considered the various arguments that Genentech has made on this point.

[89] It is worth noting that continuing the metastatic breast cancer indication pending completion of an additional study would mean that the drug would remain approved for years. While there is necessarily some uncertainty about the time that would be needed to conduct Genentech's proposed study, even the most favorable projections indicate that a substantial analysis of the results would not be available for three to four years, and the study could take longer or be infeasible. Genentech believes it could begin enrolling patients in the first quarter of 2012, and that final PFS data would become available in mid-to-late 2016, with the analysis to take additional time. Genentech believes it will be possible to construct an interim "futility analysis" that would trigger early withdrawal if some threshold is not met, "to occur" late in 2015 or in mid-2016. Genentech Post-Hearing Submission 42. However, complications are certainly possible, and planning for this study was not complete at the time of the hearing. For example, if the indication were continued, it is possible that Genentech would have difficulty enrolling patients in a trial in which some would receive paclitaxel plus Avastin (an approved drug for the indication to be tested) while others would receive paclitaxel plus a placebo. Genentech believes this problem would not significantly delay enrollment, but at this point there is uncertainty. At the hearing, Genentech indicated that it had not yet completed a feasibility assessment, and it has not proposed criteria for its interim analysis, or indicated what it believes should occur if it continues to disagree with CDER about what constitutes clinical benefit for this drug in the metastatic breast cancer context. June 29 Tr. 66:18-22.

Withdrawal here is the essential counterpart to accelerated approval. When the accelerated approval pathway was established, it was done with full recognition of the risk that drugs might be approved and later found not to confer clinical benefit to patients. FDA deemed this a risk worth taking for life-threatening illnesses in need of additional therapies, but also found it essential to mitigate that risk by providing for follow-up studies and withdrawal when benefit is not confirmed. The program has, on the whole, worked very well, making many new drugs available, particularly to cancer patients and AIDS patients, years before they would otherwise have been on the market. But when follow-up studies fail to confirm benefit, it is essential that approval be withdrawn in order to protect patients.[90]

2. Genentech's argument that accelerated approval should be continued on the basis of labeling changes and marketing restrictions

Genentech has proposed that the approval could be continued with changes in the marketing and labeling of the drug that would, in its view, focus the metastatic breast cancer indication and marketing on patients who "have the greatest unmet medical need, and present the most favorable benefit-risk profile."[91] In particular, Genentech proposes to modify Avastin's labeling to inform prescribers that it is indicated for use in patients who have "disease characteristics (e.g., aggressive HR+/HER2- or HR-/HER2- tumors) for which other therapies are considered to be less appropriate per physician assessment."[92] Genentech also proposes to implement a companion Risk Evaluation and Mitigation Strategy (REMS) "focused on an enhanced communication plan and a patient Medication Guide" that would provide additional information,

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[90] 57 Fed. Reg. at 13238.

[91] Genentech Post-Hearing Submission 37-38.

[92] Genentech Post-Hearing Submission, Appendix A, Proposed Labeling at 5. "HR" as used by Genentech refers to hormone receptor (estrogen receptor (ER) or progesterone receptor (PR)). *See id.*, Appendix C: "Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease" at 2. Tumors may be either positive or negative for hormone receptors and either positive or negative for HER2 (human epidermal growth factor receptor).

and submit promotional pieces to FDA before use. It is also "open to discussing limitations on its marketing on Avastin."[93]

The problem with this proposal is that it would create labeling and a marketing plan that are not supported by the data. The data do not demonstrate that Avastin plus paclitaxel is effective for patients with HR+/HER2- or HR-/HER2- tumors, or that the risks associated with its use are reduced in such patients. There are no data to demonstrate that they enjoyed greater PFS benefits or any OS benefit than the trial population as a whole, or that adding Avastin to the chemotherapy treatment of this group would improve their quality of life.[94] With respect to patients with triple-negative breast cancer[95] in particular, a group to which Genentech's expert gave special attention, CDER conducted an exploratory analysis of the first-line trials Genentech has submitted, segregating the triple-negative patients from other patients, and found that the overall survival and progression-free survival results of the triple-negative breast cancer patients are similar to the results for other patients.[96] Nor has Genentech identified another group of patients for whom other therapies would be "considered to be less appropriate" than Avastin.[97]

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[93] Genentech Post-Hearing Submission 38.

[94] *See* June 29 Tr. 257:19-259:8; Office Director Memo Supporting the NOOH 5 ("While it is possible that some patients may receive clinical benefit from Avastin for treatment of breast cancer, the available data are not sufficient to demonstrate that such a subgroup exists and, if so, how to identify the patients in advance."), Docket No. FDA-2010-N-0621-0145, Appendix 21. Genentech included an analysis in its posthearing submission that purports to show a benefit for patients characterized as triple negative. Genentech Post-Hearing Submission, Appendix C, "Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease." That analysis is not convincing. First, it is an exploratory analysis. As such, it may support a hypothesis for future testing, but is not itself compelling evidence. Moreover, the reported hazard ratio for PFS for this subgroup is not very different from the ratio for the study as a whole, and the confidence interval for the claimed benefit with respect to overall survival in this subgroup includes the possibility that the use of Avastin decreases rather than increases survival.

[95] Genentech refers to tumors that are ER-/PR-/HER2- as "triple negative." *See* Genentech Post-Hearing Submission, Appendix C, at 2.

[96] June 29 Tr. 258:6-258:20; CDER "Referenced Slides" 10-11, Docket No. FDA-2010-N-0621-0360.

[97] I do note that Genentech's clinical expert and some members of the public argued that increases in PFS represent a benefit because it relieves symptoms associated with tumor growth, and that this benefit is especially important for patients who are heavily tumor-burdened. As noted, however, the data as a whole do not demonstrate a substantial increase in PFS. And, the studies that surveyed patients about their experience on the drug did not show an improvement in quality of life; this was true even among women who showed objective response – a measured reduction in tumor size after therapy. June 29 Tr. 232:7-9, 233:2-4. Although it would be useful to be able to

Accordingly, FDA cannot approve labeling that would inform patients and prescribers it believes the drug is safe and effective, or incorporate the standard for "physician assessment" into the labeling. For the same reasons, the proposed REMS plan is also inappropriate. A REMS plan may be approved where FDA determines that communication regarding the drug is "necessary to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1(a)(2)(A). Here, there is no basis to conclude that the proposed communication would lead to clinical benefit that would outweigh Avastin's risks.

Genentech also argues that approval for the metastatic breast cancer indication should be maintained for patients who are triple-negative or HER2- because Avastin offers a therapeutic improvement over the combination therapies that are often indicated for these patients, and particularly when compared to the most commonly prescribed chemotherapy combinations, which offer results "much more in line with AVADO and RIBBON1 than E2100."[98] This argument repeats and depends on Genentech's view that the benefit of Avastin plus paclitaxel is characterized by E2100, a conclusion that is not viable in light of the four other trials from which data have been submitted. As a whole, the evidence available does not demonstrate that Avastin plus paclitaxel would confer meaningful clinical benefit in light of its serious risks.[99] Thus, I do

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directly compare women who were heavily burdened with symptoms at the start of the trials to other women, this cannot be done because no data were collected on patient symptoms at enrollment. From the little information that is available, it appears likely that most women in the trials (which were first-line trials) were asymptomatic or had mild symptoms at the time they enrolled. June 28 Tr. 170:11-17; June 29 Tr. 257:19-258:5.

[98] Genentech Post-Hearing Submission 26.

[99] Genentech submitted a "discussion paper" regarding the safety and efficacy profile of alternatives to Avastin in the appendix to its Post-Hearing Submission on August 4, 2011. CDER has not had an opportunity to respond to this paper, and it is questionable whether it was appropriate for Genentech to file this in a post-hearing submission that was to discuss its views of what took place in the hearing. Nevertheless, I have considered this paper in making my decision.

not find this modification to be a basis to exercise my discretion to continue the accelerated approval.[100]

3. Genentech's argument that approval should be continued while studies are completed to determine whether a subset of patients who would benefit from the drug may be identified

If it were possible to identify patients who would have a favorable response to Avastin before they begin taking the drug, we might be able to improve the risk-benefit profile of the drug by limiting the indication to those women. Genentech has proposed two hypotheses, but at this point the data do not support either.

First, Genentech has suggested that patients with high plasma levels of certain kinds of Vascular Endothelial Growth Factor (VEGF), particularly VEGF-A, "may be more likely" to benefit from Avastin.[101] There is very little evidence to support this hypothesis. Studies have not been conducted to test it, and the evidence that is currently available is, at best, mixed. In support of the hypothesis, Genentech notes that in an exploratory analysis of a subset of patients in the AVADO study, it found a favorable PFS hazard-ratio at certain VEGF-A levels, suggesting that those with high levels of VEGF-A may be more likely to derive substantial benefit from Avastin.[102] However, this kind of exploratory analysis is not able to provide a valid estimate of the magnitude of benefit. Moreover, as CDER points out and Genentech does not dispute, in the E2100 trial "there was no correlation between tumor tissue VEGF expression levels and outcomes in the subset of patients for whom tissue samples were available," and in a retrospective analysis of the AVF2119g trial, there was "no observed predictive effect of VEGF-

[100] Technically, Genentech is not proposing here to maintain approval for the indication, but rather to modify it. If I had found that its proposal had merit, this would raise some difficult procedural questions about how the modifications would be made. Because I do not find merit in the proposal, I do not address them.
[101] Genentech Request for Hearing 63. *See also* Genentech Post-Hearing Submission 42 ("[P]lasma VEGF-A *may* be a *potential* predictive marker for Avastin activity.") (emphasis added).
[102] Genentech Post-Hearing Submission 42.

A."[103] The reason Genentech has designed a study to test its hypothesis about VEGF-A is that it is simply not known whether women with higher plasma levels of VEGF-A respond better to Avastin.

Second, as noted above, Genentech has not shown that the Avastin-paclitaxel combination is appropriate for patients who are burdened with greater or more aggressive tumors, such as patients who are triple-negative or HER2 double-negative. In sum, the data do not currently identify a group of patients for whom clinical benefit is confirmed, and continuing accelerated approval while waiting for evidence is not appropriate. Genentech may, of course, continue to pursue its hypotheses by new investigations of Avastin under an investigational new drug application and FDA will carefully review the results of any such studies that are submitted.

4. Genentech's argument that FDA has maintained approval for Gemzar, and has exercised discretion to maintain approval for other drugs

Genentech argues that the Avastin efficacy data compare favorably to data that support the approval of Gemzar, another first-line treatment for metastatic breast cancer, and that Gemzar's safety profile is not substantially better than that of Avastin.[104] As noted, prior to the hearing, Dr. Midthun explained that the hearing would not extend to CDER's decisions with respect to other products for the treatment of metastatic breast cancer, or of other products approved under the accelerated approval program. Each decision to withdraw or not to withdraw the approval of a product must be made on its own merits. If the decision with respect to another product is in error, that would not justify continuing that error with respect to the metastatic breast cancer indication for Avastin. *See Edison Pharm. Co., Inc. v. Food and Drug Admin.*, 600 F.2d 831, 843 (D.C. Cir. 1979). Moreover, as a practical matter, it is not possible to evaluate the

[103] CDER Post-Hearing Submission 24 n.105.
[104] Genentech Post-Hearing Submission 2.

different circumstances associated with decisions with respect to other products in the context of this or any proceeding.[105]

Genentech argues that FDA has exercised discretion to allow time for additional studies on other occasions where the facts were significantly less compelling. In particular, it cites the examples of erbitux, midodrine[106], and doxorubicin. Again, it is simply not appropriate (and as a practical matter is not possible) for a hearing of this type to explore the multiple factors that go into decisions with respect to other products and to weigh those decisions against the one being considered in the hearing.

5. Genentech's argument that accelerated approval should be continued because CDER did not clearly communicate, or changed its mind with respect to, what was required for confirmation of clinical benefit

Genentech argues that CDER changed the standard for converting accelerated approval into regular approval midstream, and that it would have designed a different study if it had realized that the results shown in AVADO and RIBBON1 would not support approval.[107] Genentech notes that CDER had preliminary PFS data from the AVADO study when it gave accelerated approval, though those data showed an increase in median PFS of only 0.8 months. Genentech also notes that when it met with CDER in February 2009, CDER had top-line data for both AVADO and RIBBON1 (which showed increases in median PFS of 1.2 and 2.9 months), and that the minutes for that meeting state that conversion of the Avastin plus paclitaxel approval to

[105] At the time that Gemzar was approved, the available data suggested a trend in favor of extended overall survival. Ultimately, that survival benefit was not proven. Genentech, of course, is not arguing that the approval for Gemzar should be withdrawn, but rather that the PFS values from the Gemzar study should be compared to those for Avastin, despite the lack of any such survival trend for Avastin.
[106] CDER announced its decision to withdraw the accelerated approval of midodrine, and the applicant has requested a hearing on that decision. *See* Notice of Opportunity for Hearing, August 16, 2010, Docket No. FDA-2007-N-0475-0019; Genentech Request for Hearing, September 16, 2010, FDA-2007-N-0475-0026.
[107] *See, e.g.*, Genentech Post-Hearing Submission 6-7.

regular approval would follow from "demonstrated improvement in progression-free survival and evidence that survival is not impaired."[108]

Whether Genentech might have proposed a different trial to confirm benefit is not, of course, relevant to the evaluation of Avastin FDA must make today. Whatever a future trial may show, adequate and well-controlled confirmatory trials have already been conducted and data submitted, providing information about the drug that there is no public health basis to ignore. Certainly, hypothetical future results do not provide a reason to look past the data that is now before the agency.[109]

With respect to the regulatory standard, CDER points out that it informed Genentech on a number of occasions that regular approval for Avastin would depend on the magnitude of PFS improvement it could demonstrate. CDER communicated this during teleconferences in 2004[110] and 2006,[111] and in 2007 it adopted the PFS policy under which the agency intended to evaluate the magnitude of PFS differential in deciding whether it constituted clinical benefit. At the 2007

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[108] *Id.* at 7.

[109] With respect to the question of whether there may have been unfairness to Genentech, I note that Genentech designed and began the AVADO and RIBBON1 trials well before accelerated approval was given for the metastatic breast cancer indication, with the apparent goal of obtaining approval not only for the chemotherapy partners used in those trials, but also for a broader, taxane-based indication. These studies were not designed or powered to respond to the February 2009 meeting that Genentech cites, and were submitted to regulatory agencies for other countries, not just FDA.

[110] The minutes of an October 28, 2004 teleconference between Genentech and CDER to discuss study planning for the E2100 trial indicate that "Genentech asked if PFS is an adequate endpoint for full approval," and CDER replied "that it depends on the overall dataset and magnitude of PFS." October 28, 2004 Teleconference Minutes, at 3, Docket No. FDA-2010-N-0621-0145, Appendix 22. Genentech also agreed to provide survival data at the time of the PFS analysis. *Id*

[111] During a January 10, 2006 teleconference, CDER stated that "progression free survival and preliminary overall survival data from study E2100 would potentially support an accelerated approval for the use of Avastin in combination with paclitaxel for chemotherapy naïve patients with locally recurrent or metastatic breast cancer. Mature data concerning overall survival will be requested as a post-marketing commitment and would serve to convert the sBLA from accelerated approval to regular approval." Type B Meeting Minutes (January 10, 2006), Docket No. FDA-2010-N-0621-0145, Appendix 24. When Genentech "expressed concern about waiting for the survival data to convert to regular approval from accelerated approval," FDA stated that "the data needed to be mature. Progression-free survival has been discussed as an end point supporting regular approval for metastatic breast cancer. FDA will consider whether the data provided will support regular approval during the course of the review. *It depends on the strength of the data and the effect size whether approval is accelerated or regular*." *Id.* (Emphasis added.)

ODAC meeting at which Avastin's supplemental application for the metastatic breast cancer indication was discussed, representatives of CDER clearly stated that the size of the PFS differential was of central importance, and often discussed that size in terms of the 5.5-month increase in median PFS shown in E2100, a fact that Genentech appears to concede.[112] When Avastin received accelerated approval, rather than regular approval, the Director's memorandum and attached reviews noted CDER's continuing questions about the magnitude of Avastin's effect on PFS.[113] With respect to CDER's review of preliminary information from other trials, the agency did not indicate that its review constituted agreement that the trials had confirmed clinical benefit, and Genentech does not appear to have relied only on the PFS data; for example,

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[112] The briefing document that CDER prepared for the meeting stated: "The key issue of this sBLA for ODAC consideration is whether an estimated 5.5 month improvement in median PFS, with no statistically significant improvement in survival is adequate to support approval of bevacizumab with paclitaxel for first line treatment of patients with metastatic breast cancer." FDA Briefing Document for 2007 ODAC Meeting, 27. The transcript for this meeting contains many statements regarding the importance of demonstrating magnitude of benefit, and both CDER and Genentech discussed that question with reference to the number of months that median PFS had increased. *See*, *e.g.*, 2007 ODAC Meeting Tr. 15:12-16 (Dr. Pazdur: "Important considerations on the use of PFS as an endpoint should include *the magnitude of effect on PFS*, the treatment's toxicity profile, and the clinical benefits and toxicities of available therapy.") (emphasis added); *Id.* at 122:16-123:3 (Dr. Pai-Scherf (CDER): "[T]his application rests solely on evidence of an improvement on PFS in a single study. A 5.5 months improvement in PFS is claimed by Genentech. In considering Genentech's claim, the *FDA* needs to verify the robustness. That is, is there an effect? *And if there is an effect, the magnitude. That is, is the 5.5-month improvement in PFS reliable*?") (emphasis added) *Id.* at 89:5-8, 16-21 (Dr. Winer (Genentech)"[F]or progression-free survival to equal benefit, for it to be meaningful, this progression-free survival needs to be *substantial in magnitude*.... In terms of the magnitude of the benefit, *as you've heard now multiple times*, the improvement in outcome in terms of progression-free survival is substantial with a hazard ratio of. 48 *and an absolute improvement of 5-1/2 months.*") (emphasis added). *See also* June 29 Tr. 119:14-16 (Mr. Labson: "The issue isn't whether CDER said that magnitude would be considered, which I think is pretty straightforward.")

[113] *See* Dr. Richard Pazdur, Office Director's Memo re Re: STN 125085/91 (Feb. 21, 2008) , 5 ("The FDA clinical and statistical reviews and ODAC presentations state that Avastin's effect on the PFS endpoint is robust, but question the effect's magnitude."). These concerns were of sufficient importance to the Division Director, Dr. Patricia Keegan, that she recommended a complete response (i.e., no approval or accelerated approval) until the magnitude of benefit could be confirmed. Division Director Decisional Review (Feb. 21, 2008), 1-2 ("Major issues arising during this application were evidence of a treatment effect in only one of two trials and uncertainty regarding the magnitude of the effect on progression-free survival in the single positive trial. ... [T]he recommendation [of a complete response] is based on the applicant's failure to characterize the magnitude of the treatment effect, which is necessary for the determination of the relative benefits given the known risks of Avastin.") Both memoranda available in Docket No. FDA-2010-N-0621-0145, Appendix 11.

in the AVADO trial, it called out what appeared to be positive trend for Avastin with regard to OS.[114]

On balance, I believe that Genentech understood, or should have understood, that approval would turn on the magnitude of PFS gain shown. Ultimately, of course, even if I were to decide that there was a miscommunication with Genentech, that would not change my decision with respect to the approval. I must make my decision on the basis of whether the drug has been shown to provide a measurable overall benefit that would justify its use in light of its risks for the patients who might use it, based on the studies that are available.

Genentech does raise one significant issue, discussed above, about the magnitude of increase in median PFS it would have to achieve in order to convert accelerated approval for this indication to regular approval. While it seems clear that the result demonstrated by AVADO does not constitute clinical benefit,[115] and CDER has indicated that the results shown in E2100 do constitute clinical benefit, the threshold at which a trial would pass from failure to success has been difficult to draw ahead of time with great precision. Unfortunately, this problem is not easy to overcome. The agency has had limited experience using PFS as a measure of clinical benefit in the context of first-line therapy for metastatic breast cancer, and the analyses of safety and

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[114] CDER Hearing Presentation Slide 95. As noted, when the data and final analyses for AVADO were finally presented, Genentech agrees that no OS benefit was established. Genentech does not represent that CDER stated that the preliminary results of AVADO or RIBBON1 would constitute clinical benefit if confirmed in a mature submission. At the February 2009 meeting that Genentech alludes to, Genentech specifically asked whether FDA agreed that the data from AVADO and RIBBON1 "[s]upport full approval of Avastin for the treatment of patients who have not received chemotherapy for metastatic, HER2-negative breast cancer?" FDA responded: "The adequacy of the data to support expanded labeling claims will be determined upon review of the data." Type B pre-sBLA Meeting Minutes (February 26, 2009), 4, Docket No. FDA-2010-N-0621-0145, Appendix 24. When Genentech asked whether the studies had satisfied its postmarketing commitment under the accelerated approval regulations, FDA responded that "[t]he adequacy of the data to fulfill the [postmarketing commitment] can only be determined upon review of the supplement." *Id.*

[115] Median PFS gain 0.8 or 0.9 months, HR 0.62 or 0.70. Even Genentech does not argue strenuously that this study showed clinical benefit, and it has said that it respects the decision by EMA not to approve an indication for the Avastin-docetaxel combination. June 29 Tr. 129:12-17 (Dr. Horning: "[W]e do recognize that the tolerability of docetaxel in combination with Avastin is less good than with paclitaxel, and we respect the judgment of those who've used the two in combination as well as the decision that was made in Europe.")

efficacy data required to make an approval decision for a drug such as Avastin are exceedingly complicated. With respect to Avastin, CDER has now informed Genentech that demonstrating an improvement in PFS like that shown in E2100 will support conversion to regular approval, assuming there are no new safety signals to change the risk-benefit calculus and no evidence of decreased overall survival. Pending such a demonstration, or a showing of some other clinical benefit that could support approval, I conclude that the approval must be withdrawn.

6. The suggestion that accelerated approval should be continued because of the views of other regulators and expert organizations

Genentech notes that other regulators and some scientific bodies have reached a different conclusion than CDER with respect to Avastin. I will discuss these in turn, but first want to note a common theme. FDA respects and is interested in the views of other regulators and the medical community, but it must ultimately make an independent scientific judgment about the risk-benefit analysis of Avastin, adhering to controlling legal authority and on the basis of the data before us. Other regulators and medical bodies operate under their own laws or objectives, and in some cases scientists and clinicians will simply reach different conclusions about the very difficult medical questions that the evaluation of drug products may present. I also note that some experts not cited by Genentech do not find this drug safe and effective for metastatic breast cancer. In light of the nature of the disagreements Genentech has cited, I see no basis to question the conclusions announced here.

With respect to regulators, Genentech observes that other countries have approved Avastin plus paclitaxel for first-line treatment of metastatic breast cancer, and that in particular the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use

(CHMP) has done so.[116] CDER has reached different scientific conclusions than the EMA before, including with respect to Avastin. For example, CDER has granted accelerated approval for the use of Avastin for the treatment of glioblastoma multiforme, while the EMA has not approved this use.[117] With respect to the metastatic breast cancer indication, I also note that there are important areas of agreement. For example, CDER and the EMA agree that the studies submitted by Genentech show no benefit to OS or quality of life, and that the docetaxel-Avastin combination should not be approved because it showed very modest benefit in the AVADO trial.[118] The principal difference between the agencies relates to the Avastin-paclitaxel combination, with respect to which the EMA granted full approval in February 2007, before the data from AVADO and RIBBON1 were available, and before independent analysis to resolve significant methodological issues cited by CDER. *Id.* This does not suggest a basis for questioning CDER's decision.

Genentech also notes that the National Comprehensive Cancer Network (NCCN) recommended the use of Avastin plus paclitaxel in its 2010 Clinical Practice Guidelines for

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[116] Genentech Post-Hearing Submission 15-16. I also note that another important national regulatory agency, the Pharmaceutical and Medical Device Agency in Japan, has granted approval to Avastin for a somewhat different breast cancer indication. Genentech has informed FDA that that agency has recently approved the use of Avastin in combination with paclitaxel for inoperable or recurrent breast cancer, apparently without restriction to first-line therapy or to use in HER2 negative breast cancer. September 27, 2011 email communication from Genentech counsel Michael Labson to Dr. Midthun, Docket No. FDA-2010-N-0621-0535.

With respect to another U.S. Government agency, Genentech also states that, after the June hearing, the U.S. Department of Health and Human Services Center for Medicare and Medicaid Services (CMS) indicated that "for the present time Medicare would continue to cover Avastin for metastatic breast cancer." Genentech Post-Hearing Submission 44. CMS did not indicate any opinion regarding the risk-benefit analysis of the Avastin-paclitaxel combination under the FD&C Act, and operates under different legal requirements than FDA. In particular, it may decide to pay for off-label uses of approved drugs when these are prescribed by physicians. By contrast, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) has not supported Avastin for breast cancer. It concluded that: "The evidence for the effectiveness of bevacizumab in prolonging survival was not robust and overall did not show enough of a demonstrable benefit for it to be considered a cost-effective use of NHS resources." http://www.nice.org.uk/newsroom/pressreleases/AvastinBevacizumabNotRecommended.jsp. *See also* http://guidance.nice.org.uk/TA214.

[117] CDER Summary of Arguments 45.

[118] CDER Summary of Arguments 47.

Breast Cancer, and that after the June hearing it reaffirmed these guidelines.[119] While CDER, and I, respect the scientific and clinical expertise of the NCCN panels, ultimately FDA must make its decision on the basis of the evidence. I note that CDER has received advice from medical experts on the ODAC, who have extensive qualifications in clinical trial design and evaluation, and are in a better position to review and make decisions relating to this approval.[120] They have been provided with detailed information regarding the trials and data submitted to support the indication, including presentations from CDER and Genentech regarding the completeness, accuracy, and quality of the data. They are then able to make recommendations on the basis of high-level evidence, and on that basis concluded, on two occasions, that the approval should be withdrawn. The NCCN panel has a different objective in publishing its recommendation, which is to provide clinicians with ready access to synthesized information they can use in making patient decisions. NCCN's Avastin recommendation, like many NCCN recommendations, was based on "lower level evidence" which "may include non-randomized trials; case series; or when other data are lacking, the clinical experience of expert physicians."[121] I also note that, in keeping with ODAC's regulatory purpose, its members are carefully screened for covered relationships, and are not permitted to serve if these present even an appearance of a conflict that could affect their impartiality.[122] NCCN receives financial support from Genentech

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[119] Genentech Summary of Arguments 25-26; Genentech Post-Hearing Submission 43-44.

[120] The July 2010 panel included four voting members who have authored a number of peer-reviewed publications on breast-cancer treatment (Drs. Freedman, Grem, Loehrer, and Wilson), and two temporary voting members, Drs. Budzar and Mortimer, were appointed to serve because of their breast cancer experience. CDER Summary of Arguments 49, 50.

[121] *See* Genentech Post-Hearing Submission 15 (indicating that the recommendation was level 2A); *NCCN Guidelines™ and Derivative Information Products: User Guide*, available at http://www.nccn.org/professionals/transparency.asp (accessed August 12, 2011) (explaining that category 2A represents "lower-level evidence" and the meaning of that term).

[122] 5 C.F.R. § 2635.502.

to distribute independently developed content, and one-third of the members of the NCCN Breast Cancer Panel have received financial support from Genentech.[123]

7. The suggestion that ODAC members' recommendations should not be given "undue weight"

Finally, in its Post-Hearing Submission, Genentech argues that I should not give "undue weight" to the votes of the ODAC panel, arguing that the members' votes reflected pre-existing views, that the panel lacked clinical experience with breast cancer and Avastin, and that ODAC took the position that PFS gain cannot support a drug approval.[124] As I have noted throughout, the decision with respect to this approval is mine alone. While I considered the advice of the advisory committee, I did so in light of the evidence in the record, including presentations of the parties' representatives, Genentech's experts, and public comments. In addition, Genentech has not pointed to substantial evidence in support of its specific criticisms of the ODAC, and has given no reason to doubt that they attended carefully to the proceedings, clearly understood the issues presented, and gave their advice on the basis of the evidence.[125] I also note that when the hearing in this matter was granted, Dr. Midthun informed Genentech by letter that if it believed additional expertise would be helpful it would have the opportunity to present experts of its

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[123] CDER Summary of Arguments 51.

[124] Genentech Post-Hearing Submission at 44-48.

[125] With respect to the ODAC members' clinical knowledge, Genentech does not identify any clinical or practical information that, properly understood, would have led to a different recommendation, or show that ODAC members' recommendations were premised on misunderstanding of clinical information. For example, Genentech emphasizes testimony from its breast-cancer expert that there are ways to manage hypertension and proteinuria, but it gives no reason to doubt that ODAC members understood the evidence presented on this subject, and as noted above in section V.B.2., notwithstanding this evidence Avastin plainly has risks that outweigh its benefits. At bottom, Genentech's disagreement appears to be with the way ODAC experts weighed the evidence, rather than their ability to do so.

Genentech's argument that ODAC members prejudged the subject of this hearing depends mostly on the fact that some of them previously provided recommendations to CDER regarding Avastin and made public statements about those recommendations. Genentech Post-Hearing Submission 44 n.120. These statements were, however, not of a nature that would require disqualification. FDA regulations do not require ODAC members to refrain from voting more than once on a question relating to a drug or drug approval, and in fact this happens fairly often. For example, members of ODAC who voted in favor of Avastin in 2007 were not barred from voting when Genentech's sBLAs in which it sought regular approval for Avastin were discussed in 2010.

choosing.[126] Genentech availed itself of that opportunity, and I have taken its experts' views into account. Genentech's view that the ODAC rejected PFS as a basis for approval is also seriously overstated.[127] In any event, my decision in this case is based upon Genentech's failure to confirm a substantial PFS gain for Avastin, and the drug's risk profile; it is not a rejection of PFS as a basis for approval in cases where PFS gains that are substantial in light of the risks of the drug can be shown.

VI. CONCLUSION

For all of the reasons explained above, I am withdrawing the accelerated approval of Avastin for use with paclitaxel in the treatment of metastatic breast cancer. I appreciate the significant effort that Genentech has put into developing this drug for this disease, as well as for other cancers, and the excellent presentation it made in the hearing. I trust that it will continue its investigations into use of the drug in those circumstances that it believes to be promising, and if new data are submitted they will be considered. Ultimately, however, I conclude that the

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[126] February 23, 2011 letter from Dr. Midthun to counsel for Genentech and CDER, Docket No. FDA 2010-N-0621-067. This letter also informed Genentech that FDA regulations required the participation of an advisory committee at the hearing, and that the agency interprets its regulations to require that the advisory committee in this proceeding be the ODAC. Genentech did not object to this determination. The number of members seated at the hearing was a function of the number serving on the ODAC at the time of the hearing, and screening required by statutes and regulations to ensure that only members without conflicts would be seated.

[127] Genentech identifies three statements in support of its view that the ODAC rejected PFS as a possible basis for approval. Two of these statements were made by Dr. Logan and Dr. Compagni-Portis, who were stating only that it may be difficult to identify the level of PFS that constitutes clinical benefit, and did not say they opposed it as a basis for approval. Both identified Genentech's failure to confirm a substantial PFS benefit in explaining their votes. *See, e.g.*, June 29 Tr. 214:1-11, 224:22 – 225:7. A third panelist, Dr. Sekeres, also noted the failure to confirm benefit, but also that Genentech had failed to demonstrate an improvement in quality or duration of life, and this may have been part of his understanding of what was required to continue the approval. *See* June 29 Tr. 219:21-220:18; 229:16-22. I have considered Dr. Sekeres' recommendation, note Genentech's objections, and make my decision for the reasons given in the body of this opinion.

currently available data do not support continued accelerated approval of this drug for this indication.

Dated: November 18, 2011

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

Appendix 9

CDER's Review of Trial 003, CDER's Clinical Review, NDA 02194-S-023 Makena

October 5 2020

Division of Urology, Obstetrics and Gynecology (DUOG)
Clinical Review

NDA#: 021945
Trade Name: Makena
Established name: Hydroxyprogesterone Caproate
Supplement#: 0-23 (Efficacy)
Date of Submission: September 11, 2019
Applicant: AMAG Pharmaceuticals, Inc. (AMAG)

This is a DUOG clinical review to document the regulatory decision for this efficacy supplement.

On February 3, 2011, Makena received accelerated approval under section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for the reduction in the risk of recurrent preterm birth (PTB) in women with a history of a singleton spontaneous preterm birth (sPTB). For effectiveness, the new drug application (NDA) relied on data from the Maternal Fetal Medicine Unit (MFMU) Network Trial 002,[1] which, compared to placebo, Makena reduced the proportion of women delivering prior to 37 weeks gestation, a surrogate endpoint reasonably likely to predict clinical benefit to neonates. As a condition of the accelerated approval, the Applicant conducted a confirmatory trial to verify and describe Makena's benefit on neonatal outcomes from reducing the risk of recurrent birth.

Completed in 2018, this trial (Trial 003) failed to confirm the clinical benefit of decreased neonatal mortality and morbidity as measured by the neonatal composite index. Trial 003 also failed to substantiate Makena's treatment effect on the surrogate endpoint that supported the 2011 accelerated approval (gestational age at delivery).

On September 11, 2019, the Applicant submitted this supplement, seeking to revise prescribing information to include data from Trial 003. Based upon the failure of the trial to confirm clinical benefit or replicate the prior findings, there is insufficient evidence to support the efficacy of Makena. Therefore, the grounds for expedited withdrawal of approval under section 506(c)(3)(B) and (C) of the FD&C Act and 21 CFR 314.530(a)(1) and (6) are met. The Division thus concludes that the accelerated approval should be withdrawn. Therefore, the Division recommends a Complete Response for supplement 023. For details, see DUOG's decisional memo dated October 5, 2020, supporting the recommendation to withdraw approval of Makena. The Applicant is referred to the Notice of Opportunity for a Hearing letter dated October 5, 2020.

[1] Meis PJ, et al., for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate. New Engl J Med. 2003; 348: 2379-2385.

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/s/

BARBARA D WESLEY
10/04/2020 08:48:41 PM

CHRISTINE P NGUYEN
10/05/2020 08:10:05 AM

Appendix 10

Makena Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MAKENA safely and effectively. See full prescribing information for MAKENA.

MAKENA® (hydroxyprogesterone caproate injection) for intramuscular or subcutaneous use

Initial U.S. Approval: 1956

--------------------RECENT MAJOR CHANGES--------------------

Dosage and Administration, Dosing (2.1) 02/2018

Dosage and Administration, Preparation & Administration (2.2) 02/2018

--------------------INDICATIONS AND USAGE--------------------

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth (1). The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation (14). There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

__Limitation of use:__ **Makena is not intended for use in women with multiple gestations or other risk factors for preterm birth.** (1)

----------------DOSAGE AND ADMINISTRATION---------------

- Makena auto-injector: Administer subcutaneously using Makena auto-injector at a dose of 275 mg (1.1 mL) once weekly, in the back of either upper arm (2.1)
- Makena (single- and multi-dose vials): Administer intramuscularly at a dose of 250 mg (1 mL) once weekly in the upper outer quadrant of the gluteus maximus (2.1)
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation (2.1)
- Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first (2.1)

-----------------DOSAGE FORMS AND STRENGTHS------------

1.1 mL single-use auto-injector for subcutaneous use contains 275 mg of hydroxyprogesterone caproate (250 mg/mL) (3)

1 mL single-dose vial for intramuscular use contains 250 mg of hydroxyprogesterone caproate. (3)

5 mL multi-dose vial for intramuscular use contains 1250 mg of hydroxyprogesterone caproate (250 mg/mL). (3)

----------------------CONTRAINDICATIONS----------------------

- Current or history of thrombosis or thromboembolic disorders (4)
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions (4)
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy (4)
- Cholestatic jaundice of pregnancy (4)
- Liver tumors, benign or malignant, or active liver disease (4)
- Uncontrolled hypertension (4)

------------------WARNINGS AND PRECAUTIONS------------------

- Thromboembolic disorders: Discontinue if thrombosis or thromboembolism occurs (5.1)
- Allergic reactions: Consider discontinuing if allergic reactions occur (5.2)
- Decreased glucose tolerance: Monitor prediabetic and diabetic women receiving Makena (5.3)
- Fluid retention: Monitor women with conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction (5.4)
- Depression: Monitor women with a history of clinical depression; discontinue Makena if depression recurs (5.5)

----------------------ADVERSE REACTIONS------------------------

- In a study where the Makena instramuscular injection was compared with placebo, the most common adverse reactions reported with Makena intramuscular injection (reported incidence in ≥ 2% of subjects and higher than in the control group) were: injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%). (6.1)
- In studies where the Makena subcutaneous injection using auto-injector was compared with Makena intramuscular injection, the most common adverse reaction reported with Makena auto-injector use (and higher than with Makena intramuscular injection)-was injection site pain (10% in one study and 34% in another). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AMAG Pharmaceuticals at 1-877-411-2510 or FDA at 1-800-FDA-1088 or __www.fda.gov/medwatch__.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised 02/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation of use: While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. **It is not intended for use in women with multiple gestations or other risk factors for preterm birth.**

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

- Makena auto-injector: Administer **subcutaneously** using auto-injector at a dose of 275 mg (1.1 mL) once weekly (every 7 days) in the back of either upper arm by a healthcare provider
- Makena (single- and multi-dose vials): Administer **intramuscularly** at a dose of 250 mg (1 mL) once weekly (every 7 days) in the upper outer quadrant of the gluteus maximus by a healthcare provider
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation
- Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first

2.2 Preparation and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Makena is a clear, yellow solution. The solution must be clear at the time of use; replace vial if visible particles or crystals are present.

Specific instructions for administration by dosage form:

Makena single-dose or multi-dose vials (intramuscular use only)

Makena single-dose or multi-dose vials are only for intramuscular injection with a syringe into the upper outer quadrant of the gluteus maximus, rotating the injection site to the alternate side from the previous week, using the following preparation and administration procedure:

1. Clean the vial top with an alcohol swab before use.

2. Draw up 1 mL of drug into a 3 mL syringe with an 18 gauge needle.
3. Change the needle to a 21 gauge 1½ inch needle.
4. After preparing the skin, inject in the upper outer quadrant of the gluteus maximus. The solution is viscous and oily. Slow injection (over one minute or longer) is recommended.
5. Applying pressure to the injection site may minimize bruising and swelling.

   If the 5 mL multi-dose vial is used, discard any unused product 5 weeks after first use.

Makena auto-injector (subcutaneous use only)

Makena auto-injector is a single-use, pre-filled, disposable device containing a 27 gauge, 0.5 inch needle that delivers one dose subcutaneously in the back of the upper arm.

Because Makena auto-injector is preservative-free, once the cap is removed the device should be used immediately or discarded.

Rotate the injection site to the alternate arm from the previous week. Do not use in areas where the skin is tender, bruised, red, scaly, raised, thick, or hard. Avoid areas with scars, tattoos, or stretch marks.

The solution is viscous and oily. The auto-injector takes approximately 15 seconds to deliver the dose; when the viewing window is fully blocked (completely orange), the full dose has been administered.

The "Instructions for Use" contains detailed steps for administering the subcutaneous injection using the auto-injector [*see Dosage and Administration (2.3)*]. Read the "Instructions for Use" carefully before administering Makena auto-injector.

2.3 Instructions for Use (Makena Auto-injector)

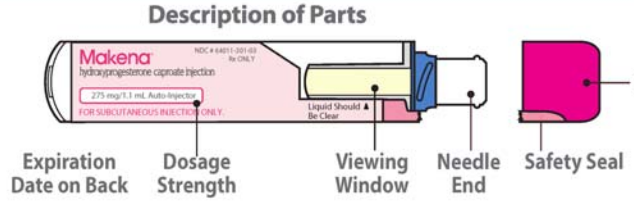
Instructions for Use: Read this carefully before each use.

FOR SUBCUTANEOUS USE ONLY

Makena®
hydroxyprogesterone caproate injection
275 mg/1.1 mL (250 mg/mL) Auto-Injector

For subcutaneous injection.
Single Use.
Administer one injection weekly.
Administration by Healthcare Professionals only.

Description of Parts



Preparation

If you need help or instructions, call:
1-800-411-2510
- **Carefully read all steps before beginning injection.**
- **Injection process must be completed without interruption.**

Supplies You Will Need
- 1 Makena Auto-Injector
- 1 alcohol swab
- 1 cotton ball or gauze

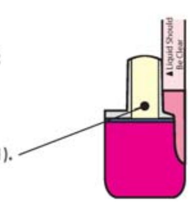
Storage Conditions
- **DO NOT** refrigerate or freeze.
- Protect from light.
- Store at 20° - 25°C (68° - 77° F).
- Keep away from children.

1 Inspect Makena Auto-Injector

- Inspect the Makena Auto-Injector for any visible damage. **DO NOT** use if it appears damaged or broken, or if cap is missing or not secure.
- Check the expiration date. **DO NOT** use if expired.
- Inspect the medication liquid through the Viewing Window; it should be clear to light yellow and free of particles. **(See Figure 1).**

DO NOT use if the liquid is cloudy or if particles are present. You may notice an air bubble, this is normal.

Figure 1:



2 Select & Prepare Subcutaneous Injection Site

Only use the back of either upper arm for injection site.

- Rotate the injection site to the alternate arm from the previous week. **(See Figure 2).**
- Wash your hands with soap and water.
- Wipe the injection site with an alcohol swab.
- Allow the site to dry on its own. **DO NOT** fan or blow on the injection site. **DO NOT** touch the site again before injecting.

DO NOT use in areas where the skin is tender, bruised, red, scaly, raised, thick, or hard.
Avoid areas with scars, tattoos, or stretch marks.

Figure 2:

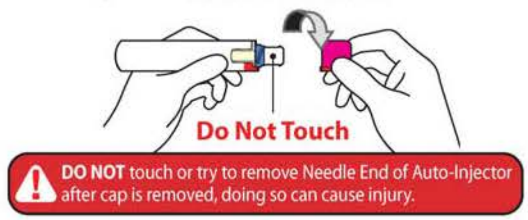
Administering Subcutaneous Injection

3 Remove Cap

- Twist the cap counter clockwise (this will break the red safety seal), and pull cap straight off. **(See Figure 3).**

After the cap is removed, a few drops of liquid may appear - this is normal.
Auto-Injector should be used or discarded once cap is removed.
DO NOT recap for later use. **DO NOT** use if device is dropped.

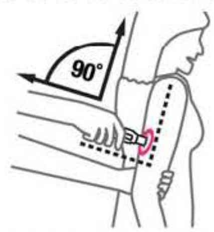
Figure 3: TWIST THEN PULL



4 Position Makena Auto-Injector

- Support the upper arm with the opposite hand. **(See Figure 4).**
- On the relaxed outstretched arm to be injected, gently place the Makena Auto-Injector at a 90° angle to the injection site (back of upper arm, **See Figure 4**).
- Check that you can see the viewing window clearly.

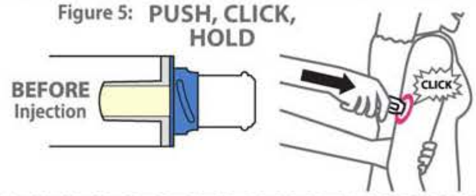
Figure 4:



5 Begin Injection

- It will take approximately 15 seconds for the full dose to be delivered.
  - Push down while supporting the upper arm with the opposite hand. A click will occur when the injection begins. **(See figure 5).**
  - Hold the Auto-Injector against the arm.

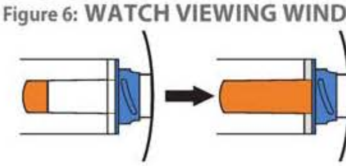
Figure 5: PUSH, CLICK, HOLD



6 Complete Injection

- While holding against the arm, watch the viewing window until it turns orange
  Verify viewing window has turned completely orange before removing from injection site.
- It is normal if there is slight bleeding after injection. If this occurs, hold a cotton ball or gauze on the area with light pressure for a few seconds. **DO NOT** rub the area.

Figure 6: WATCH VIEWING WINDOW



- **A fully blocked (completely orange) window confirms the dose was administered.**

If the Viewing Window is not blocked:
- **DO NOT** use another Makena Auto-Injector or attempt another injection.
- **Call 1-877-411-2510** for assistance.

Record the location of the injection site in the patient's record to ensure rotation of the injection site each week.

7 Disposal After Injection

- After completing injection, dispose of Makena Auto-Injector and cap in a sharps disposal container immediately after use.

FOR POSITION ONLY
128 Barcode

Distributed by: AMAG Pharmaceuticals, Inc.
Waltham, MA 02451

900232-001 rev04

3 DOSAGE FORMS AND STRENGTHS

Subcutaneous injection: 275 mg/1.1 mL clear yellow solution in single-use auto-injector.

Intramuscular injection: 250 mg/mL clear yellow solution in single-dose vials.

Intramuscular injection: 1250 mg/5 mL (250 mg/mL) clear yellow solution in multiple-dose vials.

4 CONTRAINDICATIONS

Do not use Makena in women with any of the following conditions:

- Current or history of thrombosis or thromboembolic disorders
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
- Cholestatic jaundice of pregnancy
- Liver tumors, benign or malignant, or active liver disease
- Uncontrolled hypertension

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders

Discontinue Makena if an arterial or deep venous thrombotic or thromboembolic event occurs.

5.2 Allergic Reactions

Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil. Consider discontinuing the drug if such reactions occur.

5.3 Decrease in Glucose Tolerance

A decrease in glucose tolerance has been observed in some patients on progestin treatment. The mechanism of this decrease is not known. Carefully monitor prediabetic and diabetic women while they are receiving Makena.

5.4 Fluid Retention

Because progestational drugs may cause some degree of fluid retention, carefully monitor women with conditions that might be influenced by this effect (e.g., preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction).

5.5 Depression

Monitor women who have a history of clinical depression and discontinue Makena if clinical depression recurs.

5.6 Jaundice

Carefully monitor women who develop jaundice while receiving Makena and consider whether the benefit of use warrants continuation.

5.7 Hypertension

Carefully monitor women who develop hypertension while receiving Makena and consider whether the benefit of use warrants continuation.

6 ADVERSE REACTIONS

For the most serious adverse reactions to the use of progestins, see *Warnings and Precautions (5)*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a vehicle (placebo)-controlled clinical trial of 463 pregnant women at risk for spontaneous preterm delivery based on obstetrical history, 310 received 250 mg of Makena and 153 received a vehicle formulation containing no drug by a weekly intramuscular injection beginning at 16 to 20 weeks of gestation and continuing until 37 weeks of gestation or delivery, whichever occurred first. [*See Clinical Studies (14.1).*]

Certain pregnancy-related fetal and maternal complications or events were numerically increased in the Makena-treated subjects as compared to control subjects, including miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios (Tables 1 and 2).

Table 1 Selected Fetal Complications

Pregnancy Complication	Makena n/N	Control n/N
Miscarriage (< 20 weeks)[1]	5/209	0/107
Stillbirth (≥ 20 weeks)[2]	6/305	2/153

[1] N = Total number of subjects enrolled prior to 20 weeks 0 days
[2] N = Total number of subjects at risk ≥ 20 weeks

Table 2 Selected Maternal Complications

Pregnancy Complication	Makena N=310 %	Control N=153 %
Admission for preterm labor[1]	16.0	13.8
Preeclampsia or gestational hypertension	8.8	4.6
Gestational diabetes	5.6	4.6
Oligohydramnios	3.6	1.3

[1] Other than delivery admission.

Common Adverse Reactions:

The most common adverse reaction with intramuscular injection was injection site pain, which was reported after at least one injection by 34.8% of the Makena group and 32.7% of the control group. Table 3 lists adverse reactions that occurred in ≥ 2% of subjects and at a higher rate in the Makena group than in the control group.

Table 3 Adverse Reactions Occurring in ≥ 2% of Makena-Treated Subjects and at a Higher Rate than Control Subjects

Preferred Term	Makena N=310 %	Control N=153 %
Injection site pain	34.8	32.7
Injection site swelling	17.1	7.8
Urticaria	12.3	11.1
Pruritus	7.7	5.9
Injection site pruritus	5.8	3.3
Nausea	5.8	4.6
Injection site nodule	4.5	2.0
Diarrhea	2.3	0.7

In the clinical trial using intramuscular injection, 2.2% of subjects receiving Makena were reported as discontinuing therapy due to adverse reactions compared to 2.6% of control subjects. The most common adverse reactions that led to discontinuation in both groups were urticaria and injection site pain/swelling (1% each).

Pulmonary embolus in one subject and injection site cellulitis in another subject were reported as serious adverse reactions in Makena-treated subjects.

Two clinical studies were conducted in healthy post-menopausal women, comparing Makena administered via subcutaneous auto-injector to Makena administered as an intramuscular injection. In the first study, injection site pain occurred in 3/30 (10%) of subjects who used the subcutaneous auto-injector vs. 2/30 (7%) of subjects receiving intramuscular injection. In the second study, injection site pain occurred in 20/59 (34%) of subjects who used the subcutaneous auto-injector vs. 5/61 (8%) of subjects receiving intramuscular injection.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Makena. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Body as a whole*: Local injection site reactions (including erythema, urticaria, rash, irritation, hypersensitivity, warmth); fatigue; fever; hot flashes/flushes
- *Digestive disorders*: Vomiting
- *Infections*: Urinary tract infection
- *Nervous system disorders*: Headache, dizziness
- *Pregnancy, puerperium and perinatal conditions:* Cervical incompetence, premature rupture of membranes
- *Reproductive system and breast disorders:* Cervical dilation, shortened cervix
- *Respiratory disorders*: Dyspnea, chest discomfort
- *Skin*: Rash

7 DRUG INTERACTIONS

In vitro drug-drug interaction studies were conducted with Makena. Hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations. *In vitro* data indicated that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 [*See Clinical Pharmacology (12.3)*.] No *in vivo* drug-drug interaction studies were conducted with Makena.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Makena is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Fetal, neonatal, and maternal risks are discussed throughout labeling. Data from the placebo-controlled clinical trial and the infant follow-up safety study [*see Clinical Studies (14.1, 14.2)*] did not show a difference in adverse developmental outcomes between children of Makena-treated women and children of control subjects. However, these data are insufficient to determine a drug-associated risk of adverse developmental outcomes as none of the Makena-treated women received the drug during the first trimester of pregnancy. In animal reproduction studies, intramuscular administration of hydroxyprogesterone caproate to pregnant rats during gestation at doses 5 times the human dose equivalent based on a 60-kg human was not associated with adverse developmental outcomes.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Reproduction studies of hydroxyprogesterone caproate administered to various animal species have been reported in the literature. In nonhuman primates, embryolethality was reported in rhesus monkeys administered hydroxyprogesterone caproate up to 2.4 and 24 times the human dose equivalent, but not in cynomolgus monkeys administered hydroxyprogesterone caproate at doses up to 2.4 times the human dose equivalent, every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either strain of monkey.

Reproduction studies have been performed in mice and rats at doses up to 95 and 5, respectively, times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to hydroxyprogesterone caproate.

8.2 Lactation

Risk Summary

Low levels of progestins are present in human milk with the use of progestin-containing products, including hydroxyprogesterone caproate. Published studies have reported no adverse effects of progestins on the breastfed child or on milk production.

8.4 Pediatric Use

Makena is not indicated for use in women under 16 years of age. Safety and effectiveness in patients less than 16 years of age have not been established. A small number of women under age 18 years were studied; safety and efficacy are expected to be the same in women aged 16 years and above as for users 18 years and older [*see Clinical Studies (14)*].

8.6 Hepatic Impairment

No studies have been conducted to examine the pharmacokinetics of Makena in patients with hepatic impairment. Makena is extensively metabolized and hepatic impairment may reduce the elimination of Makena.

10 OVERDOSAGE

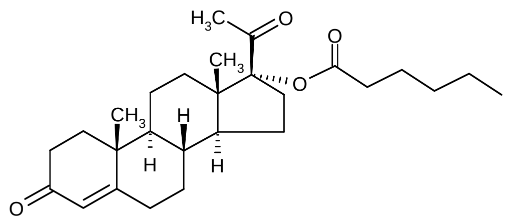
There have been no reports of adverse events associated with overdosage of Makena in clinical trials. In the case of overdosage, the patient should be treated symptomatically.

11 DESCRIPTION

The active pharmaceutical ingredient in Makena is hydroxyprogesterone caproate, a progestin.

The chemical name for hydroxyprogesterone caproate is pregn-4-ene-3,20-dione, 17[(1-oxohexyl)oxy]. It has an empirical formula of $C_{27}H_{40}O_4$ and a molecular weight of 428.60. Hydroxyprogesterone caproate exists as white to practically white crystals or powder with a melting point of 120°-124°C.

The structural formula is:



Makena is a clear, yellow, sterile, non-pyrogenic solution for intramuscular (vials) or subcutaneous (auto-injector) injection. Each 1.1 mL Makena auto-injector for subcutaneous use and each 1 mL single-dose vial for intramuscular use contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in a preservative-free solution containing castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v). Each 5 mL multi-dose vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (28.6%) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which hydroxyprogesterone caproate reduces the risk of recurrent preterm birth is not known.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Makena.

12.3 Pharmacokinetics

Absorption: Female patients with a singleton pregnancy received intramuscular doses of 250 mg hydroxyprogesterone caproate for the reduction of preterm birth starting between 16 weeks 0 days and 20 weeks 6 days. All patients had blood drawn daily for 7 days to evaluate pharmacokinetics.

Table 4 Summary of Mean (Standard Deviation) Pharmacokinetic Parameters for Hydroxyprogesterone Caproate

Group (N)	C_{max} (ng/mL)	T_{max} (days)[a]	$AUC_{(0-t)}$[b] (ng·hr/mL)
Group 1 (N=6)	5.0 (1.5)	5.5 (2.0-7.0)	571.4 (195.2)
Group 2 (N=8)	12.5 (3.9)	1.0 (0.9-1.9)	1269.6 (285.0)
Group 3 (N=11)	12.3 (4.9)	2.0 (1.0-3.0)	1268.0 (511.6)

Blood was drawn daily for 7 days (1) starting 24 hours after the first dose between Weeks 16-20 (Group 1), (2) after a dose between Weeks 24-28 (Group 2), or (3) after a dose between Weeks 32-36 (Group 3)

[a] Reported as median (range)

[b] t = 7 days

For all three groups, peak concentration (C_{max}) and area under the curve ($AUC_{(1\text{-}7\ days)}$) of the mono-hydroxylated metabolites were approximately 3-8-fold lower than the respective parameters for the parent drug, hydroxyprogesterone caproate. While di-hydroxylated and tri-hydroxylated metabolites were also detected in human plasma to a lesser extent, no meaningful quantitative results could be derived due to the absence of reference standards for these multiple hydroxylated metabolites. The relative activity and significance of these metabolites are not known.

The elimination half-life of hydroxyprogesterone caproate, as evaluated from 4 patients in the study who reached full-term in their pregnancies, was 16.4 (±3.6) days. The elimination half-life of the mono-hydroxylated metabolites was 19.7 (±6.2) days.

In a single-dose, open-label, randomized, parallel design bioavailability study in 120 healthy post-menopausal women, comparable systemic exposure of hydroxyprogesterone caproate was seen when Makena was administered subcutaneously with the auto-injector (1.1 mL) in the back of the upper arm and when Makena was dosed intramuscularly (1 mL) in the upper outer quadrant of the gluteus maximus.

Distribution: Hydroxyprogesterone caproate binds extensively to plasma proteins including albumin and corticosteroid binding globulins.

Metabolism: In vitro studies have shown that hydroxyprogesterone caproate can be metabolized by human hepatocytes, both by phase I and phase II reactions. Hydroxyprogesterone caproate undergoes extensive reduction, hydroxylation and conjugation. The conjugated metabolites include sulfated, glucuronidated and acetylated products. In vitro data indicate that the metabolism of hydroxyprogesterone caproate is predominantly mediated by CYP3A4 and CYP3A5. The in vitro data indicate that the caproate group is retained during metabolism of hydroxyprogesterone caproate.

Excretion: Both conjugated metabolites and free steroids are excreted in the urine and feces, with the conjugated metabolites being prominent. Following intramuscular administration to pregnant women at 10-12 weeks gestation, approximately 50% of a dose was recovered in the feces and approximately 30% recovered in the urine.

Drug Interactions

Cytochrome P450 (CYP) enzymes: An *in vitro* inhibition study using human liver microsomes and CYP isoform-selective substrates indicated that hydroxyprogesterone caproate increased the metabolic rate of CYP1A2, CYP2A6, and CYP2B6 by approximately 80%, 150%, and 80%, respectively. However, in another *in vitro* study using human hepatocytes under conditions where the prototypical inducers or inhibitors caused the anticipated increases or decreases in CYP enzyme activities, hydroxyprogesterone caproate did not induce or inhibit CYP1A2, CYP2A6, or CYP2B6 activity. Overall, the findings indicate that hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations.

In vitro data indicated that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Hydroxyprogesterone caproate has not been adequately evaluated for carcinogenicity.

No reproductive or developmental toxicity or impaired fertility was observed in a multigenerational study in rats. Hydroxyprogesterone caproate administered intramuscularly, at gestational exposures up to 5 times the recommended human dose, had no adverse effects on the parental (F_0) dams, their developing offspring (F_1), or the latter offspring's ability to produce a viable, normal second (F_2) generation.

14 CLINICAL STUDIES

14.1 Clinical Trial to Evaluate Reduction of Risk of Preterm Birth

In a multicenter, randomized, double-blind, vehicle (placebo)-controlled clinical trial, the safety and effectiveness of Makena for the reduction of the risk of spontaneous preterm birth was studied in women with a singleton pregnancy (age 16 to 43 years) who had a documented history of singleton spontaneous preterm birth (defined as delivery at less than 37 weeks of gestation following spontaneous preterm labor or premature rupture of membranes). At the time of randomization (between 16 weeks, 0 days and 20 weeks, 6 days of gestation), an ultrasound examination had confirmed gestational age and no known fetal anomaly. Women were excluded for prior progesterone treatment or heparin therapy during the current pregnancy, a history of thromboembolic disease, or maternal/obstetrical complications (such as current or planned cerclage, hypertension requiring medication, or a seizure disorder).

A total of 463 pregnant women were randomized to receive either Makena (N=310) or vehicle (N=153) at a dose of 250 mg administered weekly by intramuscular injection starting between 16 weeks, 0 days and 20 weeks, 6 days of gestation, and continuing until 37 weeks of gestation or delivery. Demographics of the Makena-treated women were similar to those in the control group, and included: 59.0% Black, 25.5% Caucasian, 13.9% Hispanic and 0.6% Asian. The mean body mass index was 26.9 kg/m^2.

The proportions of women in each treatment arm who delivered at < 37 (the primary study endpoint), < 35, and < 32 weeks of gestation are displayed in Table 5.

Table 5 Proportion of Subjects Delivering at < 37, < 35 and < 32 Weeks Gestational Age (ITT Population)

Delivery Outcome	Makena[1] (N=310) %	Control (N=153) %	Treatment difference and 95% Confidence Interval[2]
<37 weeks	37.1	54.9	-17.8% [-28.0%, -7.4%]
<35 weeks	21.3	30.7	-9.4% [-19.0%, -0.4%]
<32 weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]

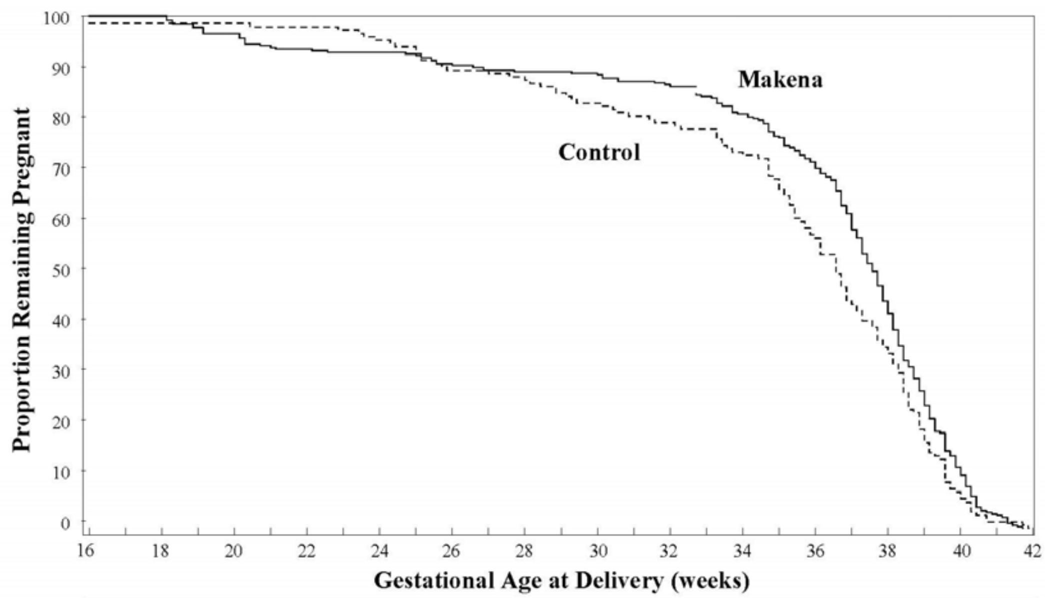
[1] Four Makena-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact (18^4, 22^0, 34^3 and 36^4 weeks).

[2] Adjusted for interim analysis.

Compared to controls, treatment with Makena reduced the proportion of women who delivered preterm at < 37 weeks. The proportions of women delivering at < 35 and < 32 weeks also were lower among women treated with Makena. The upper bounds of the confidence intervals for the treatment difference at < 35 and < 32 weeks were close to zero. Inclusion of zero in a confidence interval would indicate the treatment difference is not statistically significant. Compared to the other gestational ages evaluated, the number of preterm births at < 32 weeks was limited.

After adjusting for time in the study, 7.5% of Makena-treated subjects delivered prior to 25 weeks compared to 4.7% of control subjects; see Figure 1.

Figure 1 Proportion of Women Remaining Pregnant as a Function of Gestational Age



Number at Risk

Makena	3	108	215	296	293	286	281	280	273	259	228	141	38	0
Control	2	56	113	152	148	139	137	129	123	114	89	55	11	0

The rates of fetal losses and neonatal deaths in each treatment arm are displayed in Table 6. Due to the higher rate of miscarriages and stillbirths in the Makena arm, there was no overall survival difference demonstrated in this clinical trial.

Table 6 Fetal Losses and Neonatal Deaths

Complication	Makena N=306 [A] n (%) [B]	Control N=153 n (%) [B]
Miscarriages <20 weeks gestation [C]	5 (2.4)	0
Stillbirth	6 (2.0)	2 (1.3)
Antepartum stillbirth	*5 (1.6)*	*1 (0.6)*
Intrapartum stillbirth	*1 (0.3)*	*1 (0.6)*
Neonatal deaths	8 (2.6)	9 (5.9)
Total Deaths	**19 (6.2)**	**11 (7.2)**

[A] Four of the 310 Makena-treated subjects were lost to follow-up and stillbirth or neonatal status could not be determined
[B] Percentages are based on the number of enrolled subjects and not adjusted for time on drug
[C] Percentage adjusted for the number of at risk subjects (n=209 for Makena, n=107 for control) enrolled at <20 weeks gestation.

A composite neonatal morbidity/mortality index evaluated adverse outcomes in live births. It was based on the number of neonates who died or experienced respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, proven sepsis, or necrotizing enterocolitis. Although the proportion of neonates who experienced 1 or more events was numerically lower in the Makena arm (11.9% vs. 17.2%), the number of adverse outcomes was limited and the difference between arms was not statistically significant.

14.2 Infant Follow-Up Safety Study

Infants born to women enrolled in this study, and who survived to be discharged from the nursery, were eligible for participation in a follow-up safety study. Of 348 eligible offspring, 79.9% enrolled: 194 children of Makena-treated women and 84 children of control subjects. The primary endpoint was the score on the Ages & Stages Questionnaire (ASQ), which evaluates communication, gross motor, fine motor, problem solving, and personal/social parameters. The proportion of children whose scores met the screening threshold for developmental delay in each developmental domain was similar for each treatment group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Makena auto-injector (for subcutaneous injection)

Makena auto-injector (NDC 64011-301-03) is supplied as 1.1 mL of a clear yellow sterile preservative-free solution in an auto-injector containing a pre-filled syringe. Each 1.1 mL auto-injector contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v).

Single unit carton: Contains one 1.1 mL single-patient-use auto-injector of Makena containing 275 mg of hydroxyprogesterone caproate.

Store at 20° to 25°C (68° to 77°F). Do not refrigerate or freeze.

Caution: Protect auto-injector from light. Store auto-injector in its box.

Makena single- and multi-dose vials (for intramuscular injection)

Makena (NDC 64011-247-02) is supplied as 1 mL of a sterile preservative-free clear yellow solution in a single-dose glass vial.

Each 1 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v).

Single unit carton: Contains one 1 mL single-dose vial of Makena containing 250 mg of hydroxyprogesterone caproate.

Makena (NDC 64011-243-01) is supplied as 5 mL of a sterile clear yellow solution in a multi-dose glass vial.

Each 5 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

Single unit carton: Contains one 5 mL multi-dose vial of Makena (250 mg/mL) containing 1250 mg of hydroxyprogesterone caproate.

Store at 20° to 25°C (68° to 77°F). Do not refrigerate or freeze.

Use multi-dose vials within 5 weeks after first use.

Caution: Protect vial from light. Store vial in its box. Store upright.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Counsel patients that Makena injections may cause pain, soreness, swelling, itching or bruising. Inform the patient to contact her physician if she notices increased discomfort over time, oozing of blood or fluid, or inflammatory reactions at the injection site [*see Adverse Reactions (6.1)*].

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Waltham, MA 02451

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PATIENT INFORMATION
MAKENA (mah-KEE-na)
(hydroxyprogesterone caproate injection)
auto-injector for subcutaneous use
MAKENA (mah-KEE-na)
(hydroxyprogesterone caproate injection)
vial for intramuscular use

Read this Patient Information leaflet before you receive MAKENA. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is MAKENA?

MAKENA is a prescription hormone medicine (progestin) used in women who are pregnant and who have delivered a baby too early (preterm) in the past. MAKENA is used in these women to help lower the risk of having a preterm baby again. It is not known if MAKENA reduces the number of babies who are born with serious medical conditions or die shortly after birth. MAKENA is for women who:

- Are pregnant with one baby.
- Have had a preterm delivery of one baby in the past.

MAKENA is not intended for use to stop active preterm labor.
It is not known if MAKENA is safe and effective in women who have other risk factors for preterm birth.
MAKENA is not for use in women under 16 years of age.

Who should not receive MAKENA?

MAKENA should not be used if you have:

- blood clots or other blood clotting problems now **or** in the past
- breast cancer or other hormone-sensitive cancers now **or** in the past
- unusual vaginal bleeding not related to your current pregnancy
- yellowing of your skin due to liver problems during your pregnancy
- liver problems, including liver tumors
- high blood pressure that is not controlled

What should I tell my healthcare provider before receiving MAKENA?

Before you receive MAKENA, tell your healthcare provider about all of your medical conditions, including if you have:

- a history of allergic reaction to hydroxyprogesterone caproate, castor oil, or any of the other ingredients in MAKENA. See the end of this Patient Information leaflet for a complete list of ingredients in MAKENA.
- diabetes or pre-diabetes.
- epilepsy (seizures).
- migraine headaches.
- asthma.
- heart problems.
- kidney problems.
- depression.
- high blood pressure.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
MAKENA may affect the way other medicines work, and other medicines may affect how MAKENA works.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I receive MAKENA?

- **Do not** give yourself MAKENA injections. A healthcare provider will give you the MAKENA injection 1 time each week (every 7 days) either:
  - in the back of your upper arm as an injection under the skin (subcutaneous), **or**
  - in the upper outer area of the buttocks as an injection into the muscle (intramuscular).
- You will start receiving MAKENA injections anytime from 16 weeks and 0 days of your pregnancy, up to 20 weeks and 6 days of your pregnancy.
- You will continue to receive MAKENA injections 1 time each week until week 37 (through 36 weeks and 6 days) of your pregnancy or when your baby is delivered, whichever comes first.

What are the possible side effects of MAKENA?

MAKENA may cause serious side effects, including:

- **Blood clots**. Symptoms of a blood clot may include:
  - leg swelling
  - redness in your leg
  - a spot on your leg that is warm to the touch
  - leg pain that gets worse when you bend your foot

  Call your healthcare provider right away if you get any of the symptoms above during treatment with MAKENA.
- **Allergic reactions**. Symptoms of an allergic reaction may include:
  - hives
  - itching
  - swelling of the face

  Call your healthcare provider right away if you get any of the symptoms above during treatment with MAKENA.
- **Decrease in glucose (blood sugar) tolerance**. Your healthcare provider will need to monitor your blood sugar while taking MAKENA if you have diabetes or pre-diabetes.
- **Your body may hold too much fluid (fluid retention)**.
- **Depression**.
- **Yellowing of your skin and the whites of your eyes (jaundice)**.
- **High blood pressure**.

The most common side effects of MAKENA include:

- pain, swelling, itching or a hard bump at the injection site
- hives
- itching
- nausea
- diarrhea

Call your healthcare provider if you have the following at your injection site:

- increased pain over time
- oozing of blood or fluid
- swelling

Other side effects that may happen more often in women who receive MAKENA include:

- Miscarriage (pregnancy loss before 20 weeks of pregnancy)
- Stillbirth (fetal death occurring during or after the 20th week of pregnancy)
- Hospital admission for preterm labor
- Preeclampsia (high blood pressure and too much protein in your urine)
- Gestational hypertension (high blood pressure caused by pregnancy)
- Gestational diabetes
- Oligohydramnios (low amniotic fluid levels)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of MAKENA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MAKENA?

- **MAKENA auto-injector for subcutaneous use**:
  - Store the auto-injector at room temperature between 68°F to 77°F (20°C to 25°C).
  - Do not refrigerate or freeze.
  - Protect the auto-injector from light.
  - Store the auto-injector in its box.
- **MAKENA vial for intramuscular use**:
  - Store the vial at room temperature between 68°F to 77°F (20°C to 25°C).
  - Do not refrigerate or freeze.
  - Protect the vial from light.
  - Store the vial in its box in an upright position.

Keep MAKENA and all medicines out of the reach of children.

General information about the safe and effective use of MAKENA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use MAKENA for a condition for which it was not prescribed. Do not give MAKENA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about MAKENA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about MAKENA that is written for health professionals.

What are the ingredients in MAKENA?

Active ingredient: hydroxyprogesterone caproate

Inactive ingredients: castor oil and benzyl benzoate. 5 mL multi-dose vials also contain benzyl alcohol (a preservative).

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For more information, go to www.MAKENA.com or call AMAG Pharmaceuticals Customer Service at the toll-free number 1-877-411-2510.