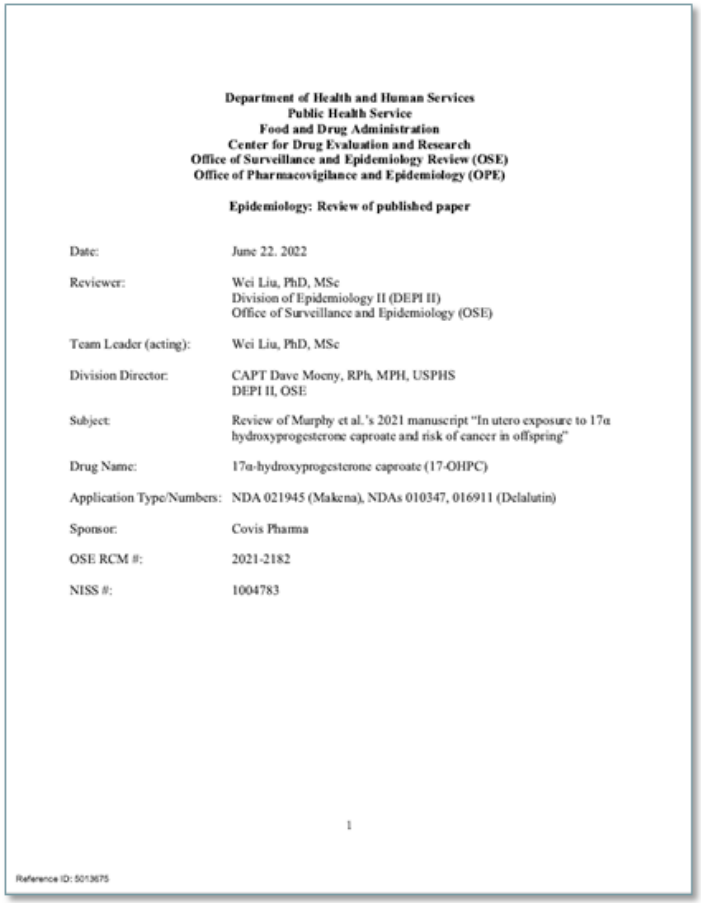
COVIS - Questions to CDER

Day 1 – October 17, 2022

CDER Evaluation of the Murphy Article

Division of Epidemiology II – 6/22/22

- "Potential for chance findings due to the large number of statistical analyses performed, the small number of exposed cases, lack of an appropriate conceptual framework to justify the proper use of statistical model, and the high likelihood for residual confounding are major study limitations."
- "not of sufficient quality to support regulatory decision-making"
- "insufficient evidence to support regulatory action"



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

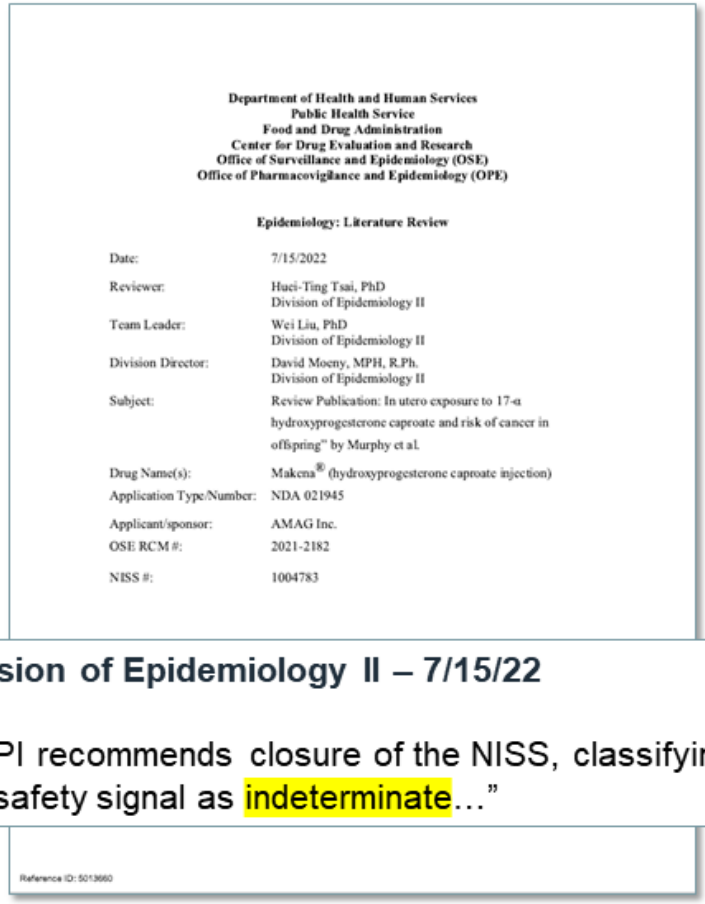
Epidemiology: Review of published paper

Date:	June 22. 2022
Reviewer:	Wei Liu, PhD, MSc Division of Epidemiology II (DEPI II) Office of Surveillance and Epidemiology (OSE)
Team Leader (acting):	Wei Liu, PhD, MSc
Division Director:	CAPT Dave Moeny, RPh, MPH, USPHS DEPI II, OSE
Subject:	Review of Murphy et al.'s 2021 manuscript "In utero exposure to 17α hydroxyprogesterone caproate and risk of cancer in offspring"
Drug Name:	17α-hydroxyprogesterone caproate (17-OHPC)
Application Type/Numbers:	NDA 021945 (Makena), NDAs 010347, 016911 (Delalutin)
Sponsor:	Covis Pharma
OSE RCM #:	2021-2182
NISS #:	1004783

1

Reference ID: 5013675

CDER Evaluation of the Murphy Article



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

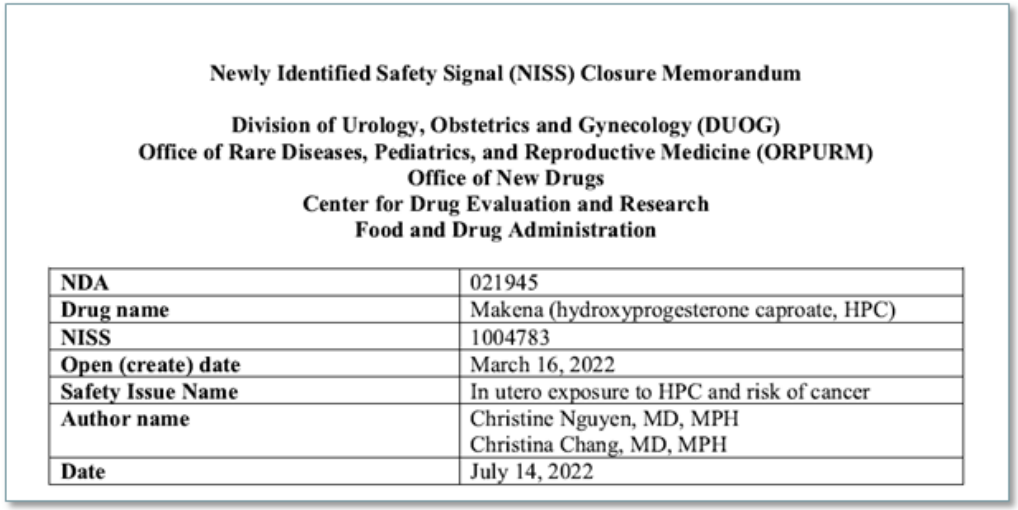
Epidemiology: Literature Review

Date:	7/15/2022
Reviewer:	Huei-Ting Tsai, PhD Division of Epidemiology II
Team Leader:	Wei Liu, PhD Division of Epidemiology II
Division Director:	David Moeny, MPH, R.Ph. Division of Epidemiology II
Subject:	Review Publication: In utero exposure to 17-α hydroxyprogesterone caproate and risk of cancer in offspring" by Murphy et al.
Drug Name(s):	Makena® (hydroxyprogesterone caproate injection)
Application Type/Number:	NDA 021945
Applicant/sponsor:	AMAG Inc.
OSE RCM #:	2021-2182
NISS #:	1004783

Reference ID: 5013660

Division of Epidemiology II – 7/15/22

"DEPI recommends closure of the NISS, classifying the safety signal as indeterminate…"



Newly Identified Safety Signal (NISS) Closure Memorandum

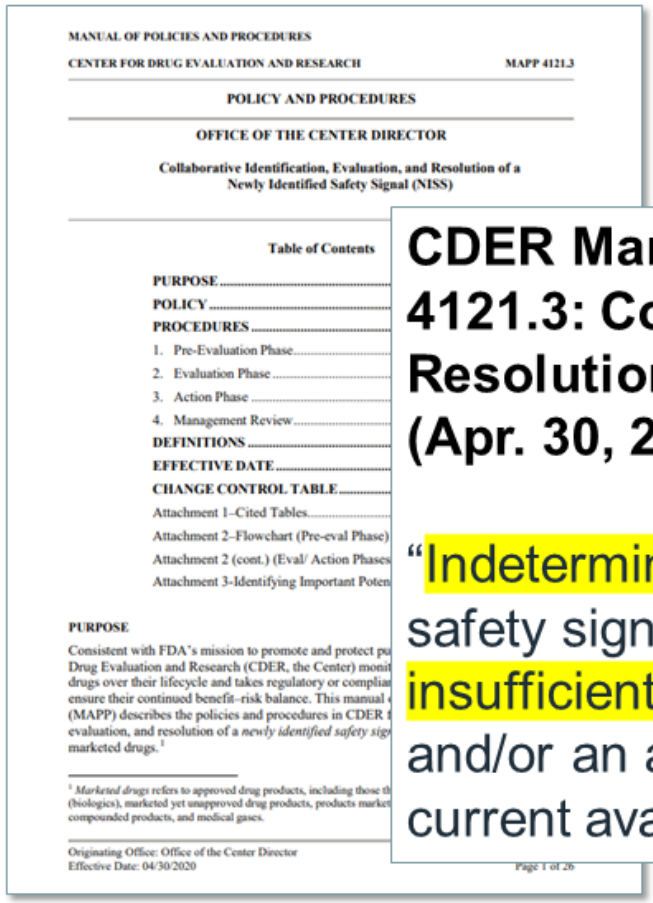
Division of Urology, Obstetrics and Gynecology (DUOG)
Office of Rare Diseases, Pediatrics, and Reproductive Medicine (ORPURM)
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

NDA	021945
Drug name	Makena (hydroxyprogesterone caproate, HPC)
NISS	1004783
Open (create) date	March 16, 2022
Safety Issue Name	In utero exposure to HPC and risk of cancer
Author name	Christine Nguyen, MD, MPH Christina Chang, MD, MPH
Date	July 14, 2022

Division of Urology, Obstetrics and Gynecology (DUOG) – 7/14/22

"DEPI recommended that this NISS be closed with a finding of an "indeterminate" status. DEPI plans to undertake active surveillance of this issue on an ongoing basis by utilizing PubMed automated search emails. DUOG agrees with this recommendation. The NISS can be closed."

CDER Evaluation of the Murphy Article



MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 4121.3

POLICY AND PROCEDURES

OFFICE OF THE CENTER DIRECTOR

Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS)

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PURPOSE

POLICY

PROCEDURES

1. Pre-Evaluation Phase
2. Evaluation Phase
3. Action Phase
4. Management Review

DEFINITIONS

EFFECTIVE DATE

CHANGE CONTROL TABLE

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Attachment 2–Flowchart (Pre-eval Phase)

Attachment 2 (cont.) (Eval/ Action Phases

Attachment 3-Identifying Important Poten

PURPOSE

Consistent with FDA's mission to promote and protect pu
Drug Evaluation and Research (CDER, the Center) monit
drugs over their lifecycle and takes regulatory or compliat
ensure their continued benefit–risk balance. This manual
(MAPP) describes the policies and procedures in CDER
evaluation, and resolution of a *newly identified safety sig*
marketed drugs.[1]

[1] *Marketed drugs* refers to approved drug products, including those th
(biologics), marketed yet unapproved drug products, products market
compounded products, and medical gases.

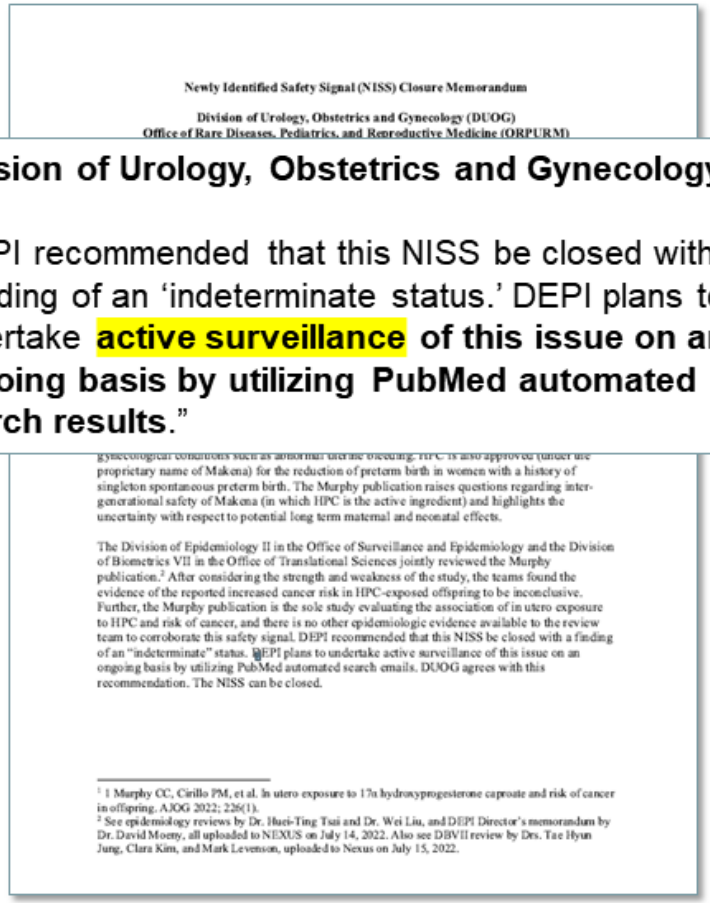
Originating Office: Office of the Center Director
Effective Date: 04/30/2020

Page 1 of 26

CDER Manual of Policies and Procedures (MAPP) 4121.3: Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS) (Apr. 30, 2020)

"Indeterminate safety signal (as defined for this MAPP): A safety signal for which current available information is insufficient to support a causal association between a drug and/or an adverse event and does not, based on the current available information, warrant further evaluation."

“Further Surveillance”



Newly Identified Safety Signal (NISS) Closure Memorandum

Division of Urology, Obstetrics and Gynecology (DUOG)
Office of Rare Diseases, Pediatrics, and Reproductive Medicine (ORPURM)

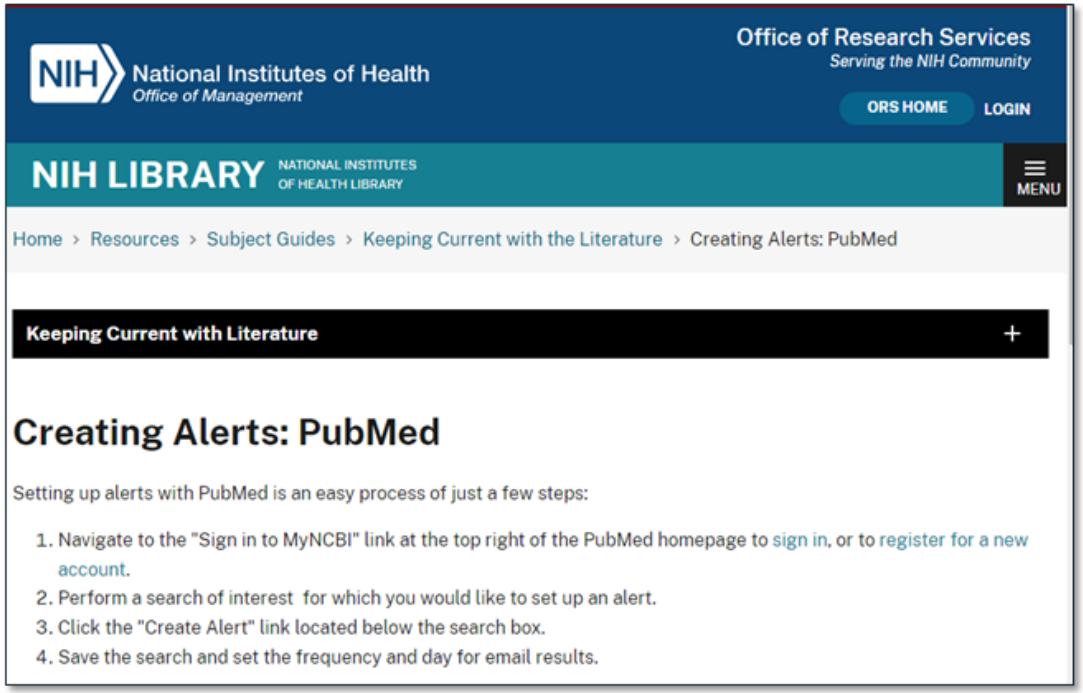
proprietary name of Makena) for the reduction of preterm birth in women with a history of singleton spontaneous preterm birth. The Murphy publication raises questions regarding inter-generational safety of Makena (in which HPC is the active ingredient) and highlights the uncertainty with respect to potential long term maternal and neonatal effects.

The Division of Epidemiology II in the Office of Surveillance and Epidemiology and the Division of Biometrics VII in the Office of Translational Sciences jointly reviewed the Murphy publication.[2] After considering the strength and weakness of the study, the teams found the evidence of the reported increased cancer risk in HPC-exposed offspring to be inconclusive. Further, the Murphy publication is the sole study evaluating the association of in utero exposure to HPC and risk of cancer, and there is no other epidemiologic evidence available to the review team to corroborate this safety signal. DEPI recommended that this NISS be closed with a finding of an “indeterminate” status. DEPI plans to undertake active surveillance of this issue on an ongoing basis by utilizing PubMed automated search emails. DUOG agrees with this recommendation. The NISS can be closed.

[1] 1 Murphy CC, Cirillo PM, et al. In utero exposure to 17α hydroxyprogesterone caproate and risk of cancer in offspring. AJOG 2022; 226(1).
[2] See epidemiology reviews by Dr. Huei-Ting Tsai and Dr. Wei Liu, and DEPI Director’s memorandum by Dr. David Moeny, all uploaded to NEXUS on July 14, 2022. Also see DBVII review by Drs. Tae Hyun Jung, Clara Kim, and Mark Levenson, uploaded to Nexus on July 15, 2022.

Division of Urology, Obstetrics and Gynecology

“DEPI recommended that this NISS be closed with a finding of an ‘indeterminate status.’ DEPI plans to undertake **active surveillance of this issue on an ongoing basis by utilizing PubMed automated search results**.”



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Keeping Current with Literature +

Creating Alerts: PubMed

Setting up alerts with PubMed is an easy process of just a few steps:

1. Navigate to the "Sign in to MyNCBI" link at the top right of the PubMed homepage to sign in, or to register for a new account.
2. Perform a search of interest for which you would like to set up an alert.
3. Click the "Create Alert" link located below the search box.
4. Save the search and set the frequency and day for email results.

CDER's Table 22 from its 2019 Briefing Book: Summary of PTB < 35^0 Weeks by Subgroup

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)
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.

FDA Briefing Document 2019 (https://www.fda.gov/media/132003/download)

Hakim et. al., 2021

Original Article

Effectiveness of 17-OHP for Prevention of Recurrent Preterm Birth: A Retrospective Cohort Study

Joe B. Hakim, BSc[1] Amy Zhou, MSc[2] Sonia Hernandez-Diaz, MD, PhD[3] Jessica M. Hart, MD[4] Blair J. Wylie, MD, MPH[4,#] Andrew L. Beam, PhD[3,5,#]

[1]Department of Health Sciences and Technology, Harvard-MIT, Cambridge, Massachusetts
[2]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts
[3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts
[4]Divisiont of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, Massachusetts
[5]Department of Biomedical Informatics, Harvard Medical School, Boston, Massachusetts

Address for correspondence Andrew L. Beam, PhD, 820C Kresge Hall 677 Huntington Avenue, Boston, MA 02115 (e-mail: andrew_beam@hms.harvard.edu).

Am J Perinatol

Hakim et. al., 2021

Supplementary Table S2 Summary statistics for the cohort matching inclusion criteria, stratified by treatment assignment

	Treated with 17-OHP	Not treated with 17-OHP	*p*-Value
Demographic factors, aggregated over zip codes			
Median income in zip code Mean (SD)	73,486.69 (28,147.72)	72,172.91 (25,763.87)	0.265
Percentage non-white population in zip code Mean (SD)	0.26 (0.20)	0.28 (0.19)	0.082
Percentage of population in zip code without high school degree Mean (SD)	0.07 (0.05)	0.07 (0.05)	0.527
Percentage of population in zip code unemployed Mean (SD)	0.25 (0.05)	0.25 (0.06)	0.399

Abbreviations: 17-OHP, 17-α-hydroxyprogesterone caproate; GA, gestational age; ICD, International Classification of Disease; PPROM, preterm premature rupture of membrane; SD, standard deviation.

Note: Categorical variables are reported as *n* (%). Continuous variables are reported as median (SD). More details including calculation of *p*-values comparing the treated and untreated groups are described in the "Statistical methods" section, "Quantitative variables" subsection.

Hakim et. al., 2021

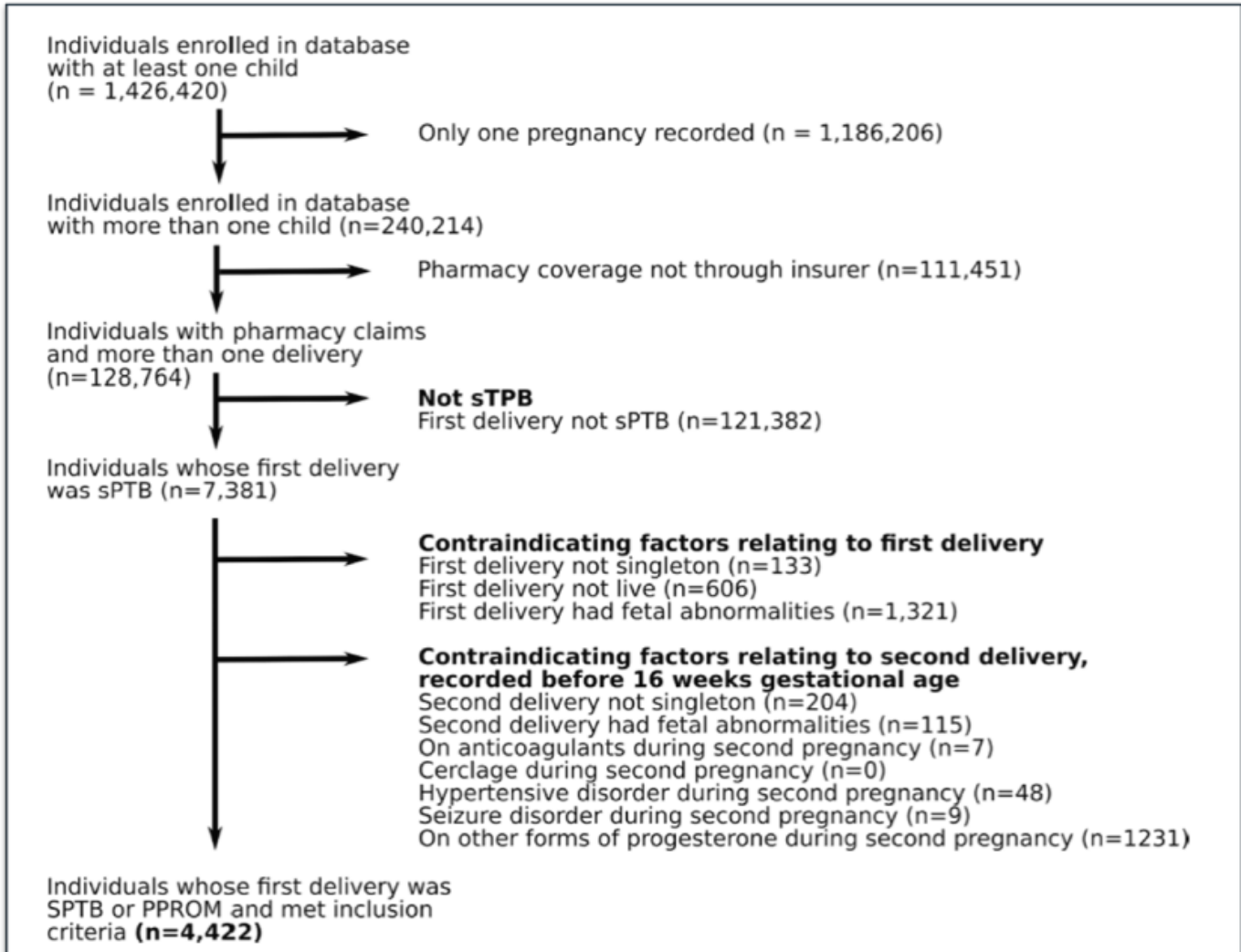

Fig. 1 Flow diagram illustrating the number of individuals matching each inclusion criteria. Abbreviations: sPTB, spontaneous preterm birth (including preterm prelabor rupture of membranes).

Wang et. al., 2021

Original Article

Eligibility, Utilization, and Effectiveness of 17-Alpha Hydroxyprogesterone Caproate (17OHPC) in a Statewide Population-Based Cohort of Medicaid Enrollees

Xi Wang, PhD[1] Stephanie M. Garcia, MPH[1] Katherine S. Kellom, BS[1] Rupsa C. Boelig, MD[2] Meredith Matone, DrPH[1,3]

[1] PolicyLab, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
[2] Department of Obstetrics and Gynecology, Department of Pharmacology and Experimental Therapeutics, Division of Maternal Fetal Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania
[3] University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

Address for correspondence Meredith Matone, DrPH, MHS, University of Pennsylvania Perelman School of Medicine; Scientific Director, PolicyLab, Children's Hospital of Philadelphia, 2716 South Street, 10-121, Philadelphia, PA 19146 (e-mail: MatoneM@email.chop.edu).

Am J Perinatol

Wang et. al., 2021

Table 3 Use of 17OHPC in eligible pregnancies from 2014 to 2016 in Pennsylvania

		n	%
Among all 17OHPC-eligible pregnancies	4,781		
Received 17OHPC prescription			
Yes	1,364	28.5	
No	3,417	71.5	
Among 17OHPC recipients	1,364		
Number of 17OHPC doses per recipient			
1–5	199	14.6	
6–10	208	15.2	
11–15	272	19.9	
≥16	685	50.2	
17OHPC treatment initiation time (Gestational week at the first 17OHPC pharmacy claim)			
< 16 weeks	436	32.0	
16–26 weeks	848	62.2	
≥27 weeks	79	5.8	

Abbreviation: 17OHPC, 17 α-hydroxyprogesterone caproate.

"Among eligible live births, 28.5% received at least one 17OHPC injection. For women with treatment initiation, 15% experienced low adherence of one to five doses, while **50% received more than 16 doses in accordance with clinical guideline recommendations**."

Wang et. al., 2021

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Abbreviation: 17OHPC, 17 α-hydroxyprogesterone caproate.

Wang et. al., 2021

Table 4 Associations of demographic and clinical characteristics with the use of 17OHPC among eligible mothers from 2014 to 2016 in Pennsylvania: Adjusted OR and 95% CI from the multivariate logistic regression model

	Eligible mothers *who received* 17OHPC (Column %)	Eligible mothers *who did not receive* 17OHPC (Column %)	Adjusted OR for 17OHPC use (95% CI) [a]
Characteristics of previous spontaneous singleton preterm birth			
Gestational age at delivery			
21–27 weeks	18.9%	7.4%	2.90 (1.92–4.38)
28–32 weeks	20.5%	9.3%	3.02 (2.32–3.94)
33–34 weeks	23.8%	16.1%	2.12 (1.74–2.59)
35–36 weeks	36.8%	67.3%	*Reference*
Child's birth weight			
< 1,500 g	27.3%	11.0%	1.77 (1.21–2.59)
1,500–2,499 g	46.8%	38.2%	1.60 (1.33–1.92)
≥2,500 g	25.9%	50.7%	*Reference*

COVIS Affirmative Presentation

Day 2 – October 18, 2022

MAKENA®
(hydroxyprogesterone caproate injection)

October 17-19, 2022

Hearing with Respect to CDER's Proposal to Withdraw Approval

Introduction

Raghav Chari, PhD

Chief Innovation Officer

COVIS Pharma

Covis Acquired AMAG Pharmaceuticals in Late 2020 and Became Sponsor of Makena in March 2021

- Acquisition occurred after the 2019 BRUDAC meeting and following CDER's proposal to withdrawal Makena from the market
- Makena is critically important for women at risk of preterm birth

Covis is committed to conducting additional studies and executing a robust plan to address the outstanding questions

Preterm Birth – Points of Agreement

1. Preterm birth is a public health priority
2. Preterm birth impacts a substantial number of women in U.S.
   - Disproportionally impacts women who are Black, other minorities, or socioeconomically disadvantaged
   - 1 in 10 babies are born prematurely in the U.S.
3. Makena and its generics are the only FDA-approved treatment for reducing the risk of preterm birth
4. Gestational age of delivery is an “intermediate clinical endpoint,” which is itself a measurement of a therapeutic effect
   - Strongly correlated with neonatal health

Meis Trial (Trial 002) – Points of Agreement

1. CDER stated Meis was **"adequate, well-controlled and very persuasive,"** and provided **"compelling"** evidence of clinical benefit[1]
2. Meis trial met its primary endpoint and all pre-specified secondaries for preterm birth
   - Makena significantly reduced preterm births < 37 weeks, < 35 weeks, and < 32 weeks gestation vs. placebo
3. Makena became widely used to reduce the risk of preterm birth in women with a history of spontaneous preterm birth
   - American College of Obstetricians and Gynecologists (ACOG)
   - Society for Maternal-Fetal Medicine (SMFM)

1. CDER 2019 Briefing Document

PROLONG Trial (Trial 003) – Points of Agreement

1. PROLONG did not verify the clinical benefit of Makena on neonatal morbidity and mortality
2. PROLONG did not show an effect on reduction of preterm birth rates
3. PROLONG enrolled different populations in terms of risk factors for preterm birth compared with Meis trial

October 2019, Bone Reproductive and Urologic Drugs Advisory Committee (BRUDAC)

- BRUDAC reached a divided conclusion
- 9 voted for CDER to pursue withdrawal
- 7 voted to leave Makena on the market with the requirement that new confirmatory data be generated
  - Of the 6 OBGYNs, 5 voted to leave Makena on the market

Covis is Committed to Confirming Clinical Benefit of Makena

1

Partial Withdrawal to Higher-Risk Target Population

- Narrow labeling to use in a higher-risk target population identified through our analysis of Meis and PROLONG
- No active promotion of Makena

2

Conduct a Randomized Controlled Trial (RCT)

- Confirm Makena's effect on intermediate clinical endpoint in the identified higher-risk target patient population – completed within 4- to 6-years

3

Optionally, Also Conduct an Observational Study

- Further validate the benefit of prolonging gestational age on neonatal morbidity and mortality with 17P treatment

Available Evidence from Meis and PROLONG Identifies Higher-Risk Target Population of Patients

1

Partial Withdrawal to Higher-Risk Target Population

- Women with ≥ 1 recent prior spontaneous preterm birth < 35 weeks **and**
- ≥ 1 additional risk factor such as
  - Prior spontaneous preterm birth < 32 weeks
  - Multiple spontaneous preterm births < 37 weeks
  - Last pregnancy within 2 years
  - Other social determinants of preterm birth

A Third RCT in Higher-Risk Target Population in U.S. is Feasible in a Reasonable Timeframe

2

Conduct Randomized Controlled Trial

- Extensive multiple stakeholder surveys support feasibility of enrolling
  - Practitioners and patients are willing to participate
- **Proposed population:** Women with ≥ 1 prior spontaneous preterm birth < 35 weeks and ≥ 1 additional risk factor
- **Trial design:** ~400 patients randomized 2:1
- **Estimated completion:** 4- to 6-years

Covis Willing to Voluntarily Withdraw Makena Based on Futility and Feasibility Assessments

2

Conduct Randomized Controlled Trial

Pre-specified criteria that would result in voluntary withdrawal:

1. Interim efficacy analysis for futility
2. Assessment of enrollment projections at Month 24 to evaluate feasibility of completing the trial in a 4- to 6-year timeframe
3. Outcome of study is negative

Potential Observational Study to Evaluate Clinical Outcomes

3

Potential Observational Study

- Establish the relationship between gestational age and neonatal outcomes in treated vs. untreated patients
- Validate benefit of weeks gained on 17P in the RCT

Question at hand, should Makena remain on the market for identified target population of higher-risk patients while additional studies are conducted?

Introduction	**Raghav Chari, PhD** Chief Innovation Officer - COVIS Pharma
Legal and Regulatory Framework	**Rebecca Wood, JD** Partner - Sidley Austin LLP
Overview of Preterm Birth	**Yolanda Lawson, MD** Associate Attending Physician – Baylor University Medical Center, Waco, Texas President Elect – National Medical Association
Meis Trial	**Baha Sibai, MD** Professor, Department of Obstetrics, Gynecology and Reproductive Sciences McGovern Medical School-UTHealth at Houston
PROLONG Trial	**Sean Blackwell, MD** Chair and Professor - Department of Obstetrics, Gynecology and Reproductive Sciences McGovern Medical School-UTHealth at Houston
Totality of Evidence	**Michael Greene, MD** Professor - Obstetrics, Gynecology and Reproductive Biology Emeritus Harvard Medical School, Boston, Massachusetts
Identification of a Potential Higher-Risk Patient Population	**Eugene Poggio, PhD** President and Chief Biostatistician Biostatistical Consulting Inc., Lexington, Massachusetts
Additional Publications Supporting Makena's Efficacy	**Raghav Chari, PhD**
Safety	**Raghav Chari, PhD**
Clinical Perspective	**Yolanda Lawson, MD**
Proposed Path Forward While Makena Remains on the Market	**Raghav Chari, PhD** **Sean Blackwell, MD**

Legal And Regulatory Framework

Rebecca K. Wood

Partner

Sidley Austin LLP

Key Points

1. The accelerated approval standard is flexible
2. Withdrawal of accelerated approval is not mandatory
3. Policy and precedent support keeping Makena on the market while additional study is undertaken

Regulatory Flexibility

- Accelerated approval is "intended to encourage" FDA "**to utilize innovative and flexible approaches . . . for patients with serious or life-threatening diseases or conditions and unmet medical needs**"

- FDA's regulations state that standards for drug approval "**demand flexibility**"

FDCA Section 506(e)(1); 21 CFR 314.105(c)

Permissive Legal Standard for Withdrawal of Approval

- FDA **"may withdraw"** accelerated approval if
  - a confirmatory trial "fails to verify and describe" the clinical benefit or
  - "other evidence demonstrates that the product is not safe or effective under the conditions of use"
- The statute is permissive, not mandatory
  - CDER acknowledges: **"CDER possesses various regulatory options when a confirmatory trial fails to verify clinical benefit"**
- FDA has the authority to keep Makena on the market while another trial is conducted

FDCA Section 506(c)(3); CDER Briefing Book page 78

FDA Policy and Precedent Considerations

1. Why did the trial fail?
2. What options are available to patients?
3. Is there a subset of patients for whom the drug may be effective?

FDA – Why did the trial fail?

"**There are many reasons that a trial fails** and that could be the size of the trial, the endpoint they used, the population that they defined. . . . **To remove a drug from the market** or even an indication **is a big deal and not in the public's best interest if you can understand why that trial failed**. . . . **We have to have that flexibility rather than just a draconian approach**."

Dr. Richard Pazdur, Director of FDA's Oncology Center of Excellence (Dec. 2019)[1]

1. Friends of Cancer Research Senate Briefing – Turning the Tables: Innovator Meets Regulator (Dec. 10, 2019)

FDA – What Options are Available for Patients?

"**FDA must carefully evaluate what other options are available to patients at the time it is considering regulatory action for failure to confirm clinical benefit**. In some cases a drug for which clinical benefit has not been confirmed may be the only approved therapeutic option for patients with the disease. Removing the drug from the market and **leaving patients with no treatment may be unacceptable**."

Dr. Billy Dunn, Director of CDER's Office of Neuroscience (Sept. 2022)

Opening Statement, Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting (Sept. 7, 2022)

FDA – Is there a Subset of Patients for Whom the Drug is Effective?

"**FDA must also consider** the possibility that, despite results from confirmatory studies that may appear to indicate that a drug does not provide clinical benefit, **there may be a subset of patients for whom the drug may nevertheless be effective**."

FDA Response to Government Accountability Office (September, 2009)

FDA Precedent - Midodrine HCl

1996 Accelerated approval granted

2007 CDER determined that confirmatory studies submitted in 2005 failed to verify clinical benefit

2010 CDER issued NOOH proposing to withdraw midodrine

2012 FDA agreed to hold NOOH in abeyance

2015 Midodrine's sponsor submitted a supplement with the results of additional studies

- **19 years** after its original approval
- **10 years** after its first "failed" confirmatory studies were submitted to FDA

2022 Midodrine remains on the market

CDER, Midodrine Update (Sept. 2010)

FDA Precedent

"Midodrine is the only drug approved for the treatment of symptomatic orthostatic hypotension (SOH) a rare but serious condition…. **If marketing approval for midodrine is withdrawn at this time, patients with SOH will be left with no approved therapeutic options**."[1]

"FDA has two goals with respect to midodrine: (1) to obtain high quality data on the effectiveness of the medication and (2) to maintain access for patients to the medication throughout this process."[2]

1. Letter from Abigail Brandel, Counsel to CDER and Carla Cartwright, Counsel to CDER to G. Matthew Warren, Senior Regulatory Counsel, Office of the Commissioner of Food and Drugs, Docket No. 2007-N-0475-0036 (Jan. 13, 2012)
2. CDER, Midodrine Update (Sept. 2010)

Compounded 17P

- If FDA withdraws a drug from the market for reasons of safety or efficacy, its active ingredient is added to the list of withdrawn or removed drugs that "may not be compounded"[1]
- In practice, that process is uncertain and may take years
  - Compounding may continue for years following withdrawal
- FDA has stated:
  - "Compounded drugs are not FDA-approved"
  - 503A compounders "are exempt from compliance with cGMPs [current Good Manufacturing Practices] requirements"
  - "Unnecessary use of compounded drug unnecessarily exposes patients to potentially serious health risks"[2]

1. 21 U.S.C. § 353a(b)(1)(C); § 353b(a)(4); 21 C.F.R. § 216.24
2. Compounding and the FDA: Questions and Answers (June 29, 2022)

Path Forward

- This is only the second time FDA has held a hearing to address a proposed withdrawal, and the first time a hearing has been held to consider the withdrawal of an entire product
- FDA Chief Scientist granted our request for a hearing

> "Covis has justified a hearing in this matter" given the "genuine and substantial issues of fact appropriate for a hearing."[1]

- FDA may exercise regulatory flexibility when a confirmatory trial fails in light of the flexible accelerated approval standard, the permissive withdrawal standard, and FDA's approach to policy and precedent

1. August 18, 2021 FDA Chief Scientist letter to Covis

Preterm Birth

Yolanda Lawson, MD

Associate Attending Physician – Baylor University Medical Center
President Elect – National Medical Association

Preterm Birth is Associated with Significant Neonatal Morbidity and Mortality

- Leading cause of neonatal and infant mortality[1]
- Higher risk of death within first 28 days of life[2]
- Significantly higher risk of short- and long-term complications[2]

Short-Term Complications

Respiratory distress syndrome

Bronchopulmonary dysplasia

Intraventricular hemorrhage

Periventricular leukomalacia

Long-Term Complications

Chronic respiratory problems

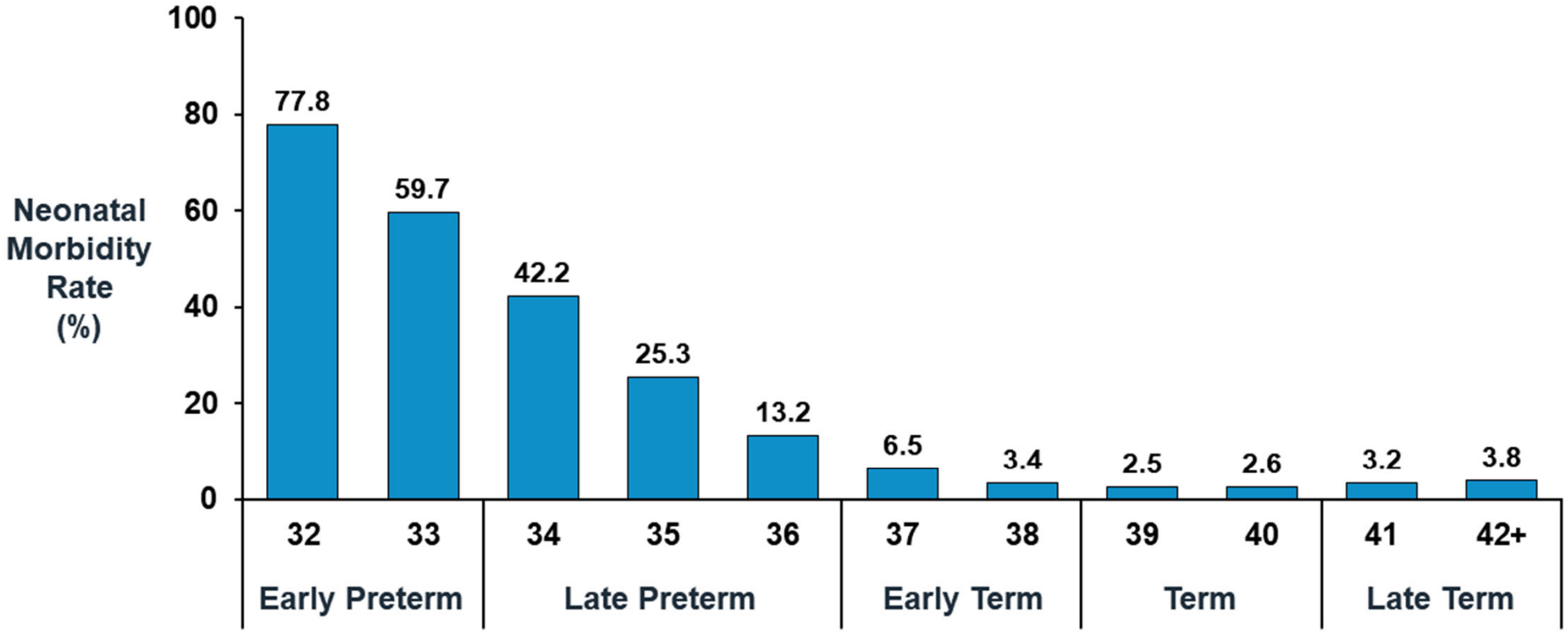
Rehospitalization

Metabolic disorders

Neurodevelopment problems

1. https://www.acog.org/womens-health/faqs/preterm-labor-and-birth
2. Simhan H. et al. (2018)

Neonatal Morbidity and Mortality Increase as Gestational Age Decreases



Todd, et al., International Journal of Population Data Science (2020)

History of Singleton Preterm Delivery is a Significant Risk Factor for Subsequent Preterm Birth

Gestational Age at First Delivery, Weeks	Total n (%)	Preterm in Second Delivery n (%)	Preterm Birth < 37 Weeks in Second Delivery Adjusted RR (95% CI)
≥ 37	46771 (92.4)	2630 (5.7)	Reference
34 to < 37	2950 (5.8)	838 (28.9)	**4.81** (4.48, 5.15)
28 to < 34	607 (1.2)	226 (37.9)	**5.98** (5.37, 6.66)
24 to < 28	152 (0.3)	61 (40.1)	**6.42** (5.33, 7.74)
20 to < 24	127 (0.3)	35 (27.8)	**4.88** (3.66, 6.50)

Laughon et al., 2014
Trend for gestational age p<0.0001
RR adjusted for maternal age, race/ethnicity, pre-pregnancy, body mass index, insurance, smoke, alcohol, illicit drug use, chronic medical disease

Preterm Birth Impacts a Substantial Number of Women in the United States

- ~130,000 pregnant women per year in the U.S. have a history of prior singleton spontaneous preterm birth
- Preterm birth disproportionally impacts specific patient populations
  - Women who are Black and other minority groups
  - Other social determinants (i.e., education, income, marital status, nutrition)

Withdrawal of Makena would have greatest impact on at-risk and disadvantaged patient populations

Meis Trial

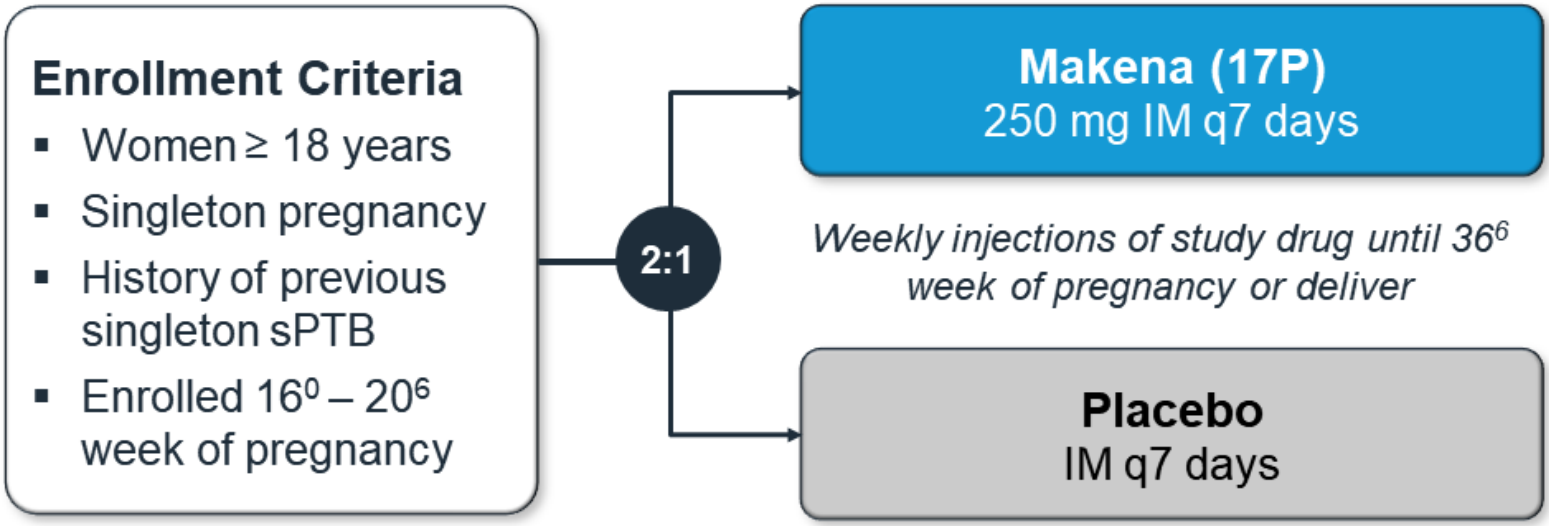
Baha Sibai, MD

Professor, Department of Obstetrics, Gynecology and Reproductive Sciences
McGovern Medical School-UTHealth at Houston
Houston, Texas

Clinical Experience with Makena and Caring for Higher-Risk Pregnant Women

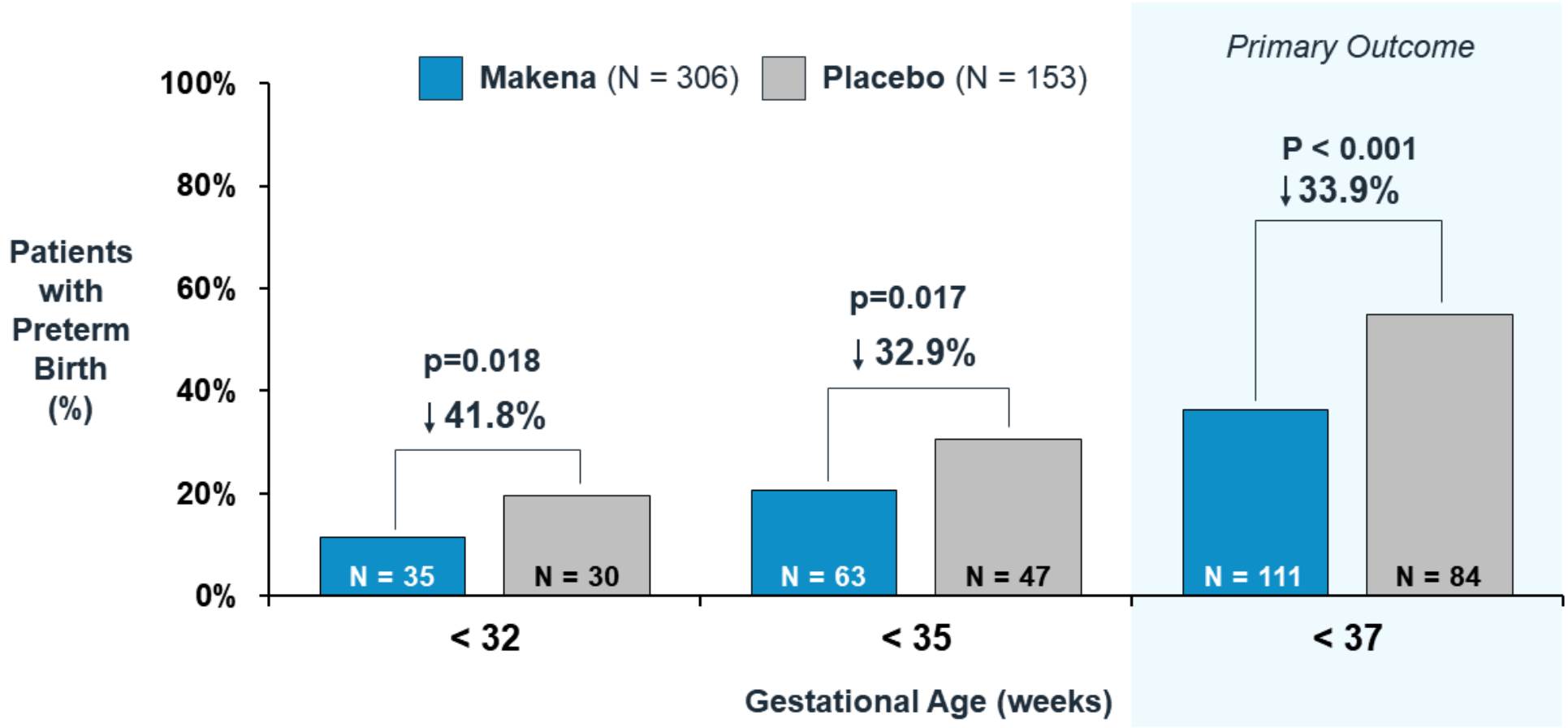
Meis Trial (Trial 002)

Meis Trial Provides Compelling Evidence of Makena's Clinical Benefit in Women with History of sPTB



- **Second planned interim analysis:** Enrollment stopped early due to significant benefit of Makena compared with placebo
  - Final analyses include 463 women, 92.6% of planned sample size

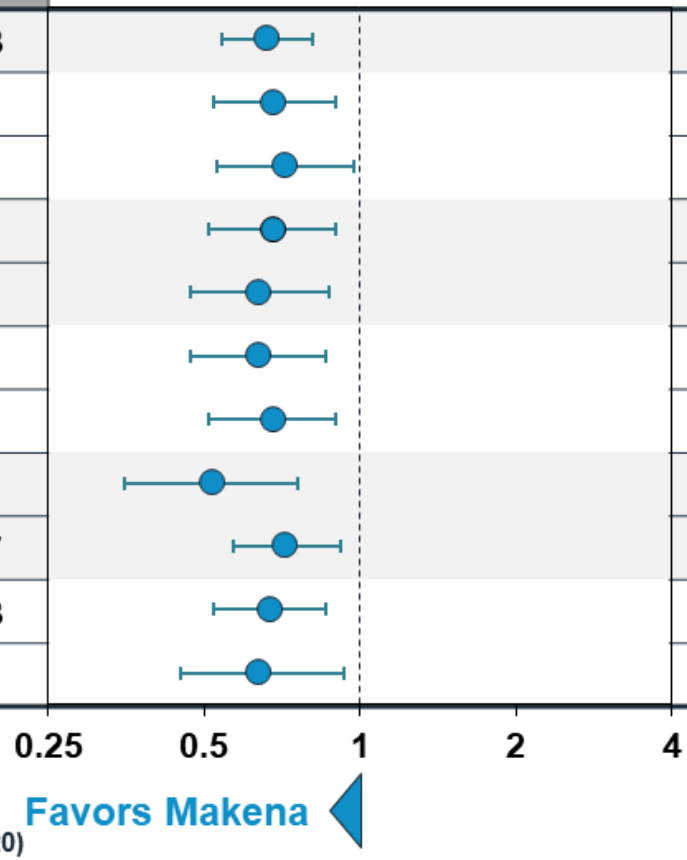
Makena Met Primary Endpoint Demonstrating Significant Reduction in Preterm Births < 37 Weeks



Meis, et al. NEJM (2003)

Meis Trial Showed Highly Significant Efficacy Across All Major Subgroups

Subgroup	Makena (n/N)	Placebo (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)
Smoking or substance use	28/85	23/36	**0.52** (0.35, 0.76)
No smoking 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)



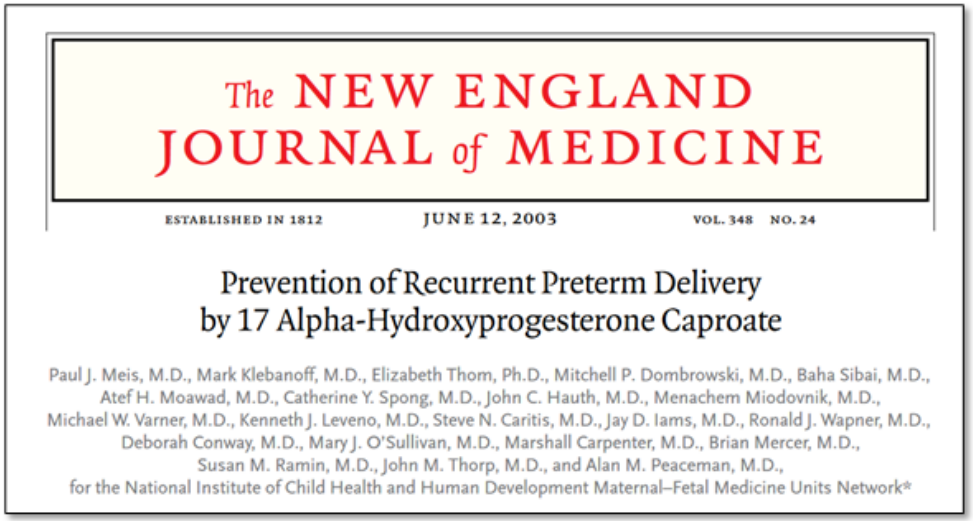
Sibai et al, Re-examining the Meis Trial for Evidence of False-Positive Results (2020)

Significant Unmet Need and Compelling Evidence of Clinical Benefit Led to Accelerated Approval

- At time of accelerated approval CDER determined Meis was "**adequate, well-controlled and very persuasive**" and provided "**compelling**" evidence of clinical benefit
- Meis trial is "**sufficiently persuasive to support drug approval** based on the findings of a single adequate and well controlled trial"

1. CDER 2019 Briefing Document

Meis Trial Results were Considered Significant Advance in the Field of Obstetrics



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*

- Relative Risk (95% CI)
  - 0.66 (0.54, 0.81)
- Absolute difference in preterm birth rate
  - 18.6%
- Number needed to treat
  - 5.4 women to prevent 1 PTB

Meis, NEJM 2003

Meis Trial Results Led to Medical Societies Recommending Progesterone Supplementation for Prevention of Recurrent PTB

"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." ACOG Committee Opinion (2008)

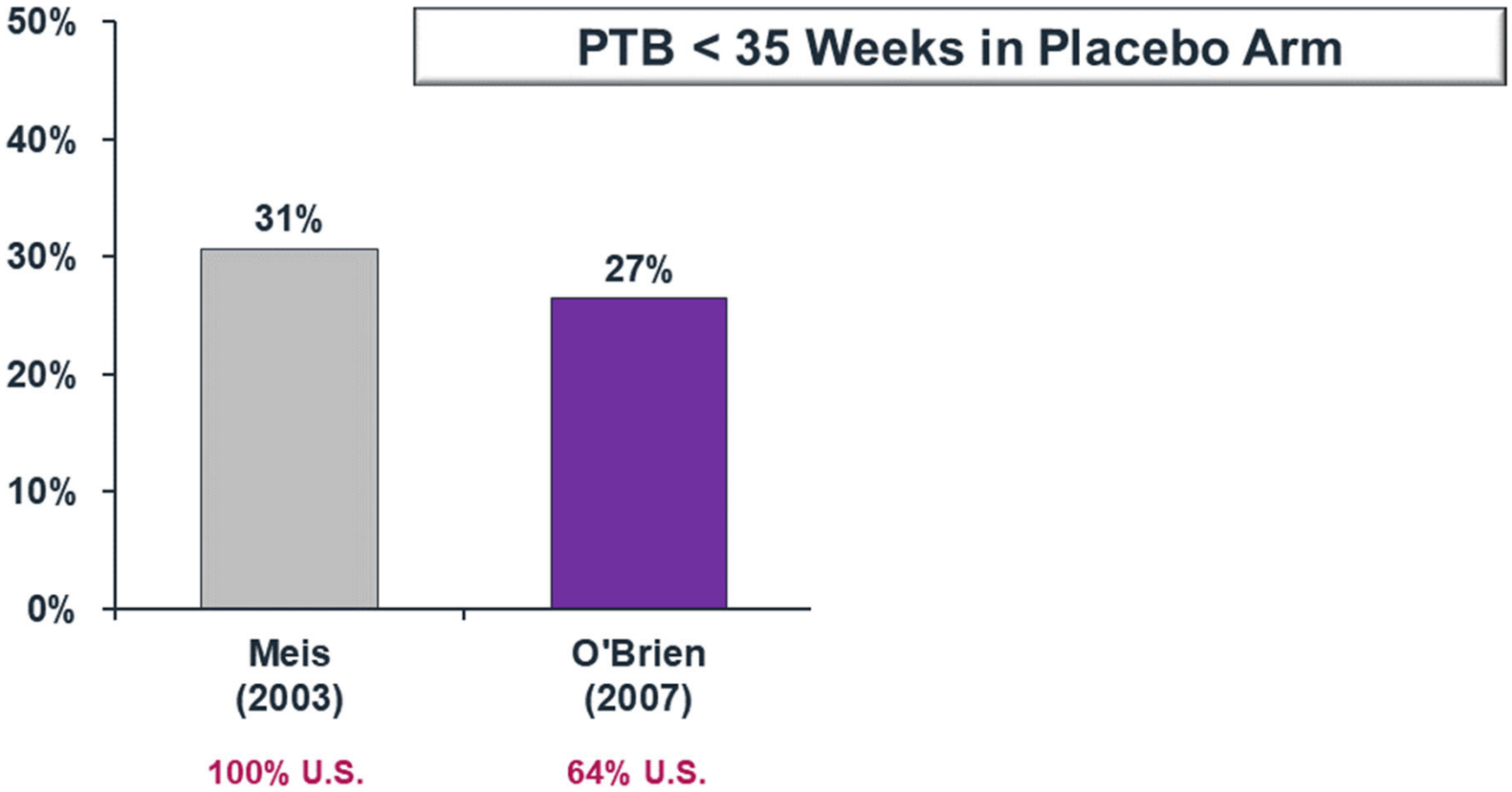
- ACOG concluded results show significant protection for recurrent PTB for all races of women

Meis Trial is Not an Outlier and Not a False Positive

1. **Meis results were so compelling that trial stopped early**
   - DSMB recommended, given robust efficacy demonstrated with Makena
   - Final data set of 463 women represented 92.6% of the planned sample size
2. **Subgroup analyses support that results are generalizable to a wide range of women with previous spontaneous preterm birth**
   - Subgroup analyses by number of prior spontaneous preterm births, race, marital status, and smoking or substance use consistently demonstrate the benefits
3. **Preterm birth rate in Meis not unexpected**
   - High proportion of patients who were Black
   - Early gestational age of prior spontaneous preterm birth
   - High proportion of women with ≥ 1 prior spontaneous preterm birth

Sibai et al, Re-examining the Meis Trial for Evidence of False-Positive Results (2020)

Placebo Arm Preterm Birth Rates Consistent in Meis and O'Brien Trials



Results of Subsequent NICHD Trial Supports Preterm Birth Rate in the Makena Arm of Meis Trial

	Meis Trial	NICHD Trial	
Baseline Characteristic	Makena (17P) N = 310	Omega-3 + 17P N = 434	Placebo + 17P N = 418
> 1 previous sPTB	28%	30%	28%
Black / African American	59%	34%	35%
Married or living with partner	51%	71%	67%
Education level, mean (years)	12	13	13
Gestational age of qualifying sPTB, mean (weeks)	31	32	31
Pregnancy Outcome (Preterm Birth)			
< 37 weeks	37%	38%	42%
< 35 weeks	21%	19%	20%
< 32 weeks	12%	10%	11%

Harper et al., Obstetrics & Gynecology (2010)
NICHD National Institute of Child Health and Human Development

27% Enrollment at One Site in Meis Trial Does Not Undermine the Results

- Preterm birth rates are higher in Southeast vs. other U.S. regions
  - Reasonable to expect one site with high enrollment
- Single Southeast center did not bias the results
  - Significant efficacy of Makena seen at other sites
    Relative Risk (95% CI) = 0.70 (0.56, 0.88)
  - Interaction term in a logistic regression analysis indicates Southeast site results were not significantly different from the other sites (p = 0.82)

Sibai, et al., Obstetrics & Gynecology (2020)

PROLONG Trial

Sean Blackwell, MD
Chair and Professor
Department of Obstetrics, Gynecology and Reproductive Sciences
McGovern Medical School-UTHealth at Houston
Houston, Texas

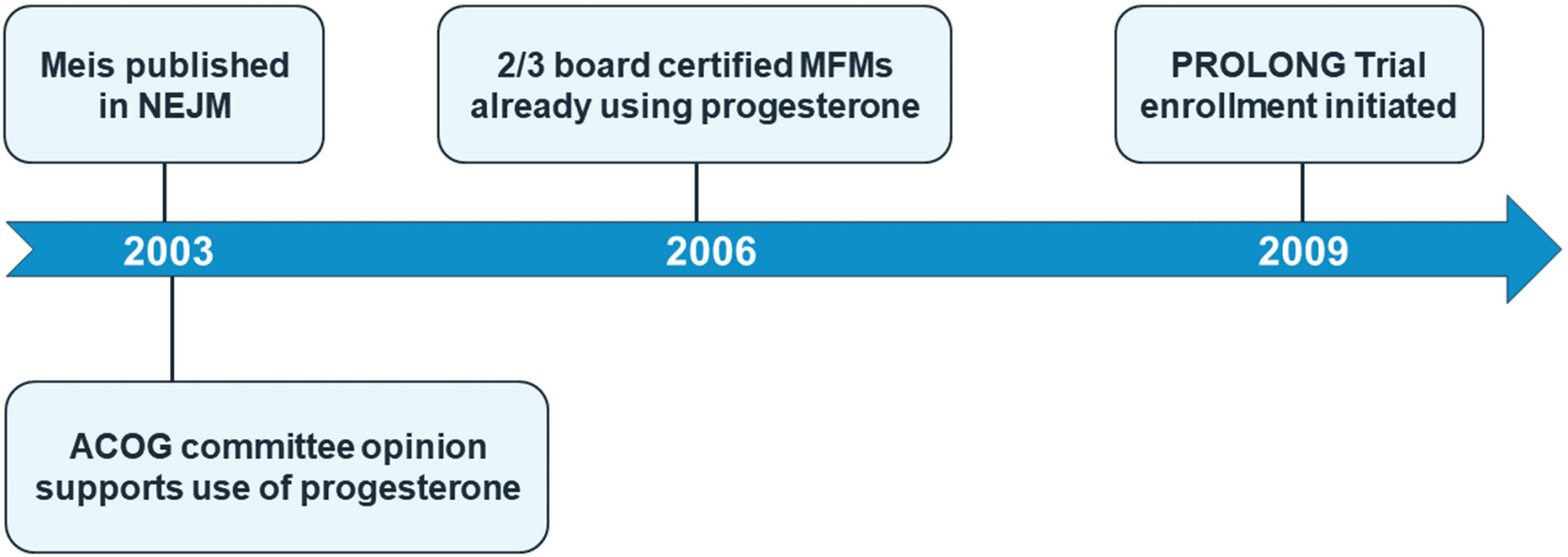
PROLONG Designed to Mirror Meis

- Identical study protocol
- Expanded recruitment to assess risks of pregnancy loss and neonatal outcomes
- Assumed same treatment effects
  - Effect size = 1/3 reduction
- No interim analyses or assessment of efficacy as trial required to be completed as part of accelerated approval

PROLONG: Baseline Recruitment Challenges

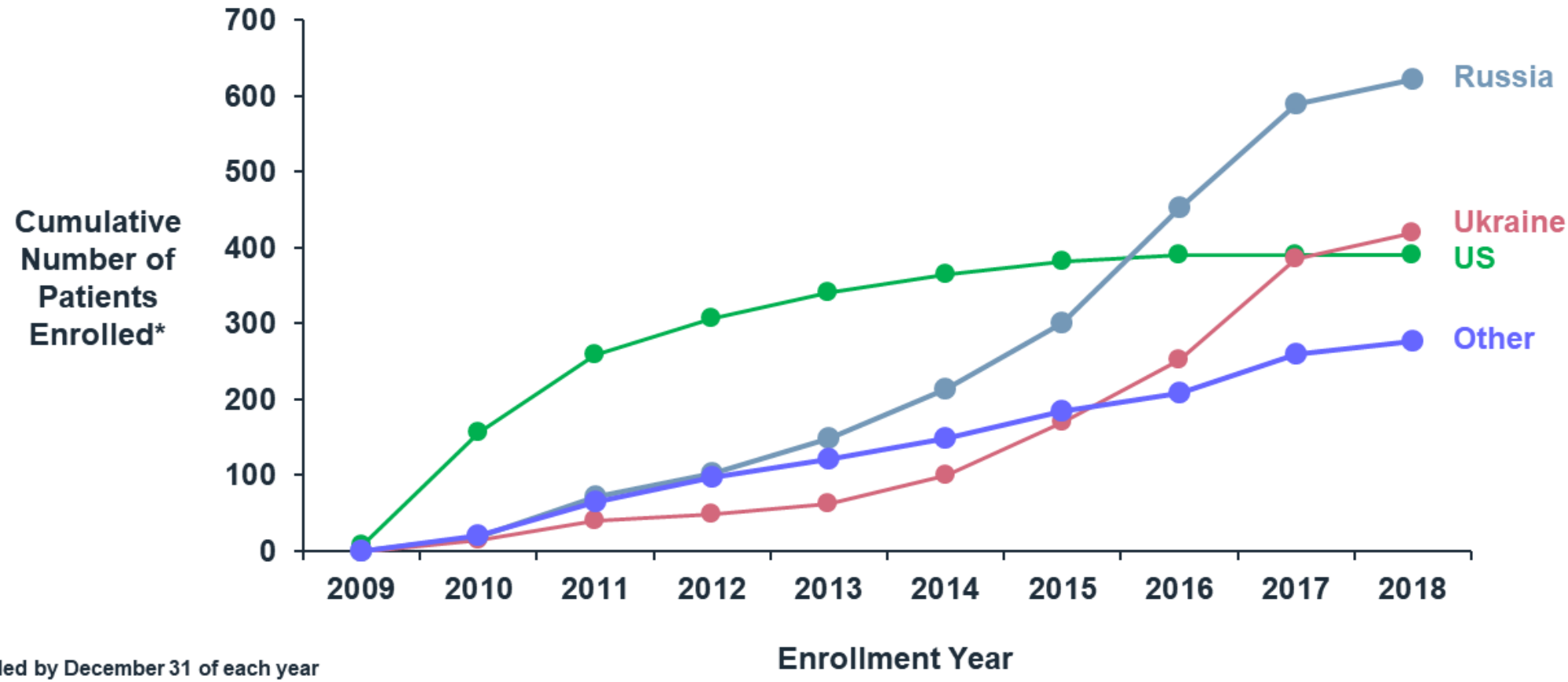
- ACOG/SMFM advocate for progestogen use as best practice
- Meis “convincing” to MFMU and other high-risk academic medical centers

PROLONG: Recruitment Challenges



Ness, AJOG, 2006

PROLONG: Enrollment (Year End)



*Enrolled by December 31 of each year
Other: Bulgaria, Canada, Czech Republic, Hungary, Italy, Spain

PROLONG Primarily Enrolled Patients Outside of the U.S. with 61% Enrolled in Ukraine and Russia

Country	Number of Patients (%) N = 1708
United States	391 (22.9)
Outside the United States	1317 (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)

23%
United States

61%
Russia / Ukraine

16%
Other OUS Countries

PROLONG Trial PTB Rate < 35 Weeks: Post Hoc Analysis of Top Enrolling U.S. Sites

	Makena	Placebo
Department of Defense	9.5%	13%
Madigan Army Medical Center	17%	8.3%
San Antonio Military Medical Center	0%	29%
Tripler Army Medical Center	0%	25%
Naval Medical Center Portsmouth	13%	0%
Top Enrolling U.S. Civilian Sites		
Rosemark Women Care Specialist (Idaho Falls, ID)	0%	7.1%
University of Louisville (KY)	13%	23%
Wheaton Franciscan Healthcare (Rancine, WI)	18%	11%
University Medical Group (Greenville, SC)	18%	25%
Watching Over Mothers and Babies Foundation (Tucson, AZ)	20%	43%
Drug Research and Analysis Corporation (Montgomery, AL)	46%	43%

- Meis Trial PTB rate < 35 weeks placebo arm = 30%

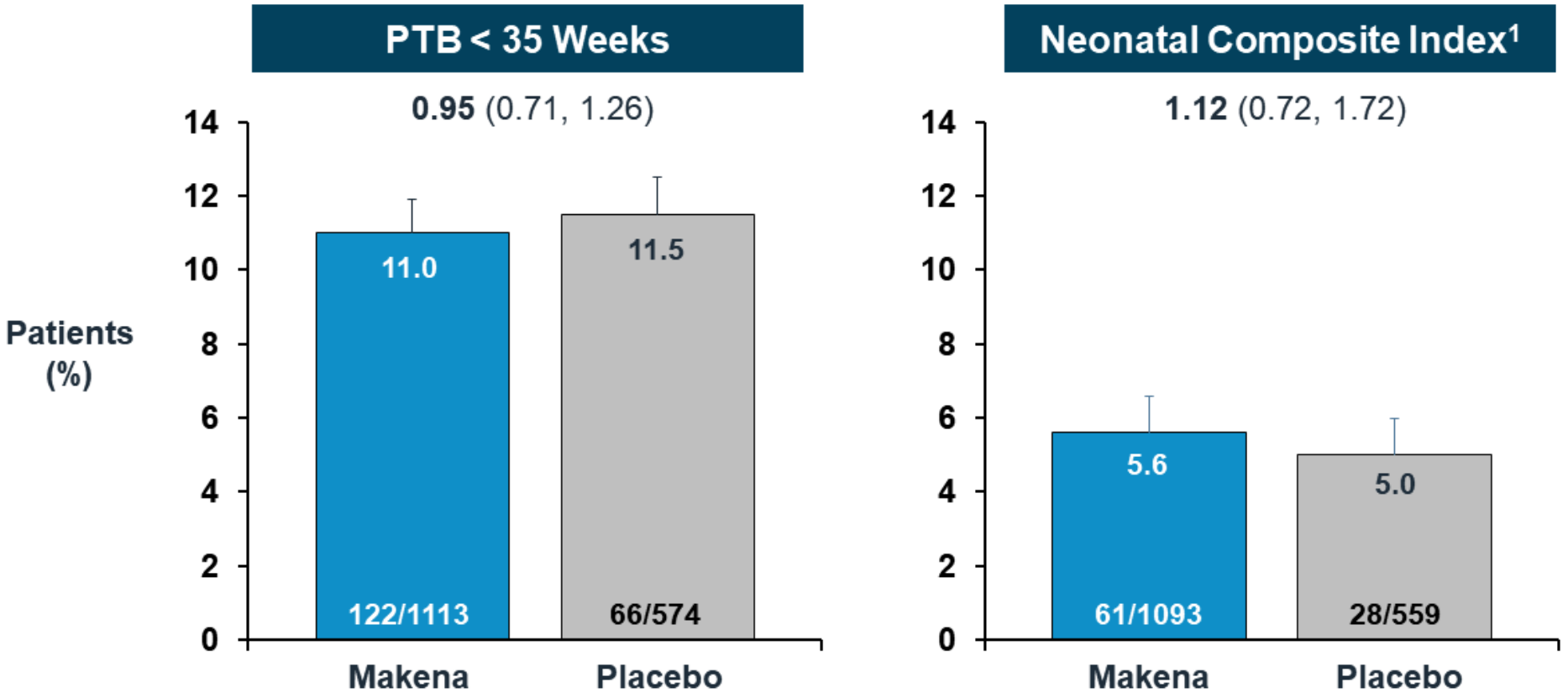
PROLONG Enrolled Lower Risk Population

- Recruitment in U.S.
  - Locations with prior PTB women, but much “lower risk” compared to Meis
- Recruitment outside the U.S.
  - NICU infrastructure & CRO relationships = Russia/Ukraine
  - Lower risk compared to U.S. population and lower than Meis

PROLONG Patients Substantially Different from Patients Enrolled in Meis

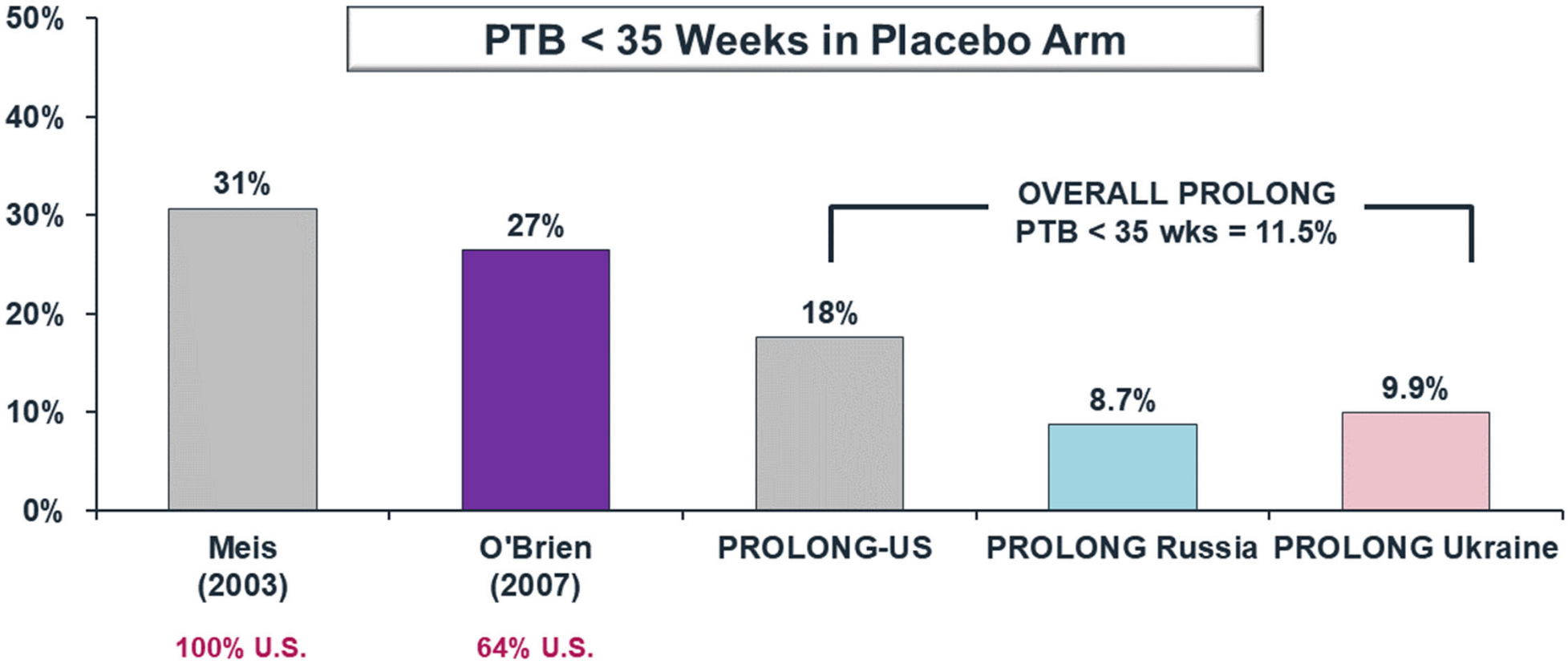
What is the Evidence?

PROLONG Did Not Demonstrate Significance on Either of its Prespecified Primary Endpoints

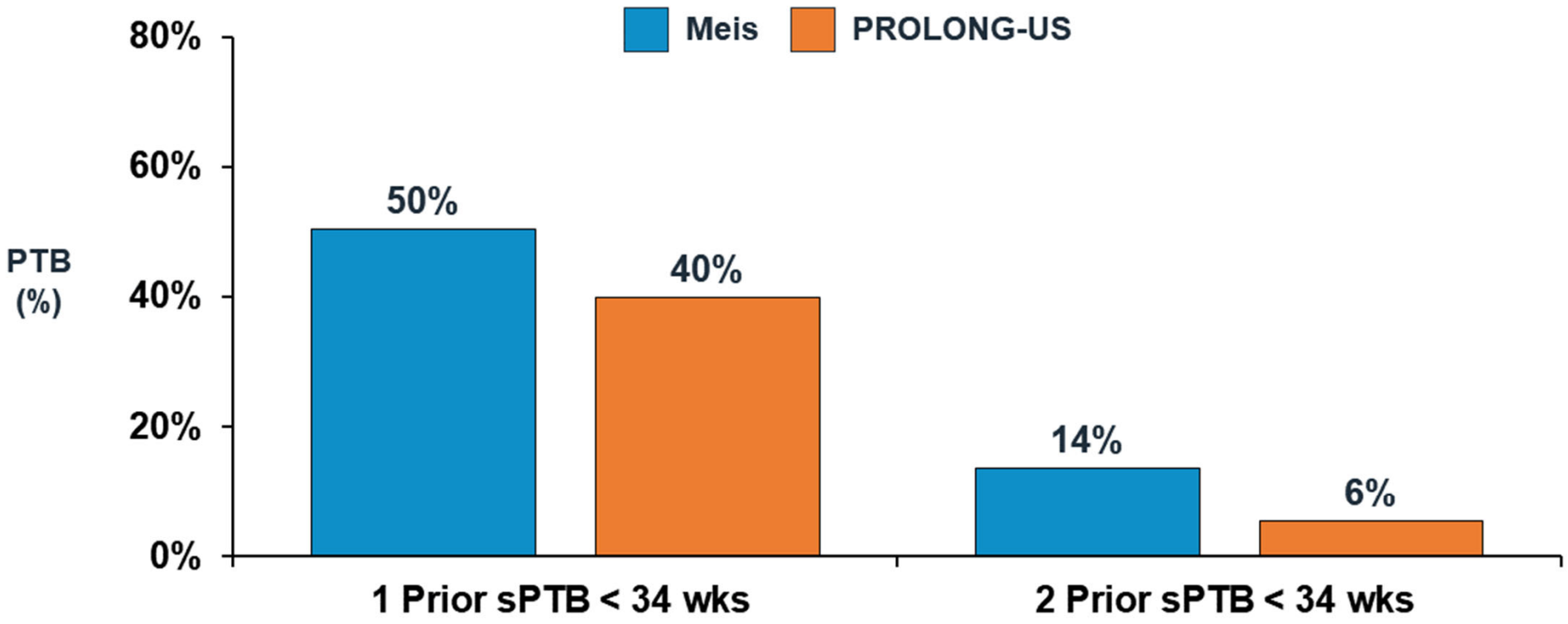


1. Composite included: Death, RDS, BPD, Grade 3 or 4 IVH, NEC and proven sepsis

Placebo Arm PTB Rates Across Different Clinical Trial Populations



Meis Trial Enrolled "Higher-Risk" Patients Prior sPTB < 34 Weeks



PROLONG Enrolled Vastly Different Population Compared with Meis Trial

Baseline Characteristics	Meis N = 463	PROLONG-OUS N = 1317	PROLONG-US N = 391
> 1 Previous spontaneous PTB	**32%** (149)	▼ **11%** (141)	▼ **27%** (107)
Black / African American	**59%** (273)	▼ **0.1%** (1)	▼ **29%** (113)
Unmarried with no partner	**50%** (233)	▼ **4%** (53)	▼ **31%** (120)
Educational ≤ 12 years	**71%** (330)	▼ **42%** (549)	▼ **50%** (197)
Any substance use during pregnancy	**26%** (121)	▼ **4%** (47)	▲ **28%** (111)

▲ **Higher risk** compared to Meis ▼ **Lower risk** compared to Meis

Summary: PROLONG Population vs. Meis

- Different clinical characteristics
  - Black race
  - Prior PTB (early PTB and number of prior early PTB)
- Only 2% of women enrolled in PROLONG had short cervix
- Lower rates recurrent PTB in placebo arm

PROLONG was a “Flawed” Trial

Prevention of recurrent PTB in singleton pregnancies

- YES, if trying to study “high-risk” women in U.S.
- THUS, its “negative findings” related to efficacy do not cancel or invalidate the positive findings of Meis

Another Trial is Needed

- Many MFM physicians continue to utilize Makena and believe access to FDA-approved medications is best practice
- SMFM continues to support Makena in the highest-risk population
- Another trial is needed to address efficacy
  - U.S. “higher-risk” population
- Continued access to Makena for clinical care until a trial is completed

Totality of the Evidence

Michael Greene, MD

Professor - Obstetrics, Gynecology and Reproductive Biology Emeritus
Harvard Medical School

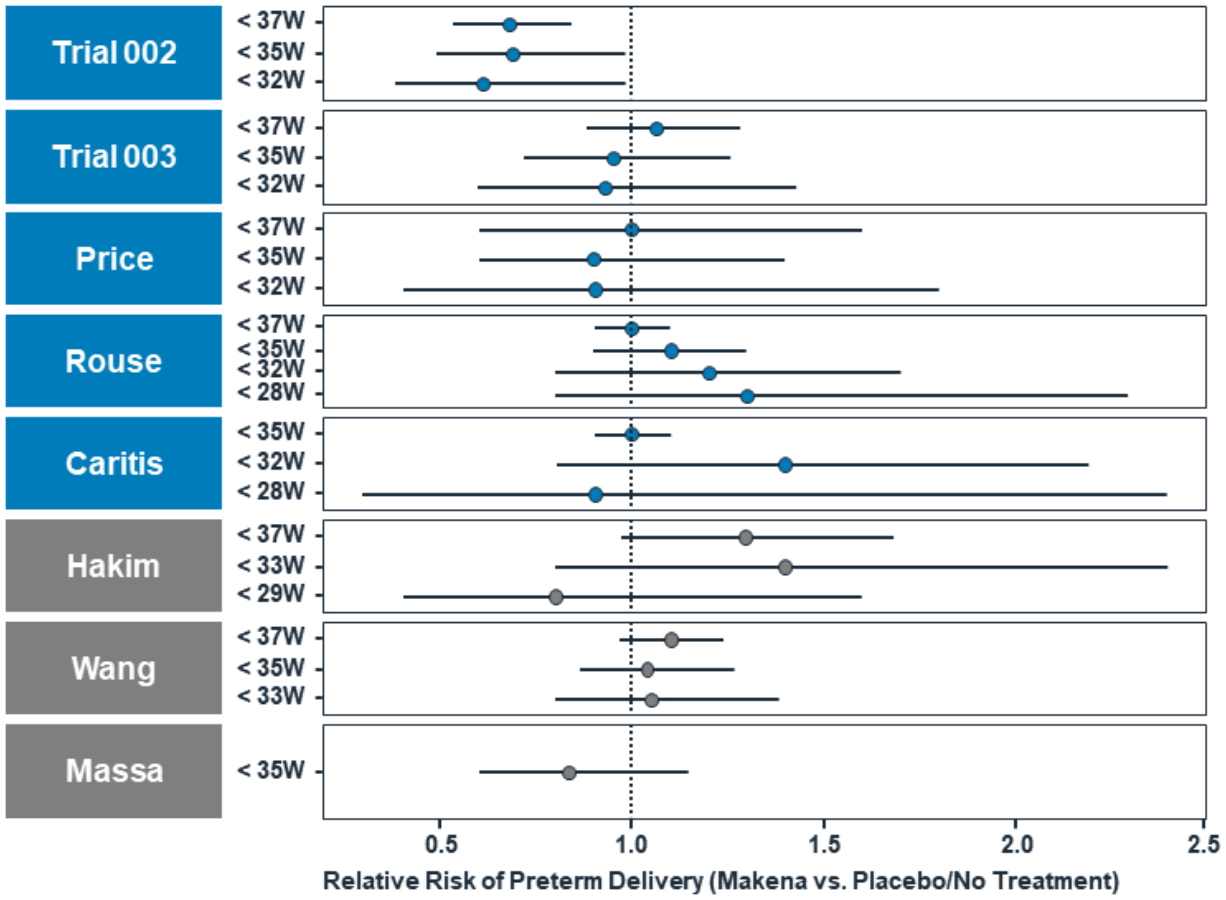
Associate Editor of New England Journal of Medicine

Background Principles

1. **Makena is indicated only for use with women with a history of a prior spontaneous preterm birth (sPTB)**
   - sPTB is significant risk factor for subsequent preterm birth[1]
2. **Makena is indicated only for use during singleton pregnancies**
   - "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]
3. **CDER has asserted that observational studies are not reliable**
   - "**Inherent limitations to observational studies** or externally controlled trials, whether retrospective or prospective… **preclude the use of these study designs to obtain reliable evidence of Makena's efficacy**"[3]

1. Laughon et al., 2014
2. Makena Product Labeling
3. CDER Briefing Document 2022

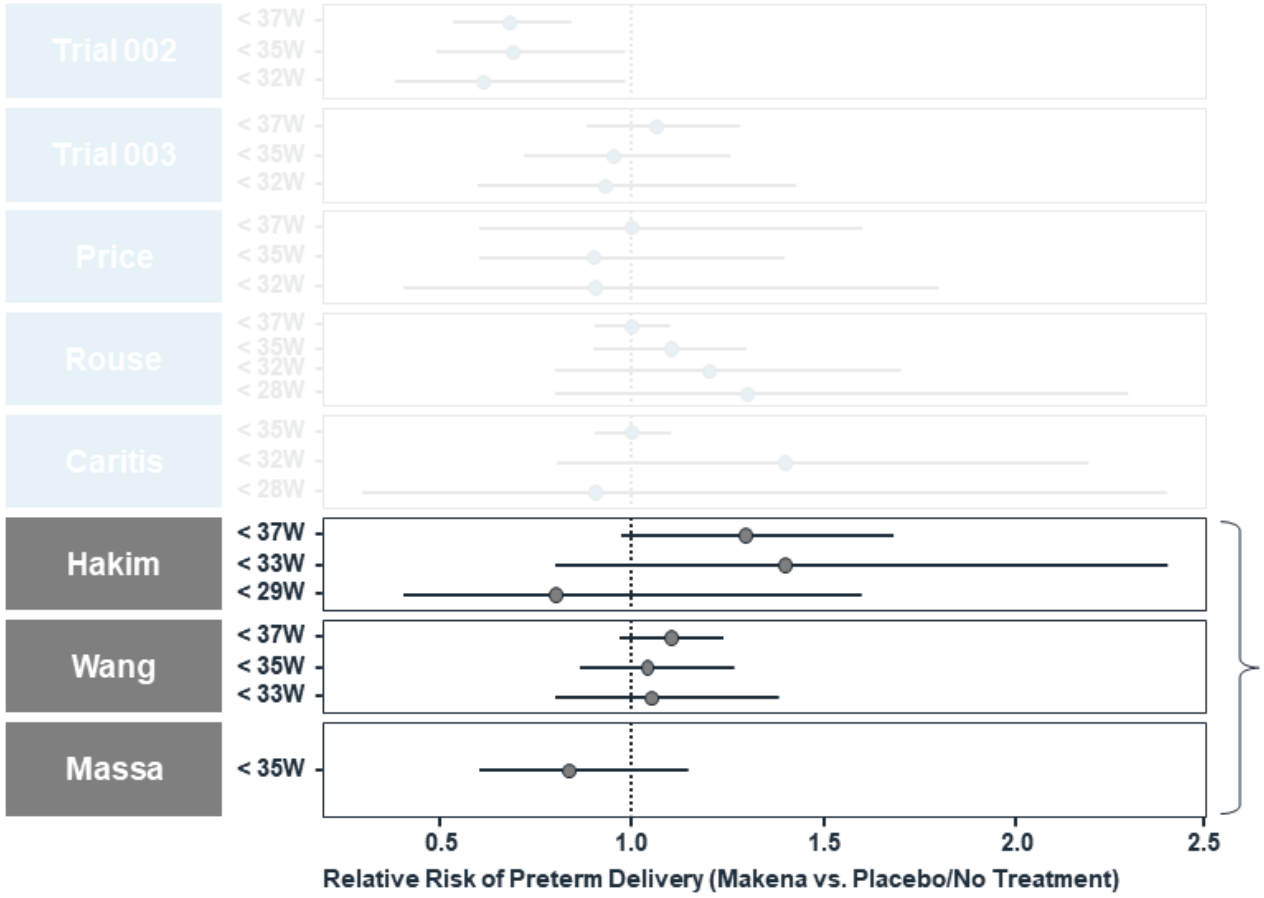
CDER's Conclusion that the Meis Trial is an Outlier Based on Figure 1 is Inappropriate



RCTs Observational

Figure adapted from CDER Briefing Document 2022

Observational Studies Have Inherent Limitations



Observational Studies

RCTs Observational

Figure adapted from CDER Briefing Document 2022

Rouse and Caritis Evaluated Efficacy of 17P in Women with Twins and Triplets

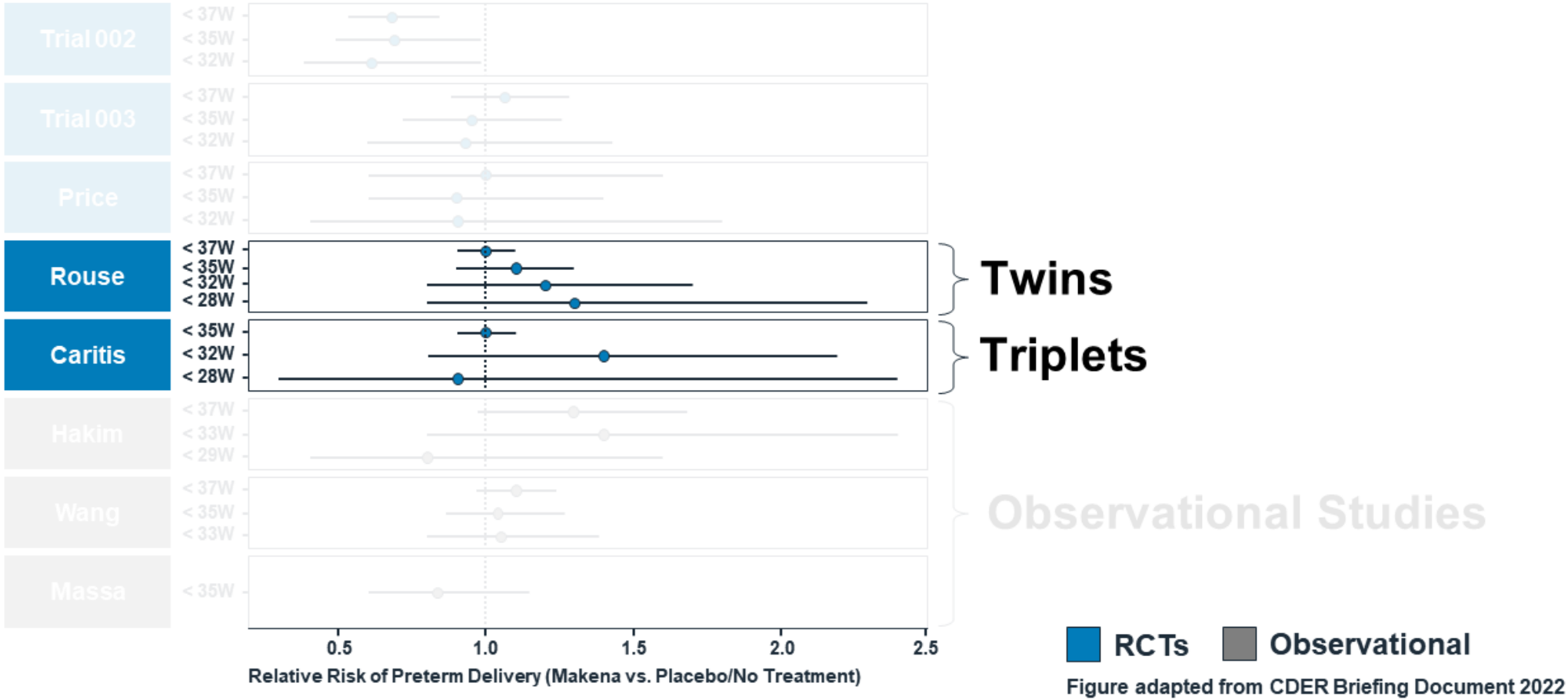


Figure adapted from CDER Briefing Document 2022

Price Evaluated Women with HIV and Affirmatively Excluded Women with a History of PTB

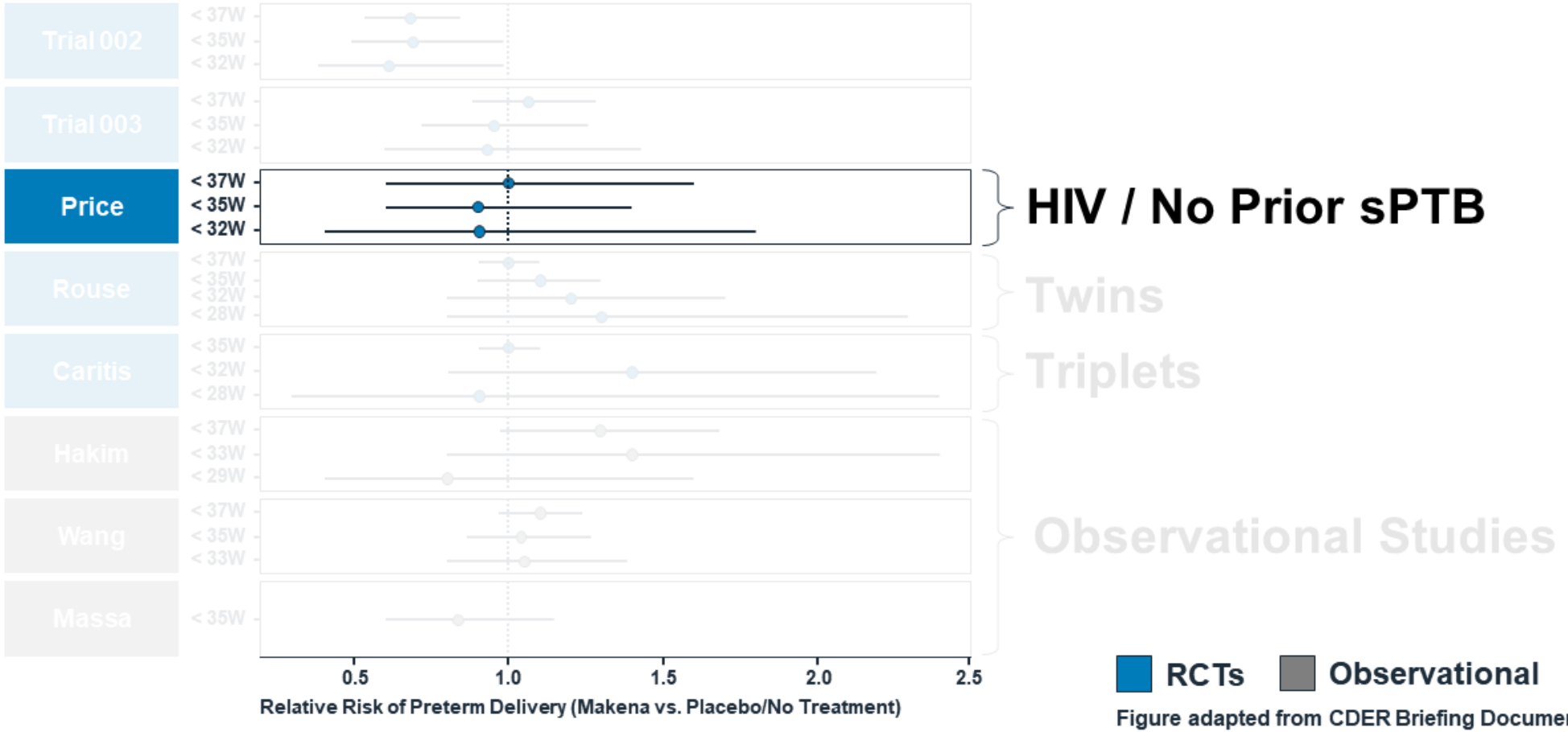
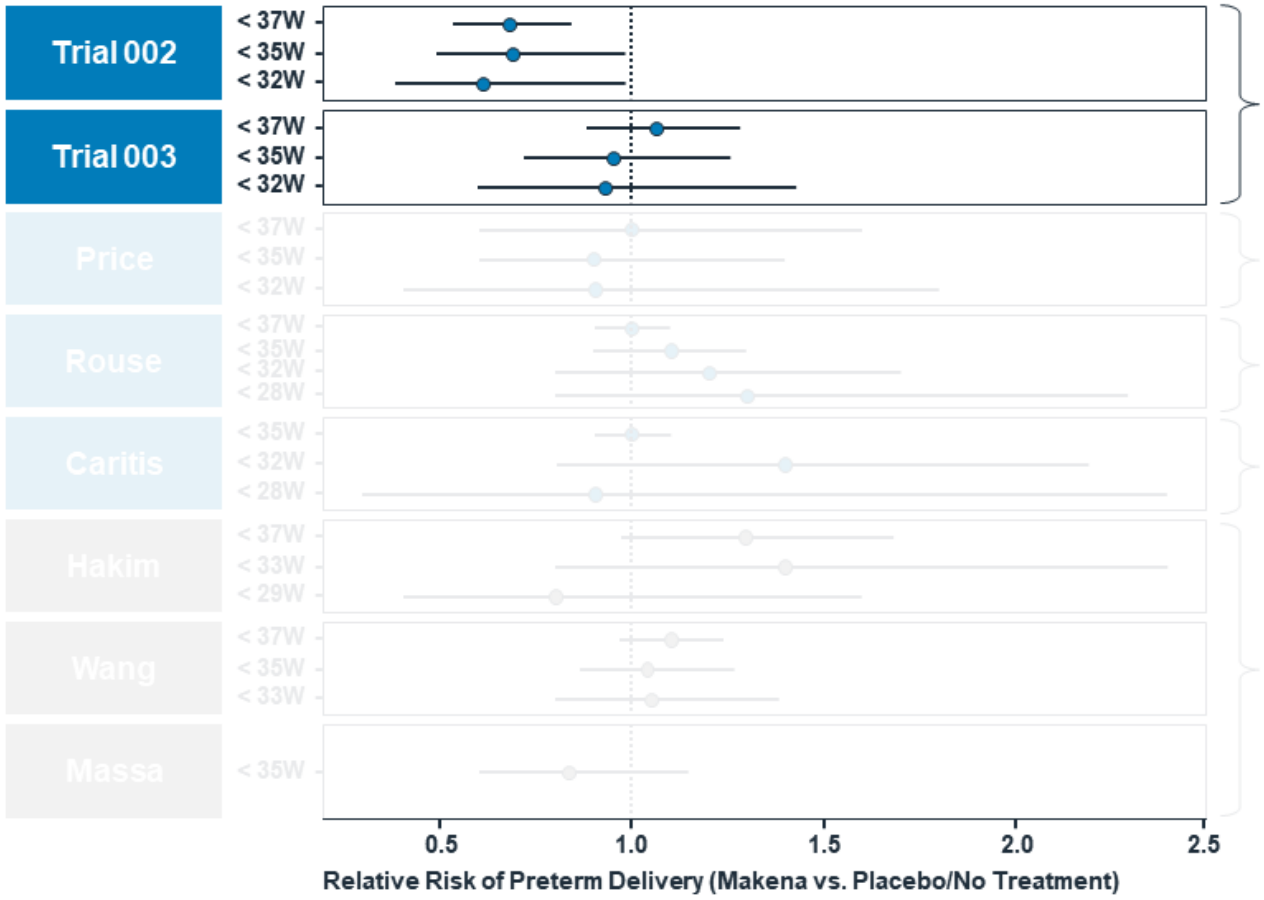


Figure adapted from CDER Briefing Document 2022

Meis (Trial 002) and PROLONG (Trial 003)



Only randomized, controlled trials relevant to Makena's efficacy

HIV / No Prior sPTB

Twins

Triplets

Observational Studies

RCTs Observational

Figure adapted from CDER Briefing Document 2022

Makena: One Positive RCT, One Failed RCT in a Different Patient Population

- Meis – indisputably robust showing of efficacy
- PROLONG – failed to confirm Meis trial

"**There are many reasons that a trial fails** and that could be the size of the trial, the endpoint they used, the population that they defined. . . . **To remove a drug from the market** or even an indication **is a big deal and not in the public's best interest if you can understand why that trial failed**. . . . We have to have that flexibility rather than just a draconian approach."

Dr. Richard Pazdur, Director of FDA's Oncology Center of Excellence (Dec. 2019)[1]

1. Friends of Cancer Research Senate Briefing – Turning the Tables: Innovator Meets Regulator (Dec. 10, 2019)

PROLONG Failed to Enroll a Population Capable of Confirming the Results Seen in the Meis Trial

Baseline Characteristics	Meis N = 463	PROLONG-OUS N = 1317	PROLONG-US N = 391
> 1 Previous spontaneous PTB	**32%** (149)	▼ **11%** (141)	▼ **27%** (107)
Black / African American	**59%** (273)	▼ **0.1%** (1)	▼ **29%** (113)
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Any substance use during pregnancy	**26%** (121)	▼ **4%** (47)	▲ **28%** (111)

▲ **Higher risk** compared to Meis ▼ **Lower risk** compared to Meis

Preterm Birth Rates in Placebo Groups Were the Most Important Difference Between the Trials

	Placebo Groups		
	Meis N = 153	**PROLONG-OUS** N = 447	**PROLONG-US** N = 131
< 37 weeks	**55%**	**20%**	**28%**
< 35 weeks	**31%**	**10%**	**18%**
< 32 weeks	**20%**	**4%**	**9%**

- Preterm birth rate in placebo group of Meis trial (31%) was used to calculate sample size of PROLONG study

My Conclusions

- PROLONG failed to confirm Meis, but
  - It is not a definitive negative study
  - It does not rule out efficacy
  - It is not conclusive
- Given the shortcomings of PROLONG
  - It cannot be used to discount Meis as a false positive
  - Meis remains substantial evidence of effectiveness in a higher-risk population

Next Steps

- A further RCT in a higher-risk population is necessary
  - Based on experience in PROLONG, additional enrollment criteria are likely necessary
  - Different endpoints also may be necessary
  - Details should be worked out collaboratively
- Makena should remain on the market while this trial is conducted
- "The widespread use of 17OHP after accelerated approval has not uncovered important safety signals."[1]
- Labeling revisions would be a reasonable accommodation

1. Greene et al., NEJM 2020

Final Points to Consider

1. Given what we know about risk factors for recurrent preterm birth, were the populations enrolled in Meis and PROLONG sufficiently similar to allow for a meaningful comparison?
2. Are the observed rates of preterm birth in the placebo arms of the two trials sufficiently similar that they can be confidently said to represent two populations at similar risk?

Identification of a Potential Higher-Risk, Target Patient Population

Eugene Poggio, PhD

Founder, President, and Chief Biostatistician

Biostatical Consulting Inc.

Meis vs. PROLONG

- As discussed, results for Meis and PROLONG studies differed substantially
  - Meis met its primary and secondary endpoints for PTB
  - PROLONG did not meet either of its co-primary endpoints
- As also discussed, Meis and PROLONG enrolled vastly different populations
  - In particular, they differed in risk factors for PTB, Meis patients being at higher risk
- Covis believes difference in results is due to difference in risk

Analyses Investigated Risk Factors of Preterm Birth from Three Data Sources

1. Dorsata medical records database for obstetrics among participating health systems
   - ~1700 pregnancies with confirmed prior preterm birth
   - Only untreated subjects were included (N=1187)
2. Meis trial
   - Placebo patients only (N=153)
3. PROLONG trial
   - Placebo patients only (N=133)

Logistic Regression Models

- **Dependent variable:** Delivery < 34 weeks
- **Factors considered:**
  - Demographic characteristics
  - Medical history (e.g., diabetes, hypertension)
  - Obstetrical history
  - Substance use (smoking, alcohol, drugs)

Identified Risk Factors for Preterm Birth

- Obstetrical history risk factors
  - Mean gestational age of prior spontaneous deliveries (mGA)
  - Gestational age of most recent prior spontaneous delivery (mrpGA)
  - ≥ 1 spontaneous preterm birth < 32 weeks
  - ≥ 2 spontaneous preterm births < 37 weeks
- Other risk factors
  - Race (Black vs. Non-Black)
  - Inter-pregnancy interval (IPINT)
  - Smoking (yes / no)

Endpoints

- Meis and PROLONG had dichotomous primary endpoints
  - Meis: PTB < 37 weeks
  - PROLONG: PTB < 35 weeks (and neonatal composite index)
- In order to increase sensitivity to detecting treatment effects, most of our post hoc analyses used a continuous endpoint
  - Time from randomization to delivery
  - Capped at 35 weeks so that increases would more clearly reflect a clinical benefit
- Analyzed using linear regression model with treatment, GA at randomization, and mrpGA / mGA as predictor variables

Gestational Age at Randomization

- In its review of the Meis study, FDA noted there was little evidence of any treatment effect in patients randomized at GAs ≥ 20 weeks
  - Covis agrees
- Accordingly, in all the analyses presented below in both Meis and PROLONG, subjects who were randomized at GAs ≥ 20 weeks have been excluded

NDA 21945, Statistical Review (2006)

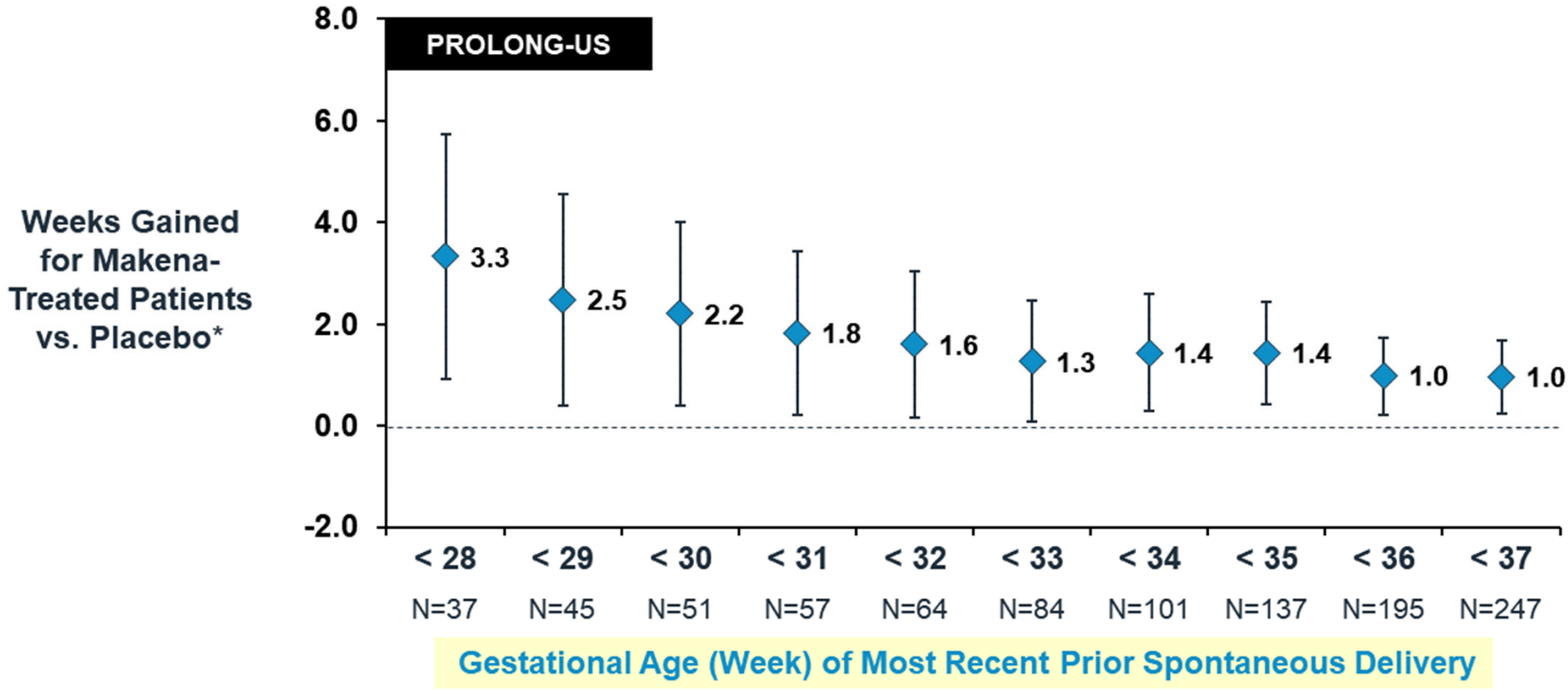
PROLONG: U.S. vs. Ex-U.S.

- U.S. population more representative of relevant population for FDA decision-making
- Ex-U.S. population is different population with different health care system
- Sample size for U.S. population is sufficient for our purposes
- Ex-U.S. PROLONG represents low-risk population based on risk factors
- Accordingly, all of the analyses presented below for PROLONG are for the U.S. patients only

Important Caveats

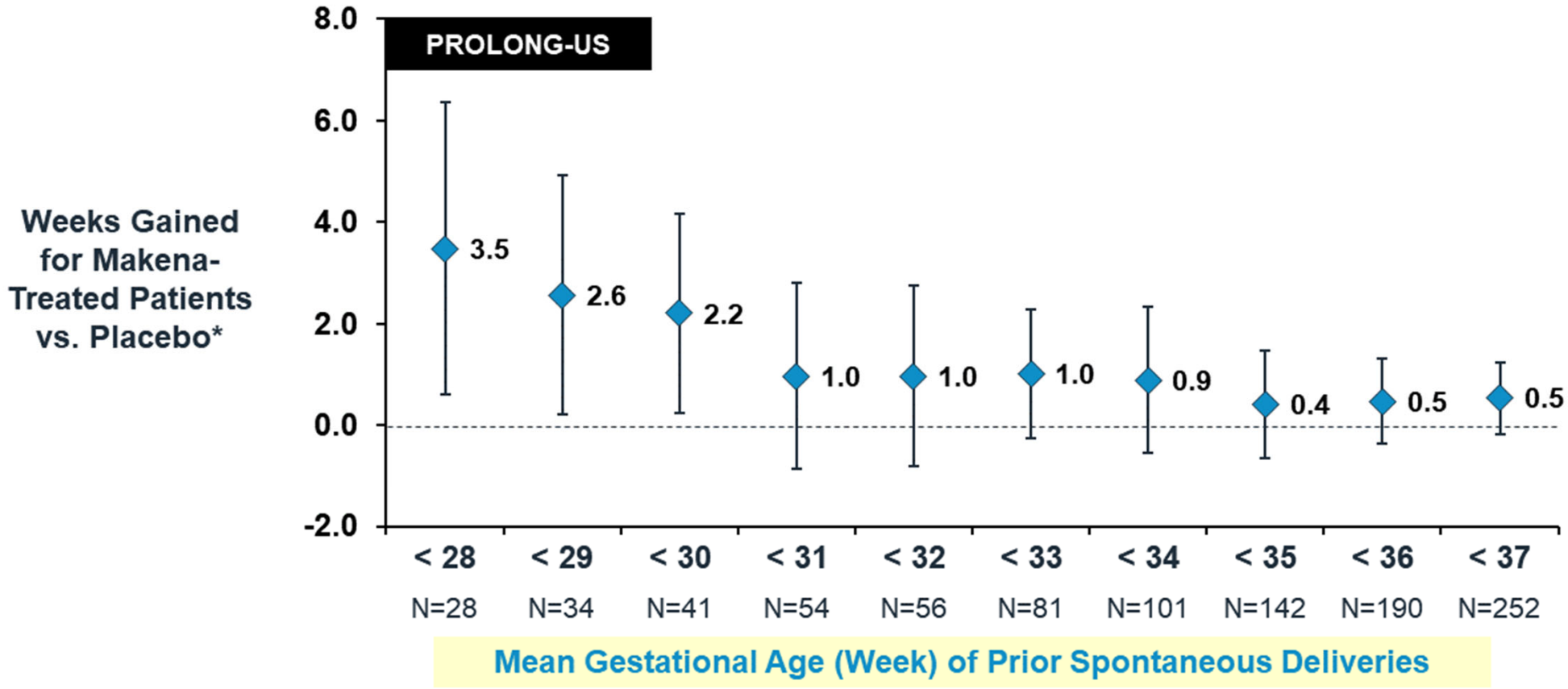
- Post hoc analyses
  - Not pre-specified
- Multiple comparison issues
  - Multiple subgroups
  - Multiple endpoints
- Hypothesis generating

PROLONG-US: Treatment Effect Favoring Makena is Higher Among Patients With More Severe Recent Birth History



*Results from linear regression model for weeks gained with treatment, gestational age at randomization, and mrpGA as predictor variables.

PROLONG-US: Treatment Effect Also Increases with Risk Based on Mean Gestational Age of Prior Deliveries



*Results from linear regression model for weeks gained with treatment, gestational age at randomization, and mGA as predictor variables.

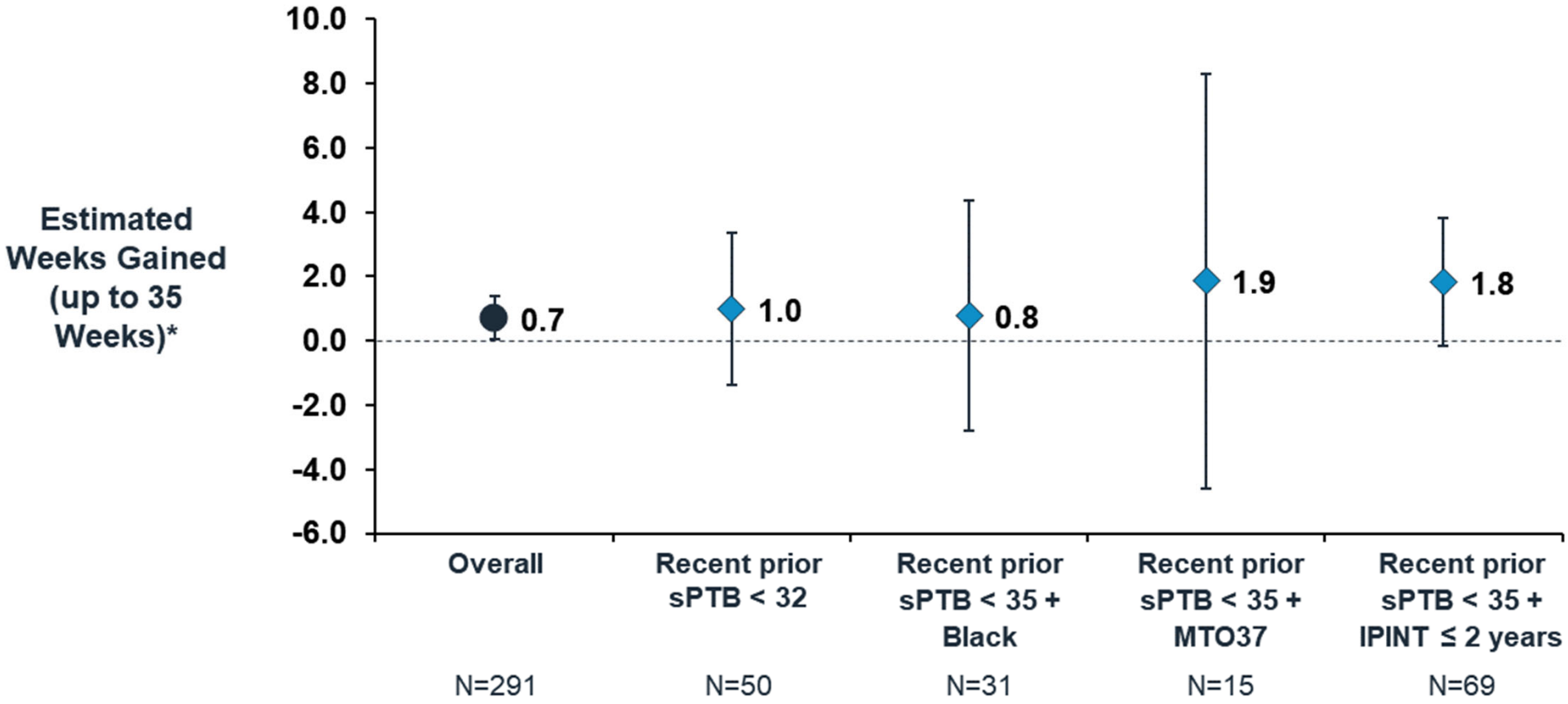
Results in PROLONG-US Show Greater Treatment Effect with Greater Risk

- Strong trend in weeks gained from 1 to > 3 as most recent gestational age categories decrease from < 37 to < 28
- Similarly strong trend in weeks gained from 0.5 to > 3 as mean gestational age categories decrease from < 37 to < 28

Selected Potential Higher-Risk Subgroups

- Based on these results and published literature on preterm birth risks, we examined selected higher-risk subgroups
  - Recent spontaneous preterm birth (sPTB) < 32 weeks
  - Recent sPTB < 35 weeks and multiple sPTBs < 37 weeks
  - Recent sPTB < 35 weeks and short interpregnancy interval (≤ 2 years)
  - Recent sPTB < 35 weeks and Black race

PROLONG-US Results for Higher-Risk Subgroups



*Results from linear regression model for weeks gained with treatment, gestational age at randomization, and mrpGA as predictor variables.

Higher-Risk Target Population Analyzed

- Women with ≥ 1 recent spontaneous preterm birth < 35 weeks and ≥ 1 additional risk factor
  - Recent prior spontaneous preterm birth < 32 weeks
  - Multiple prior spontaneous preterm births < 37 weeks
  - Last pregnancy within 2 years
  - Women who are Black

Results in Higher-Risk Target Patient Population for Continuous Endpoint: Nominally Statistically Significant

Study	N	Estimated Difference in Time from Randomization to Delivery (up to 35 weeks)[1]	95% CI
PROLONG-US	87	1.86	(0.18, 3.54)
Meis	164	1.33	(0.08, 2.59)

1. Estimates are from model with time from randomization to delivery (capped at 35 weeks gestation) as outcome variable and treatment, gestational age at randomization, and mrpGA as predictor variables.

Results in Higher-Risk Target Patient Population for Dichotomous Endpoints: Favorable Point Estimates in PROLONG and Nominally Statistically Significant in Meis

Study	N	Endpoint	Odds Ratio	95% CI
PROLONG-US	87	PTB < 37	0.69	(0.28, 1.73)
		PTB < 35	0.55	(0.19, 1.58)
		PTB < 32	0.36	(0.09, 1.44)
Meis	164	PTB < 37	0.24	(0.12, 0.48)
		PTB < 35	0.35	(0.18, 0.70)
		PTB < 32	0.33	(0.15, 0.70)

Estimates are from logistic regression model with preterm birth (either < 32, < 35, or < 37) as outcome variable and treatment as predictor variable.

Summary

- Have identified a target patient population of higher-risk subjects for which:
  1. New endpoint of weeks from randomization to delivery is nominally statistically significant in both Meis and PROLONG-US
  2. Old primary endpoints of PTB < 35 and PTB < 37 are nominally statistically significant in Meis and have favorable point estimates in PROLONG-US

Additional Publications Supporting Makena's Efficacy

Raghav Chari, PhD

Chief Innovation Officer

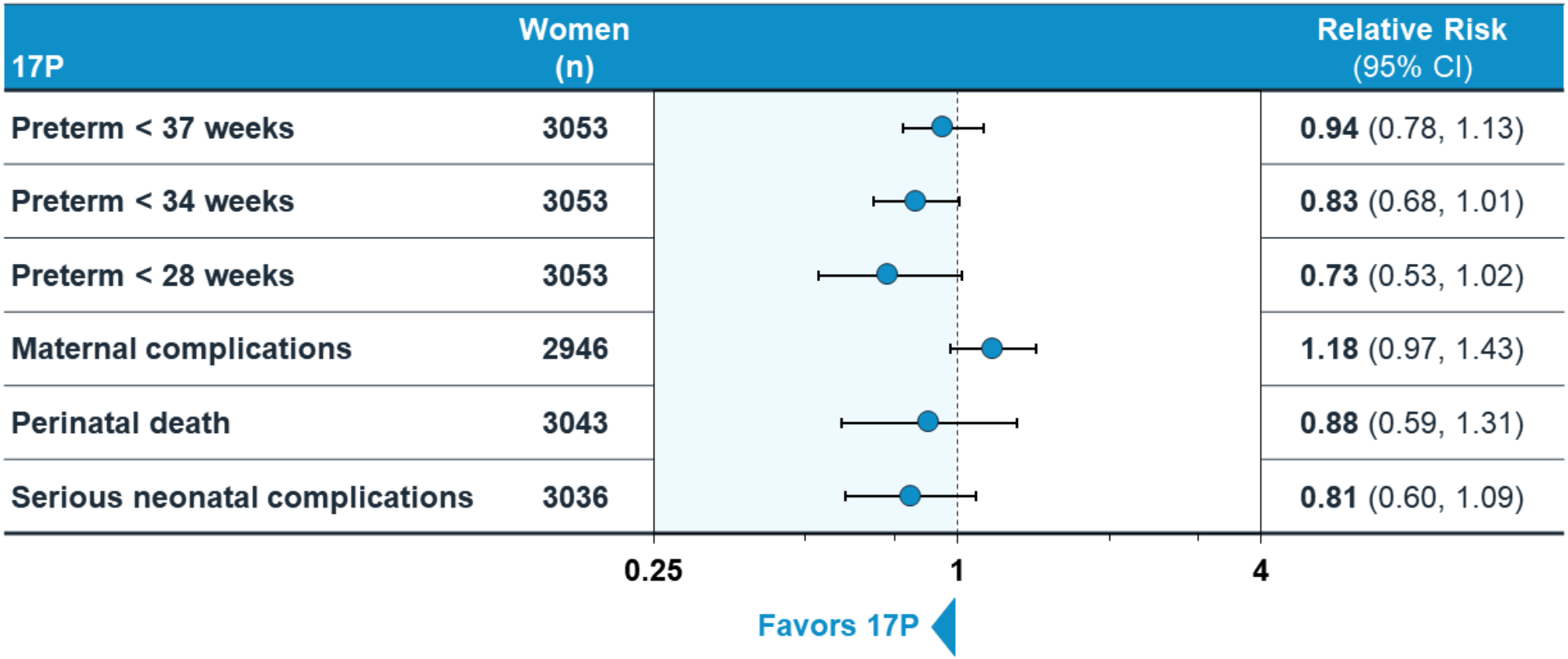
COVIS Pharma

EPPPIC is Largest Existing Individual Patient Data Meta-Analysis of Progestogens Used to Prevent PTB

- Includes participant-level data from 31 trials
  - > 11,000 women
  - > 16,000 offspring
- Includes 5 randomized trials for intramuscular 17P in singleton gestation pregnancies
- First meta-analysis of 17P in singleton gestation pregnancies

The EPPPIC Group, Lancet (2021)
EPPPIC = Evaluating Progestogens for Preventing Preterm Birth International Collaborative

EPPPIC Meta-Analysis Shows Makena Reduces Risk of Early PTB



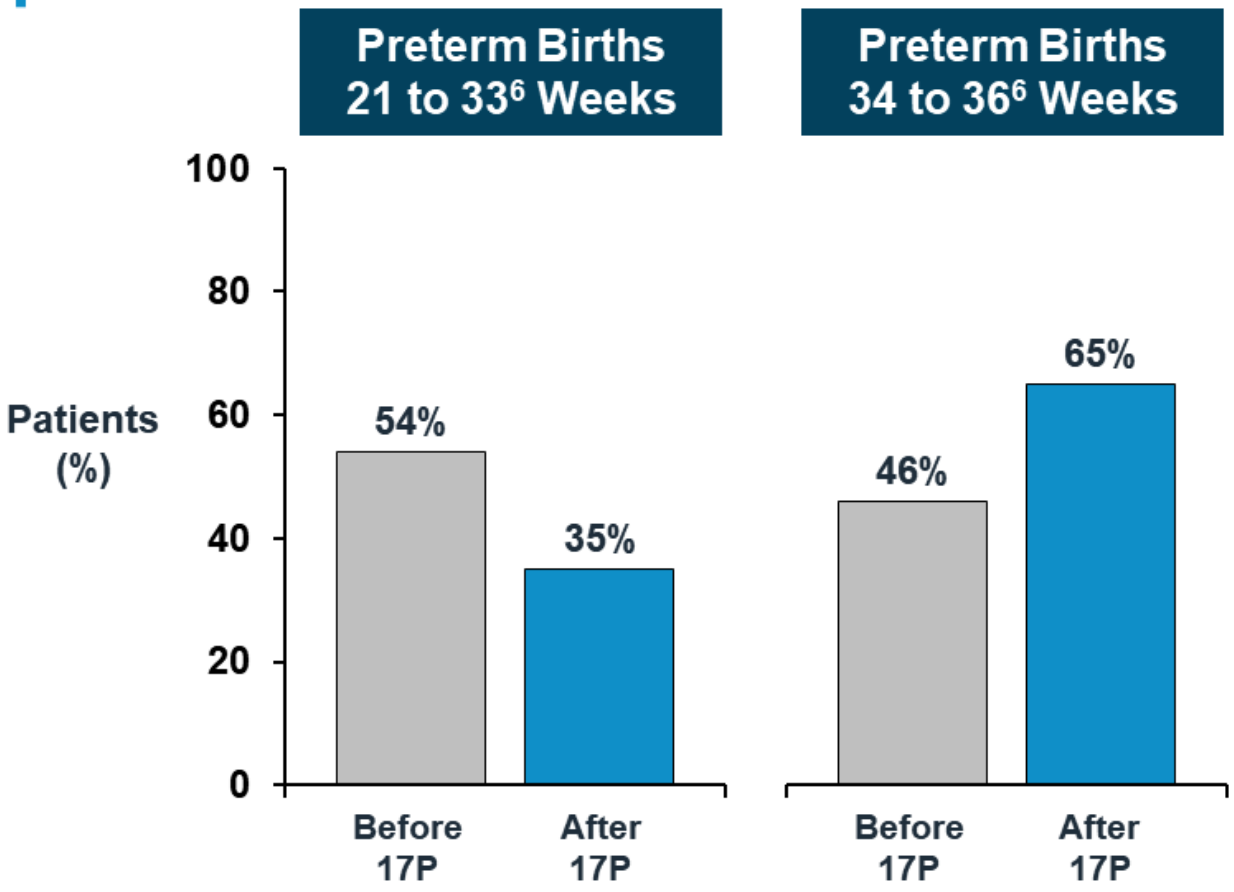
The EPPPIC Group, Lancet (2021)

Observational Study by Bastek et al. Further Characterizes Efficacy of 17P

- Comparison of pre-term birth rate and gestational age distribution
  1. Pre-17P (Jan 2004 - Dec 2005)
  2. Post-17P (Jan 2008 - Dec 2009)
     - Policy change in 2006 established 17P as standard of care and it was prescribed to all eligible women

Bastek et al., Maternal Child Health Journal, (2011)

Bastek et al. Shows 17P was Associated with a Meaningful Delay in Preterm Birth



- No difference in proportion of preterm births < 37 weeks
- 17P associated with delay in preterm birth by 10 days
- Authors explained:

  "evidence that 17-OHPC may have brought us closer towards mitigating the adversity associated with prematurity, which is of great public health significance."

Bastek et al., Maternal Child Health Journal (2011)

Bastek et al. Shows Women Receiving 17P More Likely to Deliver a Preterm Infant During Late Preterm

Gestational Age Range (Weeks)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
$21^0 – 23^6$	**0.38** (0.16, 0.90)	**0.39** (0.16, 0.93)
$24^0 – 27^6$	**0.67** (0.31, 1.46)	**0.67** (0.31, 1.47)
$28^0 – 32^6$	**0.56** (0.31, 1.01)	**0.53** (0.29, 0.96)
$32^0 – 34^6$	**0.77** (0.43, 1.39)	**0.75** (0.42, 1.36)
$34^0 – 36^6$	**2.21** (1.45, 3.39)	**2.30** (1.49, 3.54)

Bastek et al., Maternal Child Health Journal (2011)

Safety

Raghav Chari, PhD
Chief Innovation Officer
COVIS Pharma

Meis Established Makena's Favorable Safety Profile

"**There were no safety findings in the original NDA** submission of April 2006, based on data from Study 002…. Supportive Study 001, Study 17P-FU…. or published medical literature **that would have precluded approval of HPC for the proposed indication**."

CDER's Medical Review of Makena NDA

- Most common AE was injection site reactions
- Non-significant trend toward an increase in 2nd trimester miscarriage rate and stillbirth rate with Makena
- No difference between Makena and placebo arms
  - Incidence of pregnancy complications
  - Overall incidence of combined fetal and neonatal mortality
- Follow-up study showed Makena is safe for fetus when given in 2nd and 3rd trimesters

PROLONG Reaffirmed Positive Safety Profile of Makena Demonstrated in Meis Trial

Summary of TEAE's	Makena N = 1128	Placebo N = 578
Any AEs	57.9%	58.1%
Any maternal pregnancy complication	10.0%	11.1%
Any AEs leading to study drug withdrawal	1.0%	0.9%
Any SAEs	3.0%	3.1%
Maternal deaths	0	0

- No clinically meaningful difference in safety profile between groups

PROLONG Showed Consistent, Favorable Maternal and Fetal Safety Comparable to Placebo

	Makena N = 1130	Placebo N = 578	Relative Risk (95% CI)
Fetal / early infant death	**1.7%**	**1.9%**	**0.87** (0.42, 1.81)
Miscarriage (< 20 weeks)	**0.5%**	**1.3%**	**0.32** (0.09, 1.14)
Stillbirth (≥ 20 weeks)	**1.1%**	**0.5%**	**2.07** (0.59, 7.29)
Early infant deaths	**0.3%**	**0.4%**	**0.73** (0.12, 4.48)

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

CDER's slides from 2019 BRUDAC

Pooled Safety Data Demonstrate Favorable Safety Profile for Makena Compared to Placebo

	Integrated Safety (Meis and PROLONG)	
	Makena N = 1130	**Placebo** N = 578
Admission for preterm labor	**16.4%**	**14.4%**
Preeclampsia or gestational hypertension	**5.2%**	**5.1%**
Nausea	**5.1%**	**4.5%**
Gestational diabetes	**3.6%**	**3.8%**
Headache	**5.0%**	**3.8%**
Injection site pruritus	**4.2%**	**3.8%**
Injection site swelling	**4.0%**	**1.9%**
Back pain	**3.8%**	**2.9%**
Vomiting	**3.6%**	**3.3%**
Urticaria	**3.0%**	**2.3%**

Sibai et al. Journal of Perinatology (2021)

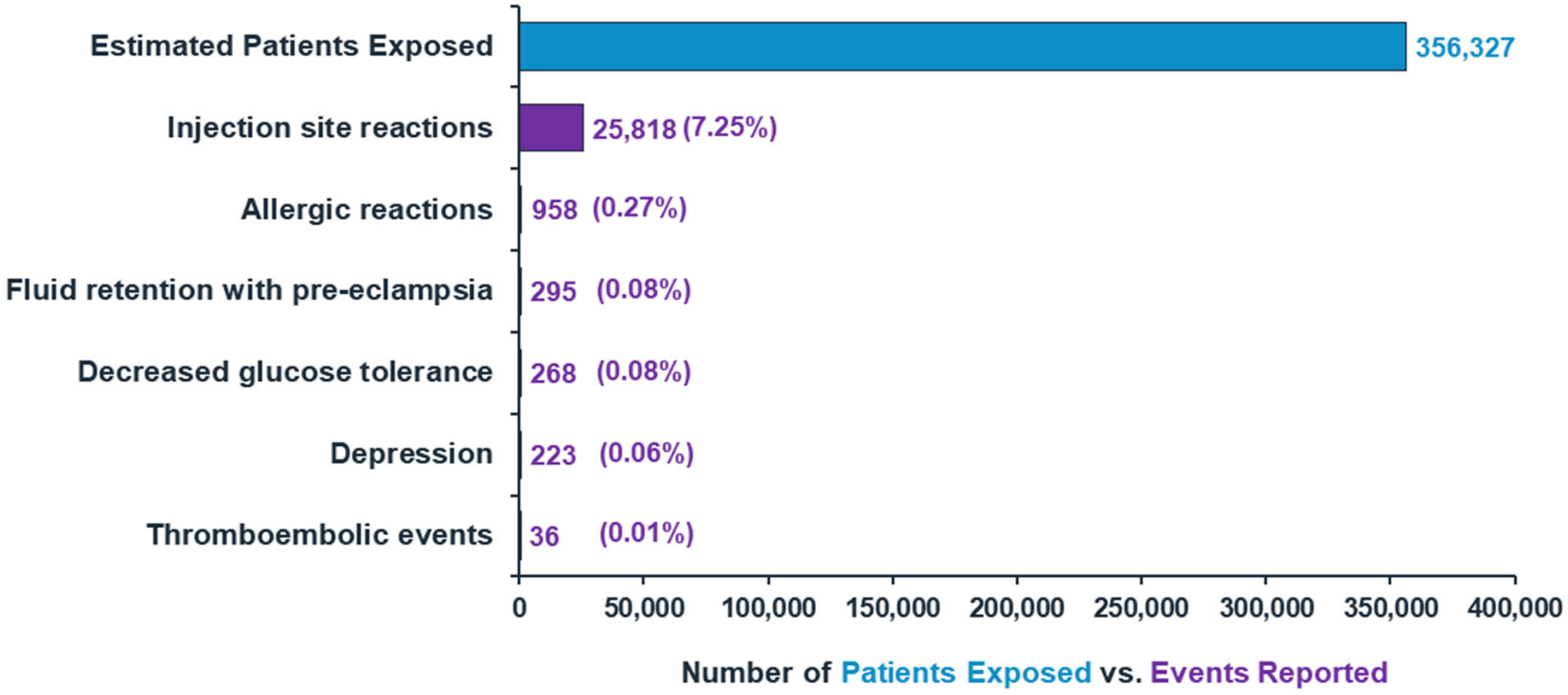
Real-World Use for Over A Decade Supports Positive Safety Profile of Makena

- While **more than 350,000 women** have been treated with Makena in the last decade, **no new safety concerns, signals, or risks** have been identified
- The known potential risks of Makena are already described in its labeling (e.g., thromboembolic events, depression, allergic reactions, decreased glucose retention, fluid retention, injection site reactions)

Reported AEs in > 350,000 women treated are consistent with Makena's labeled safety profile

Covis Data on File (August 31, 2022)

Real-World Use for Over A Decade Supports Positive Safety Profile of Makena



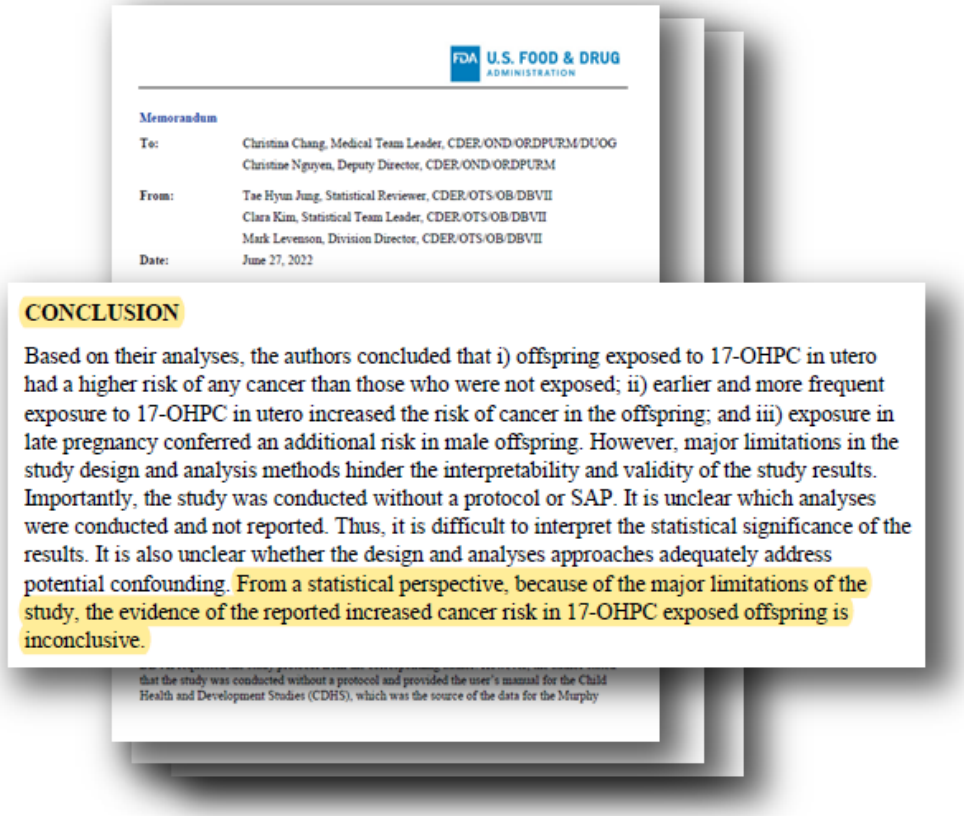
Covis Data on File (August 31, 2022)

Murphy Article is Neither Reliable Nor Relevant to Considerations of Safety and Efficacy of Makena

1. Article describes a retrospective analysis of Delalutin, not Makena
   - Both contain 17P but have key differences with respect to indication, timing, and frequency of administration
2. Murphy article has several methodological flaws that undermine the validity of its conclusions
3. Two expert statisticians have submitted declarations pointing to various deficiencies in study design and analysis
4. ACOG announced, "**Due to the limitations in the design, the study's findings are not conclusive and should not influence practice**"
5. CDER's internal documents also acknowledge the numerous flaws

Murphy et al., Am. J. Obstet. Gynecol. (2022)

CDER's Internal Documents Acknowledge Numerous Flaws In Murphy



U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: Christina Chang, Medical Team Leader, CDER/OND/ORDPURM/DUOG
Christine Nguyen, Deputy Director, CDER/OND/ORDPURM

From: Tae Hyun Jung, Statistical Reviewer, CDER/OTS/OB/DBVII
Clara Kim, Statistical Team Leader, CDER/OTS/OB/DBVII
Mark Levenson, Division Director, CDER/OTS/OB/DBVII

Date: June 27, 2022

CONCLUSION

Based on their analyses, the authors concluded that i) offspring exposed to 17-OHPC in utero had a higher risk of any cancer than those who were not exposed; ii) earlier and more frequent exposure to 17-OHPC in utero increased the risk of cancer in the offspring; and iii) exposure in late pregnancy conferred an additional risk in male offspring. However, major limitations in the study design and analysis methods hinder the interpretability and validity of the study results. Importantly, the study was conducted without a protocol or SAP. It is unclear which analyses were conducted and not reported. Thus, it is difficult to interpret the statistical significance of the results. It is also unclear whether the design and analyses approaches adequately address potential confounding. From a statistical perspective, because of the major limitations of the study, the evidence of the reported increased cancer risk in 17-OHPC exposed offspring is inconclusive.

that the study was conducted without a protocol and provided the user's manual for the Child Health and Development Studies (CDHS), which was the source of the data for the Murphy

"There are significant issues with attempting to apply the results of the Murphy study to the current regulatory and clinical environment"

- CAPT David Money, Director, Division of Epidemiology II (DEPI II), Office of Surveillance and Epidemiology (OSE), CDER

Murphy "provides insufficient evidence to support regulatory action regarding a long-term cancer risk in offspring who were exposed in utero to 17-OHPC"

The study's limitations "preclude this study from contributing definitively to this drug safety issue"

- Wei Liu, Team Leader, DEPI II, OSE, CDER

Compounded Drugs are Not Subject to Rigorous Safety and Quality Controls

- Compounded drugs do not have FDA-approved labeling
- 503A compounding pharmacies exempt from good manufacturing practices
  - 130 warning letters and more than 100 recalls
- **26 recalls of compounded 17P between 2013-2019**
  - Lack of sterility assurance
  - Product contamination
  - Bacteria and fungi in suspension fluid

Gandell et al., Current Medical Research and Opinion (2020)

Clinical Perspective
Medical Community Supports Makena as an Important Treatment Option

Yolanda Lawson, MD

Associate Attending Physician – Baylor University Medical Center
President Elect – National Medical Association

Why Does Makena Matter to Clinicians?

- Preterm birth is a serious medical condition, affecting a significant number of women and their babies
  - Lower gestational age at delivery, greater the risk to the baby
  - 2 weeks of added gestational age before 35 weeks can significantly reduce risks to the baby
- Preterm birth has an enormous impact on the emotional and economic well-being of women and their families
- Greater risk of preterm birth for women who are Black or other minority groups
- It is important for Makena to remain as a treatment option to support clinical decision-making

Compounded 17P is an Imperfect Alternative

- Clinicians are accustomed to compounding when an approved treatment is not available
  - Covis' recent survey of ~400 obstetricians, gynecologists, and maternal-fetal medicine specialists shows that **> 25% would be very likely to recommend compounded medication if there is no approved alternative**
- Compounded drugs may have issues with purity, consistency, and quality
- Some communities lack access to compounding pharmacies, creating further equity issues

Safety Profile of Makena as Reported with Real-World Use Consistent with My Clinical Experience

- > 350,000 women have been treated with Makena
- No new safety concerns, signals, or risks have been identified
- Known potential risks of Makena, already described in its labeling
  - Injection site reactions are common with any injected product

Covis Data on File (August 31, 2022)

Medical Community Continues To Support 17P as an Important Treatment Option

Following CDER's proposal to withdraw Makena (Oct. 5, 2020)

"At this time, ACOG recommendations remain unchanged . . . Current guidelines in the United States recommend the use of progesterone supplementation in women with prior spontaneous preterm birth. Consideration for offering 17-OHPC to women at risk of recurrent preterm birth should continue to take into account the body of evidence for progesterone supplementation, the values and preferences of the pregnant woman and the resources available."

American College of Obstetricians and Gynecologists (ACOG) Statement on FDA Proposal to Withdraw 17p Hydroxyprogesterone Caproate (Oct. 2020)

Medical Community Continues To Support 17P as Important Treatment Option

Following CDER's proposal to withdraw Makena (Oct. 5, 2020)

> "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"

Society for Maternal-Fetal Medicine (SMFM) Statement (Oct. 2020)

Many Organizations Agree Makena Should Remain Available as a Treatment Option

- American Association of Birth Centers
- American Society for Reproductive Medicine
- Association of Women's Health, Obstetric and Neonatal Nurses
- Black Mamas Matter Alliance
- Black Women's Health Imperative
- Expecting Health
- Healthy Mothers, Healthy Babies
- HealthyWomen
- In Our Own Voice
- Jewish Women International
- Miracle Babies
- Mom Congress
- National Birth Equity Collaborative
- National Black Midwives Alliance
- National Black Nurses Association
- National Coalition for Infant Health
- National Consumers League
- National Medical Association
- National Minority Qualify Forum
- National Partnership for Women & Families
- New Voices for Reproductive Justice
- PA Foundation
- Perinatal Health Equity Foundation
- Preterm Birth Prevention Alliance
- Sidelines High-Risk Pregnancy Support
- SisterReach
- SisterSong – The National Women of Color Reproductive Justice Collective
- Southern Birth Justice Network
- SPARK Reproductive Justice Now!
- 1,000 Days
- 2020 Mom

"A decision to withdraw approved 17P products may deepen profound existing maternal and infant health inequities in the U.S. We urge you to not withdraw 17P treatments, so that all pregnant people will continue to be empowered with access to a safe treatment option for preterm birth."

- Black Women's Health Imperative

Proposed Path Forward While Makena Remains on the Market

Raghav Chari, PhD

Covis is Committed to Confirming Clinical Benefit of Makena

1

Partial Withdrawal to Higher-Risk Target Population

- Narrow labeling to use in a higher-risk target population identified through our analysis of Meis and PROLONG
- No active promotion of Makena

2

Conduct a Randomized Controlled Trial (RCT)

- Confirm Makena's effect on intermediate clinical endpoint in the identified higher-risk target patient population – completed within 4- to 6-years

3

Optionally, Also Conduct an Observational Study

- Further validate the benefit of prolonging gestational age on neonatal morbidity and mortality with 17P treatment

Analyses Support a Higher-Risk Population

Proposed Higher-Risk Population

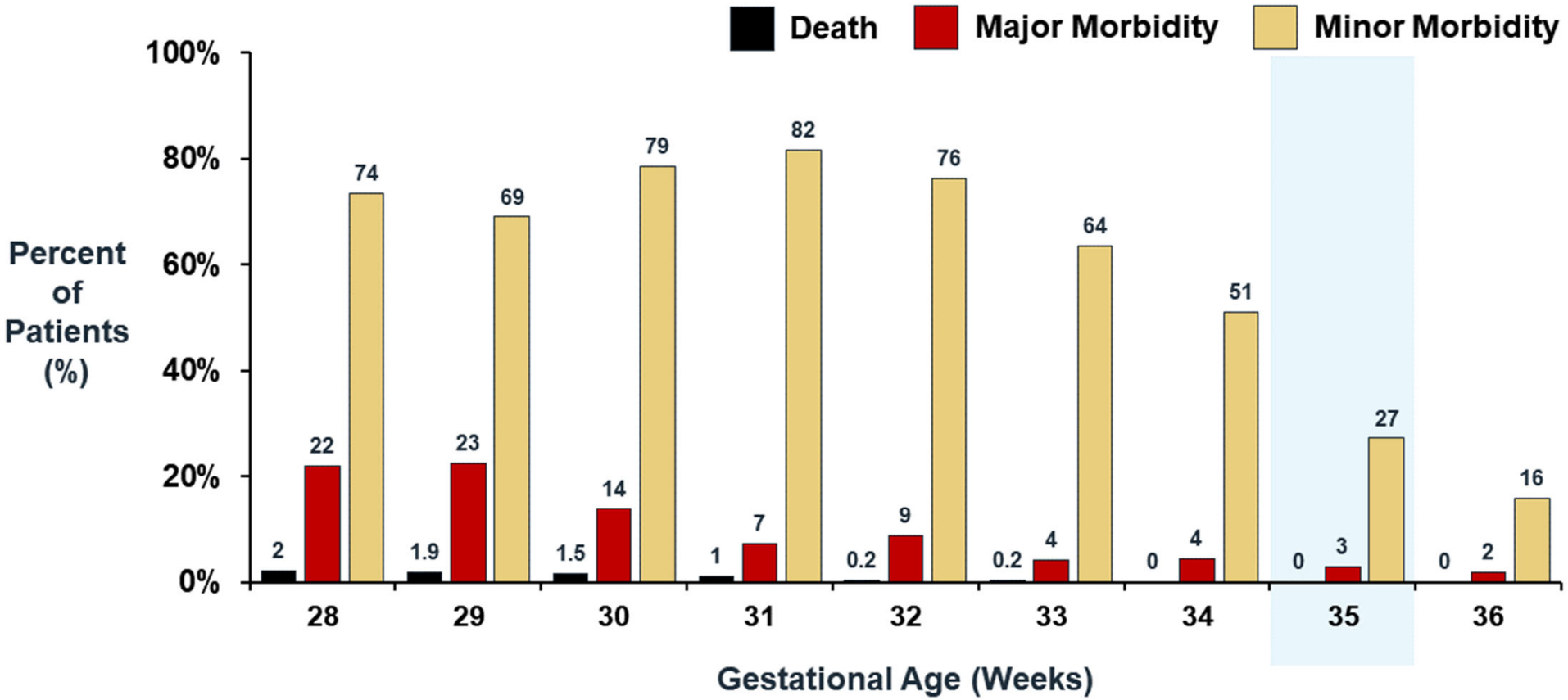
- Women with ≥ 1 recent prior spontaneous preterm birth < 35 weeks **and**
- ≥ 1 additional risk factor such as
  - Prior spontaneous preterm birth < 32 weeks
  - Multiple spontaneous preterm births < 37 weeks
  - Last pregnancy within 2 years
  - Other social determinants of preterm birth

Covis Proposes Conducting an RCT With Time-from-Randomization-to-Birth as the Primary Endpoint

Proposed Randomized Controlled Trial

- **Proposed population:** Women with ≥ 1 prior spontaneous preterm birth < 35 weeks and ≥ 1 additional risk factor
- **Trial design**: ~400 patients randomized 2:1
- **Primary endpoint:** Increase in time-from-randomization-to-birth for Makena vs. placebo, capped at 35 weeks gestation
- **Estimated completion:** 4- to 6-years

Clinical Relevance of Efficacy Endpoint of Gestational Age of Prolonging a Pregnancy



Manuck et al., Am. J. Obstet. Gynecol. (2016)

Proposed Inclusion Criteria for RCT will Improve Enrollment of Higher-Risk Patients

Key Inclusion Criteria

1. Previous singleton qualifying sPTB < 35 weeks occurred within the last 5 years and ≥ 1 additional risk factor
2. Documented medical history of first trimester ultrasound to calculate gestational age of qualifying delivery

Sample Size Estimates for Endpoint: Time-from-Randomization-to-Delivery (Weeks), Capped at 35 Weeks Gestation

Difference in Means	Allocation (17P: Placebo)	Sample Size		
		17P	Placebo	Total
1.0	1:1	191	191	382
	2:1	286	143	429
2.0	1:1	49	49	98
	2:1	74	37	111

1. Two-sample t-test
2. Two-sided Alpha = 0.05
3. Difference in Means (17P - Placebo): 1.0 or 2.0 weeks
4. Common SD: 3.0
5. Power = 90%

Feasibility Assessments Suggest a Randomized Controlled Trial Can Be Conducted in U.S.

MFMU Network Survey

Sean Blackwell, MD

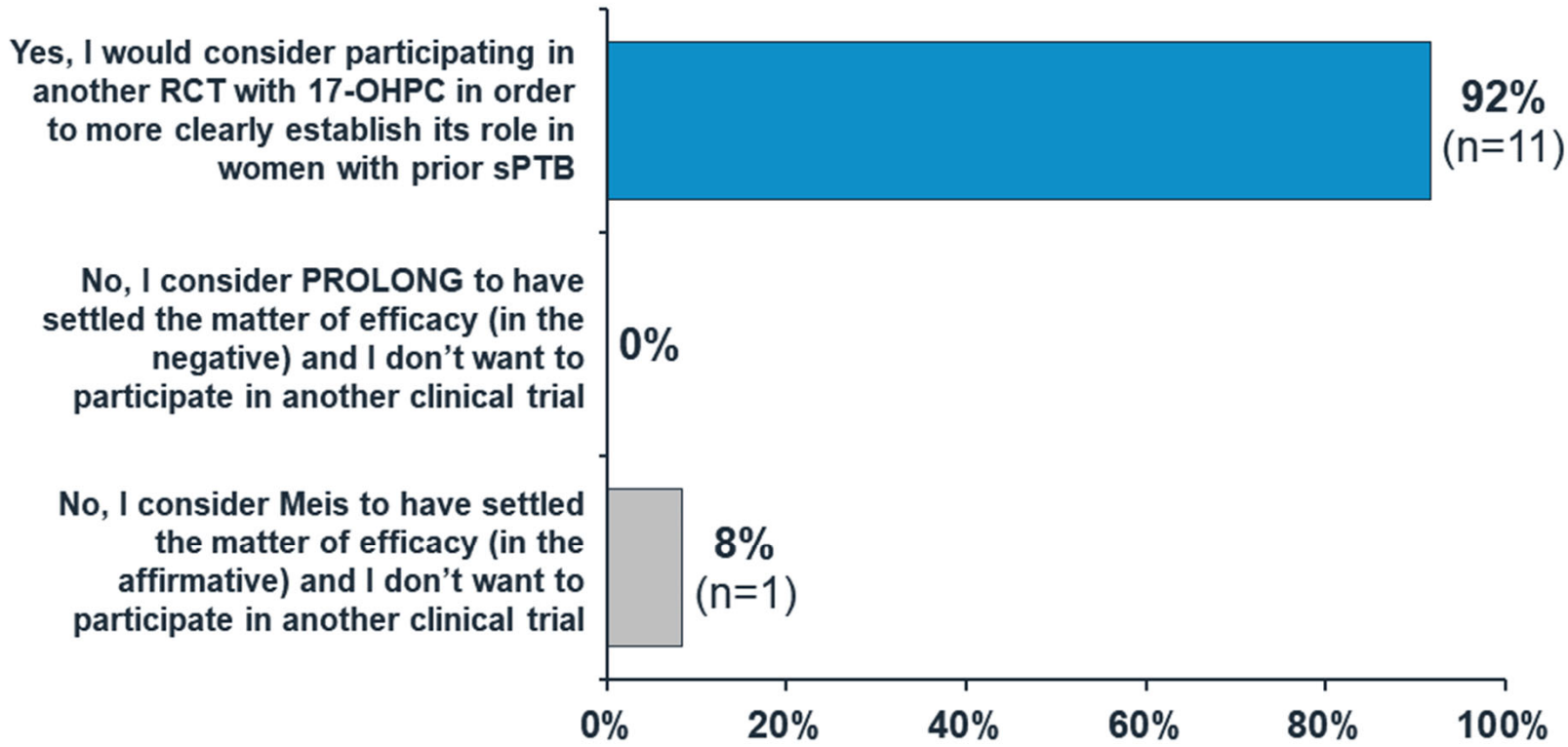
Chair and Professor

Department of Obstetrics, Gynecology and Reproductive Sciences

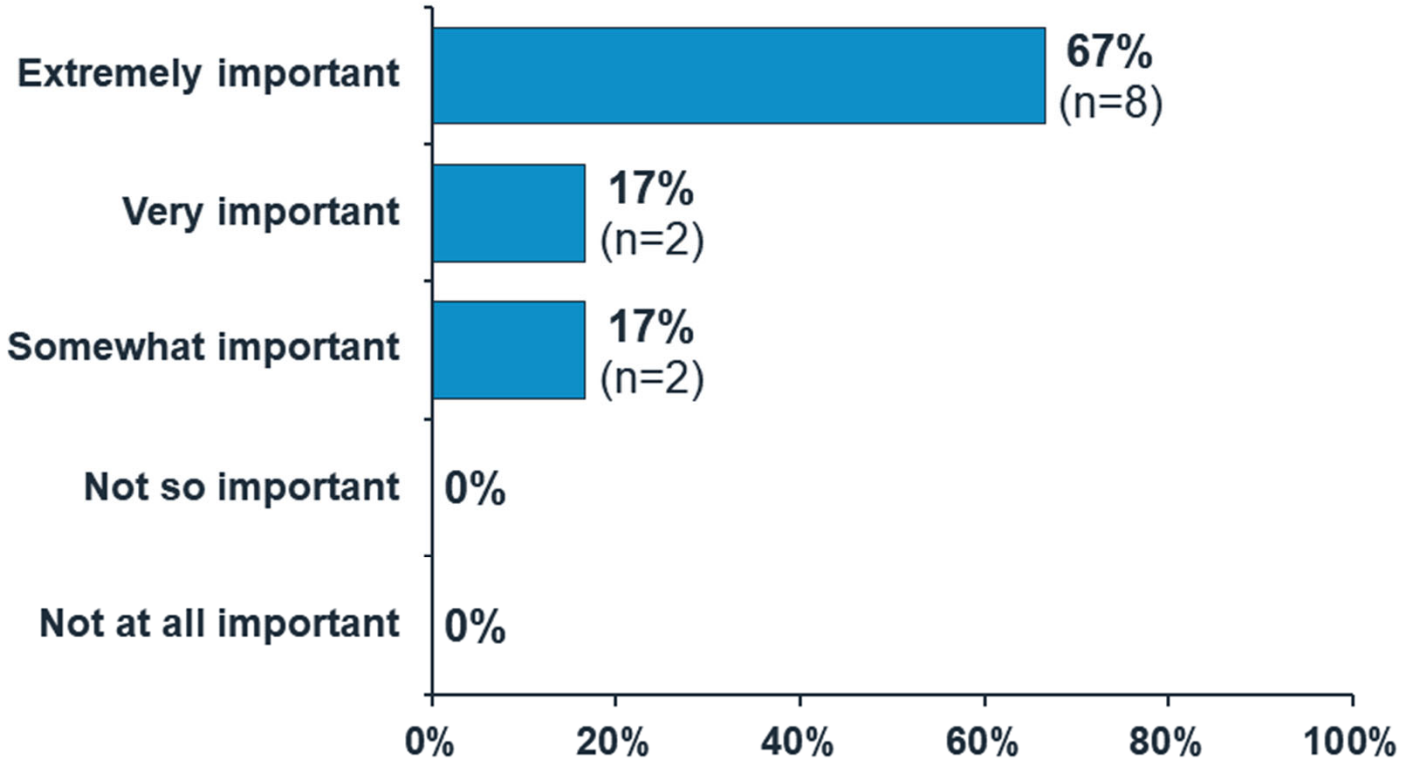
McGovern Medical School-UTHealth at Houston

Houston, Texas

Q1 What is your level of interest in participating in another 17-OHPC Trial? It would be only in the US, placebo-controlled, and involve women with singleton pregnancy and prior sPTB.

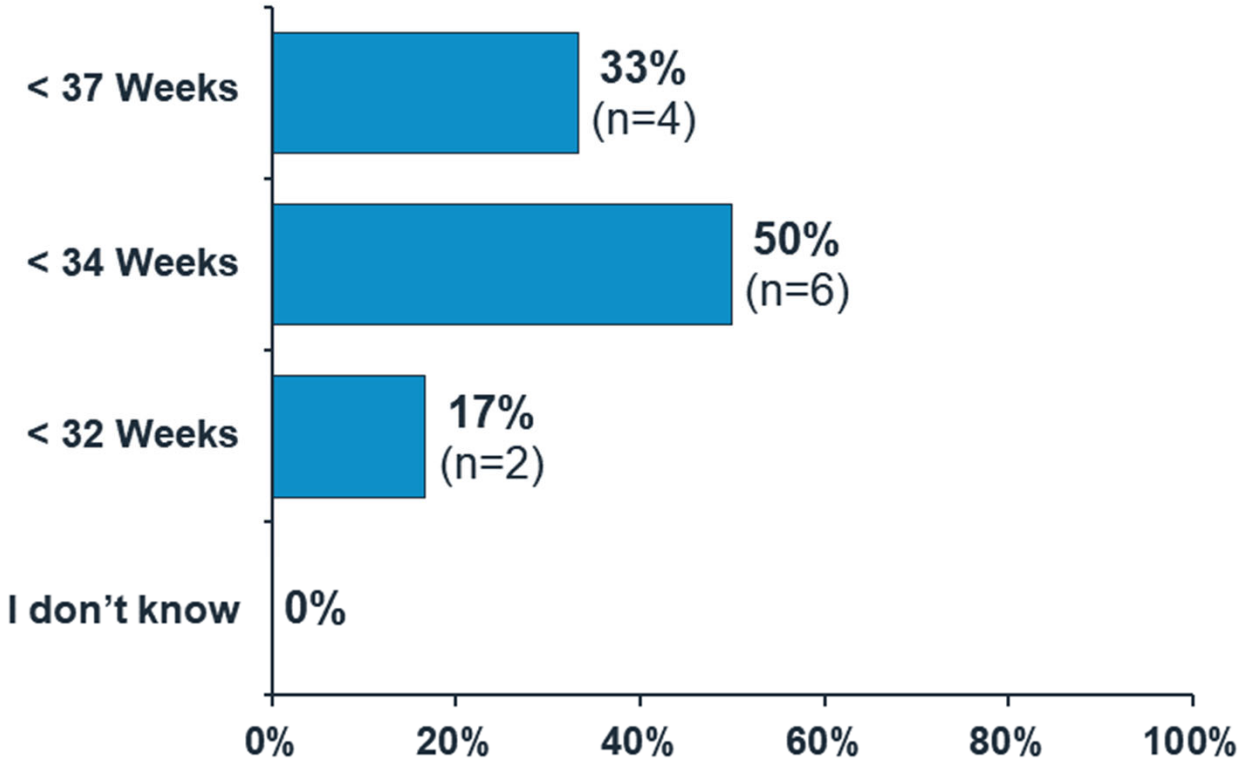


Q2 If another RCT was conducted in women with a prior sPTB (17-OHPC vs. placebo), in your opinion, how important is the following study design issue? After randomization, a short cervix developed (transvaginal ultrasound ≤ 25 mm) and the protocol allows for (rescue with) cerclage placement.



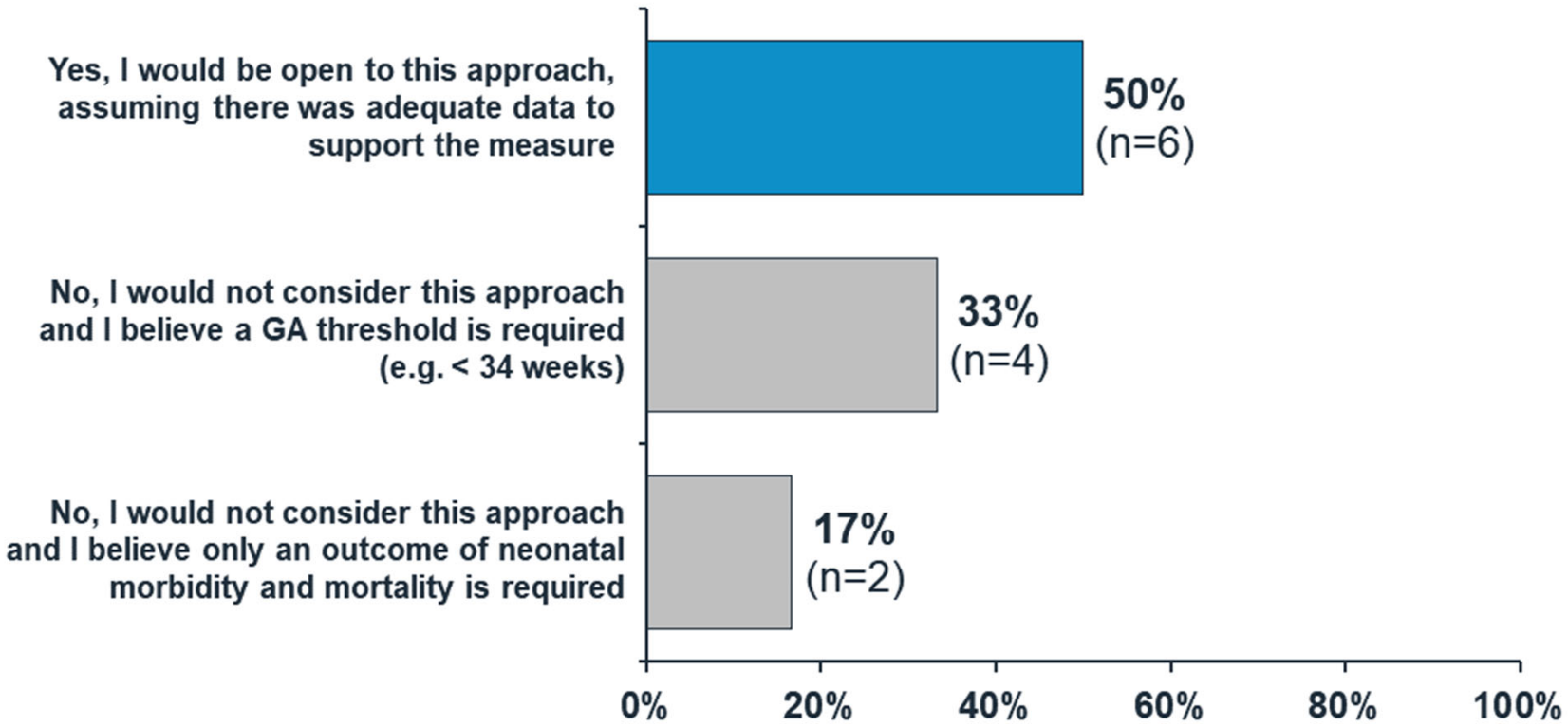
Q3

In order to increase the "risk profile" of women eligible for the RCT, having a lower gestational age threshold for a qualifying sPTB has been discussed. This may identify women more likely to respond to 17OHPC. In both Meis and PROLONG, women qualified after a prior sPTB < 37 weeks. What is your opinion on the best GA (weeks) entry threshold?



Q4

What is your opinion regarding evaluating the primary outcome in a different manner? Would you consider a "delay in delivery" that had clinical meaning (e.g. 7 days difference between placebo vs. 17 OHPC)? This delay in delivery could be a continuous outcome (days) or viewed as a "time to event" metric.



Covis Identified Additional Non-Academic Sites Willing to Participate in an RCT

- Formal RCT feasibility assessment
  - ~100 patients/year available from 19 U.S., 10 OUS sites (~66 patients/year if focused on U.S. only)
- Survey conducted within Dorsata practice network
  - ~60-180 patients per year from this network

Covis has Surveyed Providers to Assess Feasibility of Enrolling RCT

- 40% of physicians who use progesterone medication for patients at risk of spontaneous PTB recommend the therapy by injection
- 80% say they are likely to recommend a pregnant patient enroll in a placebo-controlled study when the product is FDA approved
  - 39% if the product has not been approved by the FDA
  - 15% if the product has had its marketing approval withdrawn

Covis Has Surveyed Patients to Assess Feasibility of Enrolling in an RCT

- Survey included 325 patients with a history of spontaneous PTB
- 95% say it is important that treatment options to reduce the risk of another preterm birth be approved by FDA
- 68% would take an approved prescription drug during pregnancy that is intended to prevent recurrent preterm birth and is being studied
  - Only 37% would be willing to take a drug being studied that is not approved

Covis Willing to Voluntarily Withdraw Makena Based on RCT Futility and Feasibility Assessments

Proposed Randomized Controlled Trial

Pre-specified criteria that would result in voluntary withdrawal:

1. Interim efficacy analysis for futility
2. Assessment of enrollment projections at Month 24 to evaluate feasibility of completing the trial in a 4- to 6-year timeframe
3. Outcome of study is negative

Potential Observational Study to Evaluate Clinical Outcomes

Potential Observational Study

- Establish the relationship between gestational age and neonatal outcomes in treated vs. untreated patients
- Validate benefit of weeks-gained on 17P in the RCT

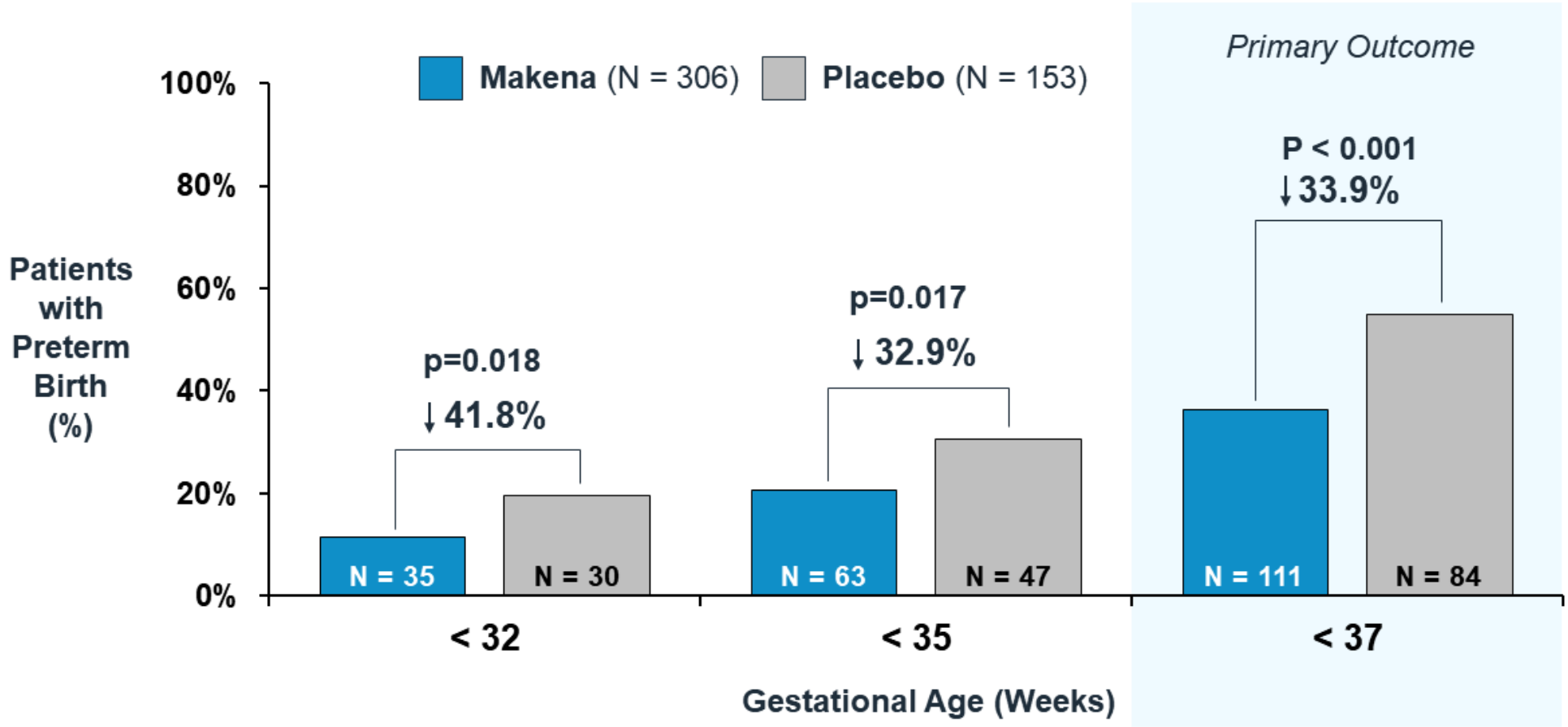
COVIS Position on Questions Presented

Question 1: Do findings from PROLONG verify clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

Findings from PROLONG Do Not Verify Clinical Benefit of Makena

Question 2: Does available evidence demonstrate that Makena is effective for its approved indication?

Makena Met Primary Endpoint Demonstrating Significant Reduction in Preterm Births < 37 Weeks



Meis et al., NEJM 2003

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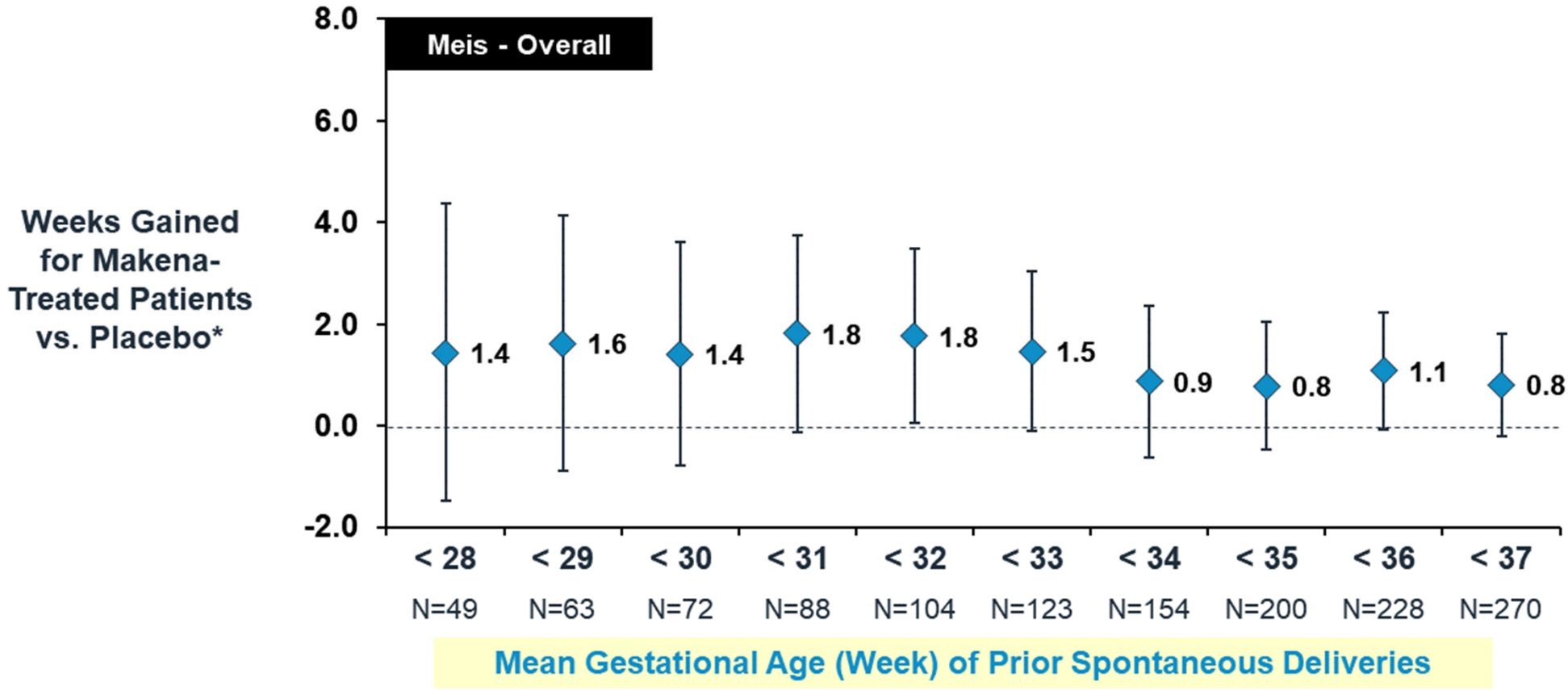
COVIS Backup - Slides Shown

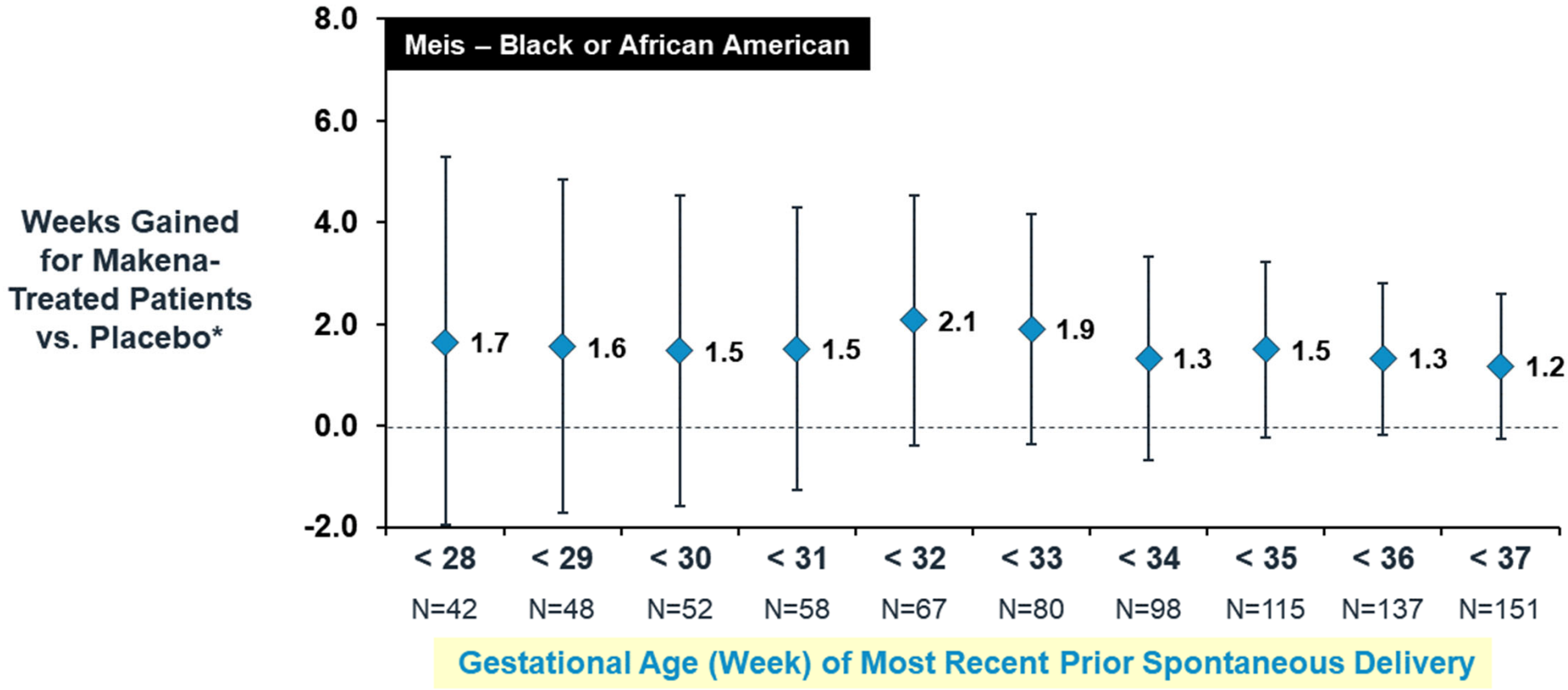
Day 2 – October 18, 2022

Meis: Weak Suggestion of Increased Treatment Effect with Increases in Risk Based on Mean Gestational Age of Prior Deliveries



*Results from linear regression model for weeks gained with treatment, gestational age at randomization, and mGA as predictor variables.

Meis: Large Increase in Treatment Effect Among Blacks (a Risk Factor)



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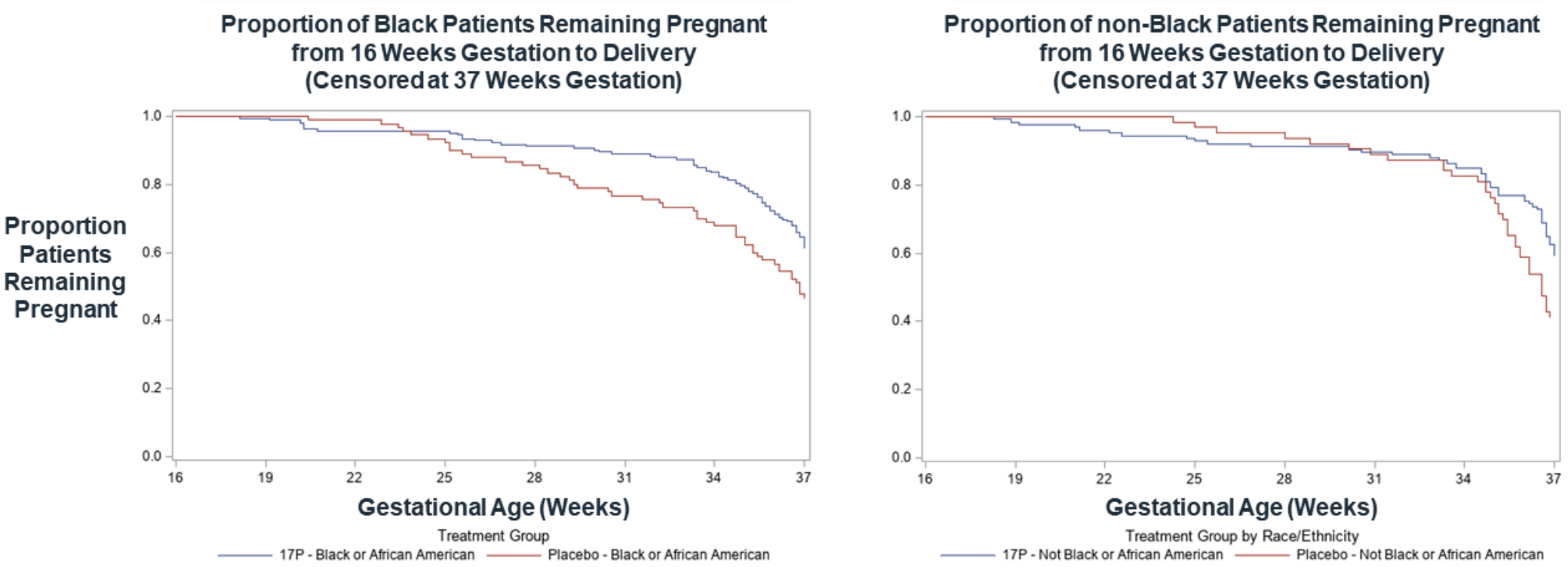
Meis (Black): Estimated Treatment Effect (Weeks Gained) for 17P in Subgroups Defined by Mean Gestational Age (mGA) of Prior Deliveries Among Subjects Randomized at <20 Weeks GA

mGA Subgroup	Total (N)	Estimated Treatment Effect (weeks gained)	Lower (95% CL)	Upper (95% CL)	p-value
mGA< 28	34	2.81	-1.34	6.96	0.1766
mGA< 29	40	2.83	-1.02	6.68	0.1451
mGA< 30	48	2.47	-0.78	5.73	0.1328
mGA< 31	58	2.83	0.07	5.59	0.0448
mGA< 32	68	2.28	-0.16	4.73	0.0667
mGA< 33	78	2.06	-0.21	4.33	0.0746
mGA< 34	100	1.62	-0.28	3.52	0.0939
mGA< 35	124	1.29	-0.35	2.94	0.1221
mGA< 36	144	1.66	0.19	3.13	0.0273
mGA< 37	168	1.41	0.09	2.73	0.0369

Meis (Overall): Visual Inspection of Time-to-Delivery Curves Suggests Differential Treatment Effect by Race

Black patients: Benefit of 17P apparent early (from ~25 weeks gestation)

Non-Black patients: Benefit of 17P apparent later (after ~35 weeks gestation)



Meis: Estimated Weeks Gained (Capped at 37) for High-Risk Subgroups

Subgroups	Total (N)	Estimated Treatment Effect (weeks gained)	(95% CI)	p-value
Overall	459	0.72	(-0.07, 1.52)	0.0740
Randomized at GA < 20 - Overall	31	1.26	(0.21, 2.31)	0.0190
mrpGA < 35	193	1.28	(-0.19, 2.75)	0.0879
mrpGA < 35 and black	115	1.99	(0.02, 3.96)	0.0478
mrpGA < 35 and ipint ≤ 5	165	1.87	(0.39, 3.35)	0.0135
mrpGA < 35 and mto37	62	3.38	(1.03, 5.74)	0.0056
mrpGA < 35 and ipint ≤ 5 and mto37	56	4.09	(1.80, 6.38)	0.0008
mrpGA < 35 and ipint ≤ 5 and black	96	2.68	(0.65, 4.72)	0.0104
mrpGA < 35 and mto37 and black	44	2.36	(-0.57, 5.29)	0.1112

PROLONG – Power Considerations

- **Power for PTB < 37 weeks and < 35 weeks in PROLONG by Relative Reduction**

Placebo Rate	5%	10%	20%	25%	30%	35%
21.9% (< 37 weeks)	6.8	18.4	56.0	76.0	90.1	97.2
11.5% (< 35 weeks)	6.4	10.1	29.8	45.0	**58.9**	74.5

Retrospective Observational Study Comparing Frequencies of Neonatal Morbidity, Death and Length of Stay

- Retrospective individual case review for qualifying subjects

Treatment Groups

- **17P-Treated Mothers** (as indicated per Makena label)
- **Untreated Mothers**

Gestational Age Ranges

< 28	28-29	29-30	30-31	31-32	32-33	33-34	34-35	35-37

- **Endpoint:** Comparison between event rates (or changes of rates)
  - **Outcomes*:** Major morbidity, minor morbidity and death
  - **Timepoints:** All gestational age ranges

*Major and minor morbidities as defined in Manuck (2016) et al.

IRESSA (gefitinib) Label Change

- Indication was changed to patients "who, in the opinion of their treating physician, are currently benefiting, or have previously benefited, from gefitnib treatment."
- Change in "Indications and Usage" from May 2004 to June 2005:

IRESSA is indicated as monotherapy for the continued treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies who are benefiting or have benefited from IRESSA.

In light of positive survival data with other agents including another oral EGFR inhibitor, physicians should use other treatment options in advanced non-small cell lung cancer patient populations who have received one or two prior chemotherapy regimens and are refractory or intolerant to their most recent regimen.

The effectiveness of IRESSA was initially~~is~~ based on objective response rates (see CLINICAL PHARMACOLOGY- Clinical Studies section). ~~There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.~~Subsequent studies intended to demonstrate an increase in survival have been unsuccessful. Specifically, results from a large placebo-controlled randomized trial in patients with advanced NSCLC who progressed while receiving or within 90 days of the last dose of chemotherapy or were intolerant to the most recent prior chemotherapy regimen, did not show an improvement in survival (see CLINICAL PHARMACOLOGY- Clinical Studies section). . . .

FDA, New Labeling and Distribution Program for Gefitnib (Iressa) (2005)

Women with Severe Pre-eclampsia

Outcome	Expectant Management (N = 49)	Aggressive Management (N = 46)
GA at delivery (Weeks)	30.8	32.9
Neonatal outcome		
RDS	50%	22%
NEC	11%	0%
BPD	9%	4%
IVH	7%	2%

Sibai 1995

Women with Pre-term rupture of Membranes

Outcome	Antibiotics (N = 300)	Placebo (N = 314)
Median time to delivery (days)	6.1	2.9
Neonatal outcomes		
Composite	44%	53%
RDS	41%	49%
NEC	2%	6%
IVH	6%	8%

Mercer 1997

COVIS – Closing Statement

Day 3 – October 19, 2022

MAKENA®
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October 17-19, 2022

Hearing with Respect to CDER's Proposal to Withdraw Approval

Proposed Path Forward While Makena Remains on the Market

Raghav Chari, PhD

Chief Innovation Officer

Covis Pharmaceuticals

Covis is Committed to Confirming Clinical Benefit of Makena

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Covis Proposes Conducting an RCT With Time-from-Randomization-to-Birth as the Primary Endpoint

Proposed Randomized Controlled Trial

- **Proposed population:** Women with ≥ 1 prior spontaneous preterm birth < 35 weeks and ≥ 1 additional risk factor
- **Trial design**: ~400 patients randomized 2:1
- **Primary endpoint:** Increase in time-from-randomization-to-birth for Makena vs. placebo, capped at 35 weeks gestation
- **Estimated completion:** 4- to 6-years

Covis has Surveyed Providers to Assess Feasibility of Enrolling RCT

- 40% of physicians who use progesterone medication for patients at risk of spontaneous PTB recommend the therapy by injection
- 80% say they are likely to recommend a pregnant patient enroll in a placebo-controlled study when the product is FDA approved
  - 39% if the product has not been approved by the FDA
  - 15% if the product has had its marketing approval withdrawn

Covis Willing to Voluntarily Withdraw Makena Based on RCT Futility and Feasibility Assessments

Proposed Randomized Controlled Trial

Pre-specified criteria that would result in voluntary withdrawal:

1. Interim efficacy analysis for futility
2. Assessment of enrollment projections at Month 24 to evaluate feasibility of completing the trial in a 4- to 6-year timeframe
3. Outcome of study is negative

Potential Observational Study to Evaluate Clinical Outcomes

Potential Observational Study

- Establish the relationship between gestational age and neonatal outcomes in treated vs. untreated patients
- Validate benefit of weeks-gained on 17P in the RCT

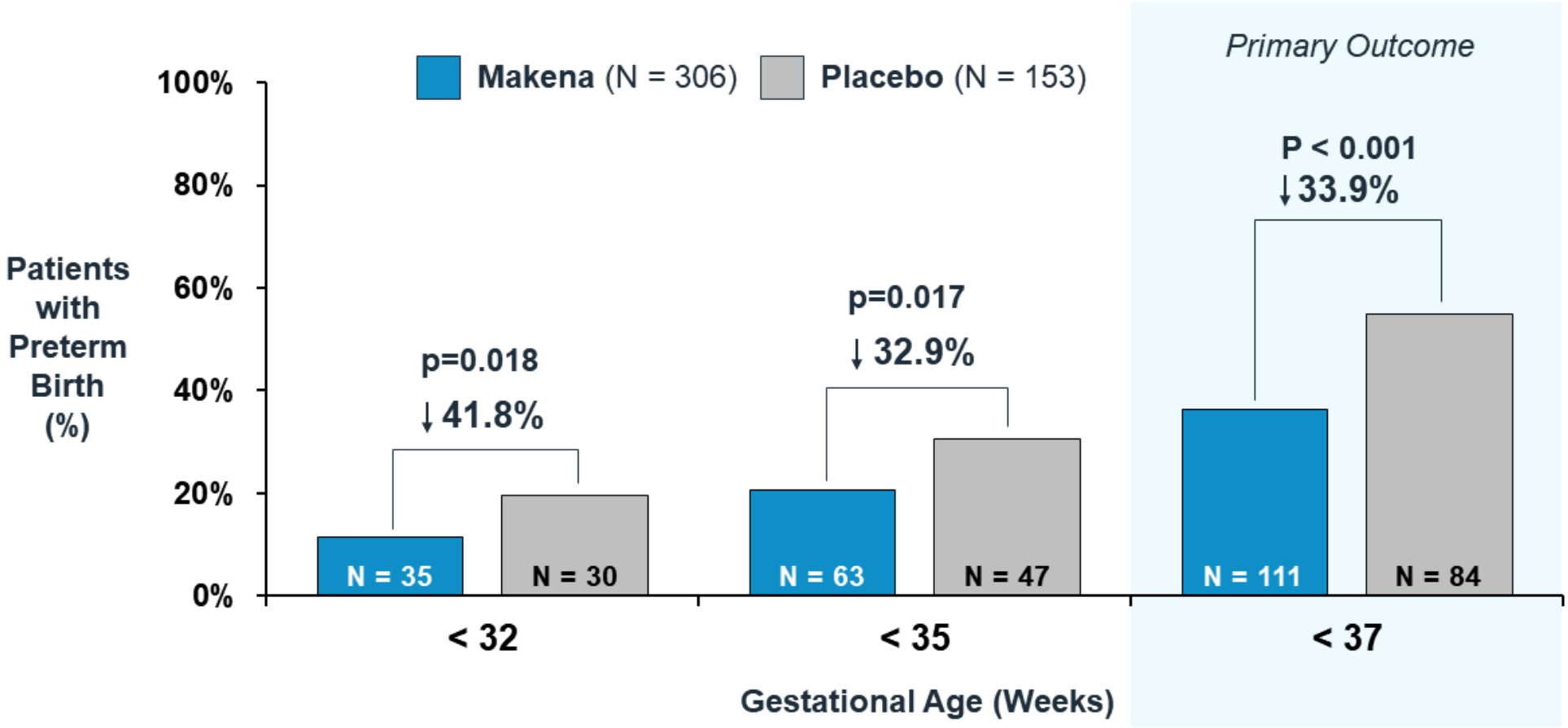
COVIS Position on Questions Presented

Question 1: Do findings from PROLONG verify clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

Findings from PROLONG Do Not Verify Clinical Benefit of Makena

Question 2: Does available evidence demonstrate that Makena is effective for its approved indication?

Makena Met Primary Endpoint Demonstrating Significant Reduction in Preterm Births < 37 Weeks



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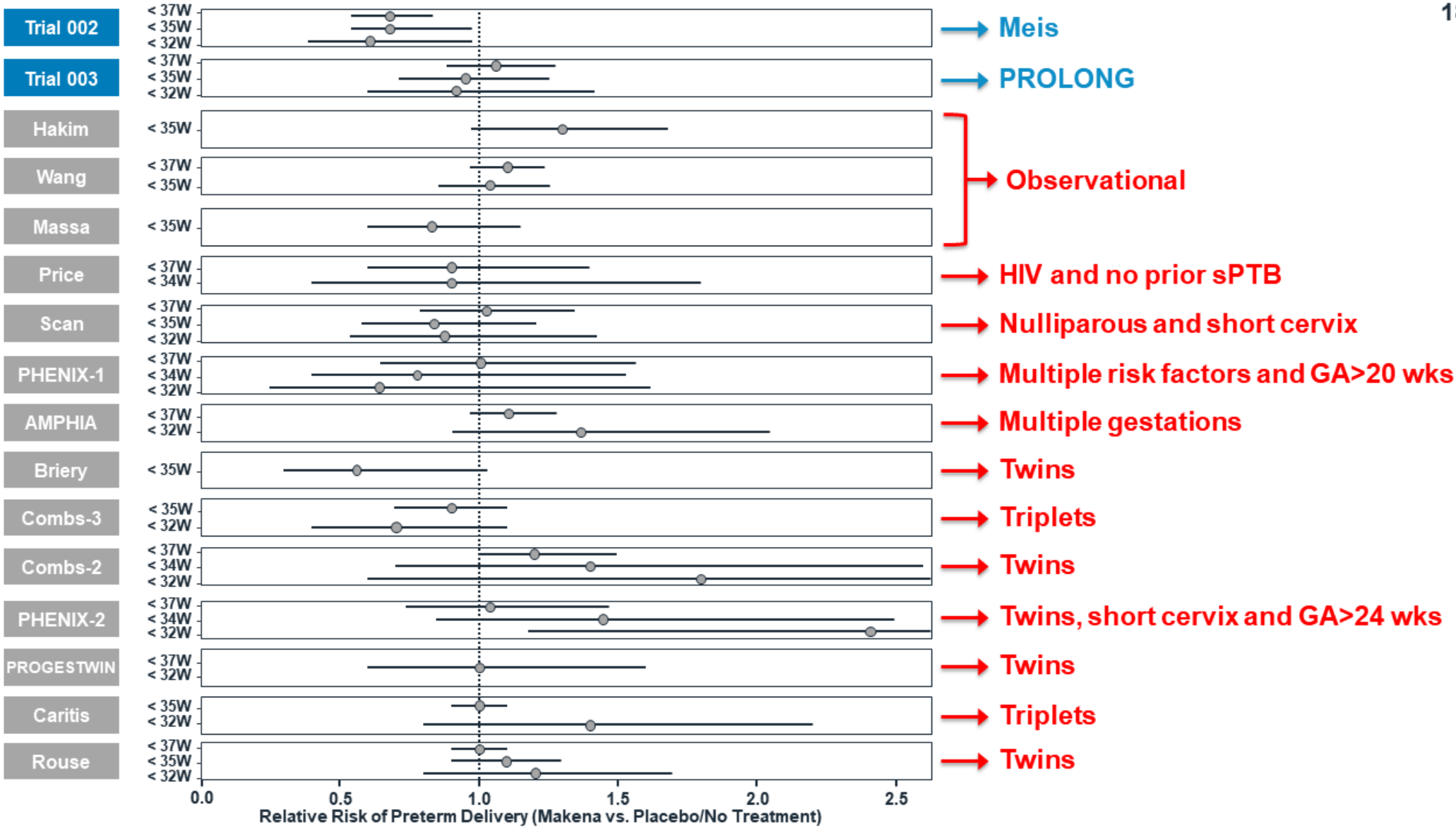
Trial 002
< 37W
< 35W
< 32W
Meis
Trial 003
< 37W
< 35W
< 32W
PROLONG
Hakim
< 35W
Wang
< 37W
< 35W
Massa
< 35W
Observational
Price
< 37W
< 34W
HIV and no prior sPTB
Scan
< 37W
< 35W
< 32W
Nulliparous and short cervix
PHENIX-1
< 37W
< 34W
< 32W
Multiple risk factors and GA>20 wks
AMPHIA
< 37W
< 32W
Multiple gestations
Briery
< 35W
Twins
Combs-3
< 35W
< 32W
Triplets
Combs-2
< 37W
< 34W
< 32W
Twins
PHENIX-2
< 37W
< 34W
< 32W
Twins, short cervix and GA>24 wks
PROGESTWIN
< 37W
< 32W
Twins
Caritis
< 35W
< 32W
Triplets
Rouse
< 37W
< 35W
< 32W
Twins
0.0
0.5
1.0
1.5
2.0
2.5
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Pooled Safety Data Demonstrate Favorable Safety Profile for Makena Compared to Placebo

	Integrated Safety (Meis and PROLONG)	
	Makena N = 1130	**Placebo** N = 578
Admission for preterm labor	**16.4%**	**14.4%**
Preeclampsia or gestational hypertension	**5.2%**	**5.1%**
Nausea	**5.1%**	**4.5%**
Gestational diabetes	**3.6%**	**3.8%**
Headache	**5.0%**	**3.8%**
Injection site pruritus	**4.2%**	**3.8%**
Injection site swelling	**4.0%**	**1.9%**
Back pain	**3.8%**	**2.9%**
Vomiting	**3.6%**	**3.3%**
Urticaria	**3.0%**	**2.3%**

Sibai et al. Journal of Perinatology (2021)

Permissive Legal Standard for Withdrawal of Approval

- FDA "**may withdraw**" accelerated approval if
  - a confirmatory trial "fails to verify and describe" the clinical benefit or
  - "other evidence demonstrates that the product is not safe or effective under the conditions of use"
- The statute is permissive, not mandatory
  - CDER acknowledges: "**CDER possesses various regulatory options when a confirmatory trial fails to verify clinical benefit**"
- FDA has the authority to keep Makena on the market while another trial is conducted

FDCA Section 506(c)(3); CDER Briefing Book page 78

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