FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

OFFICE OF THE COMMISSIONER

HEARING INVOLVING THE OBSTETRICS, REPRODUCTIVE AND UROLOGIC DRUGS ADVISORY COMMITTEE (ORUDAC)

Tuesday, October 18, 2022

8:20 a.m. to 4:02 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

OBSTETRICS, REPRODUCTIVE AND UROLOGIC DRUG ADVISORY COMMITTEE MEMBERS (Voting)

Joseph P. Alukal, MD

Associate Professor

Department of Urology

Columbia University Irving Medical Center

New York, New York

Esther Eisenberg, MD, MPH

Program Director, Reproductive Medicine and Infertility Program
Fertility and Infertility Branch
Division of Extramural Research
National Institute of Child Health and Human Development
National Institutes of Health (NIH)
Bethesda, Maryland

Margery Gass, MD

(Chairperson)
Professor of Clinical Emerita
University of Cincinnati College of Medicine
Fred Hutchinson Cancer Research Center
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Michael K. Lindsay, MD, MPH

Luella Klein Professor

Division of Maternal-Fetal Medicine

Department of Gynecology and Obstetrics

Emory University School of Medicine

Atlanta, Georgia

Mary B. Munn, MD

Professor and Chairman

Division of Maternal Fetal Medicine

Department of Obstetrics and Gynecology

The University of South Alabama Children's and Women's Hospital

Mobile, Alabama

Kristine E. Shields, MSN, DrPH

(Consumer Representative)

Shields' Medical Writing & Consulting, LLC

Pipersville, Pennsylvania

OBSTETRICS, REPRODUCTIVE AND UROLOGIC DRUG ADVISORY COMMITTEE MEMBER (Non-Voting)

Michelle C. Fox, MD, MPH, FACOG

(Industry Representative)

Distinguished Investigator, Global Clinical Development

Global Clinical Development

Merck Research Laboratories

126 East Lincoln Avenue

Rahway, New Jersey

TEMPORARY MEMBERS (Voting)

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Professor and Chair

Department of Obstetrics & Gynecology

Associate Dean for Women's Health Research & Policy

Oregon Health & Science University

Portland, Oregon

Susan S. Ellenberg, PhD

Professor Emerita, Biostatistics

Medical Ethics and Health Policy

Perelman School of Medicine

University of Pennsylvania

Philadelphia, Pennsylvania

Annie Ellis

(Patient Representative)

White Plains, New York

Lorie M. Harper, MD, MSCI

Associate Professor

Department of Women's Health

Division Chief, Maternal-Fetal Medicine

University of Texas at Austin, Dell Medical School

Austin, Texas

Cassandra E. Henderson MD, CDCES

Maternal Fetal Medicine Consultant

Garden OB GYN

Physician Advisor, Rockwood Partners DPP

New York, New York

Mark L. Hudak, MD

Professor and Chair of Pediatrics

Chief, Division on Neonatology

University of Florida College of Medicine - Jacksonville

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Anjali Kaimal, MD, MAS

Professor and Vice Chair of Clinical Operations

Department of Obstetrics and Gynecology

Morsani College of Medicine

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Tampa, Florida

Mara McAdams-DeMarco, PhD

Associate Professor of Surgery and

Population Health

Associate Vice Chair for Research, Department of

Surgery

New York University

New York, New York

Sarah G. Običan, MD

Associate Professor

Division Director, Maternal Fetal Medicine

University of South Florida

Tampa, Florida

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:20 a.m.)

Call to Order

Reconvening Statement

DR. WITTEN: Good morning, and welcome to day 2 of this hearing. My name is Celia Witten, and I'm the presiding officer for the hearing. I now call to order day 2 of the October 17th through 19th 2022 hearing conducted with the Obstetrics, Reproductive and Urologic Drugs Advisory Committee. Dr. Moon Hee Choi is the designated federal officer for this hearing and will begin with the roll call.

Dr. Choi?

Roll Call

DR. CHOI: Good morning. My name is Moon Hee Choi, and I am the acting designated federal officer for this hearing. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Alukal?

DR. ALUKAL: I'm Dr. Joseph Alukal. I'm a urologist on faculty at Columbia University.

DR. CHOI: Dr. Eisenberg?

DR. EISENBERG: Esther Eisenberg. I am an OB/GYN and program director of the Reproductive Medicine and Infertility section of NICHD.

DR. CHOI: Thank you.

Dr. Fox?

DR. FOX: Hi. Good morning. My name is Michelle Fox. I'm the industry representative. I'm an OB/GYN and work at Merck Pharmaceuticals in late-stage clinical research.

DR. CHOI: Thank you.

Dr. Gass?

DR. GASS: Margery Gass, OB/GYN, a clinical professor emeritus, University of Cincinnati.

DR. CHOI: Thank you.

Dr. Lindsay?

DR. LINDSAY: Michael Lindsay, director of Maternal-Fetal Medicine, Emory University.

DR. CHOI: Thank you.

Dr. Munn?

DR. MUNN: Hey. I'm Mary Munn. I'm maternal-fetal medicine and chairman of the

Department of OB/GYN at the University of South Alabama.

DR. CHOI: Dr. Shields?

(No response.)

DR. CHOI: Dr. Shields?

MR. KAWCZYNSKI: Dr. Shields, you have your phone muted.

DR. SHIELDS: Yes. Can you hear me now?

MR. KAWCZYNSKI: Yes, ma'am.

DR. CHOI: Yes.

DR. SHIELDS: I'm Kris Shields. I'm the community representative. I'm a retired OB/GYN nurse practitioner. I have a doctorate in public health.

DR. CHOI: Thank you.

Dr. Caughey?

DR. CAUGHEY: Hi. Aaron Caughey, maternal-fetal medicine, professor and chair, Department of OB/GYN at Oregon Health and Science University.

DR. CHOI: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: I'm Susan Ellenberg. I'm professor of Biostatistics, Medical Ethics, and Health Policy at the Perelman School of Medicine, University of Pennsylvania.

DR. CHOI: Thank you.

Ms. Ellis?

MS. ELLIS: Hi. I'm Annie Ellis. I'm serving as a patient representative. I have a history of preterm birth, as well as my daughter.

DR. CHOI: Thank you.

Dr. Harper?

DR. HARPER: Good morning. I'm Lorie Harper. I'm the division chief of Maternal-Fetal Medicine at the University of Texas at Austin, Dell Medical School.

DR. CHOI: Thank you.

Dr. Henderson?

DR. HENDERSON: Good morning. I'm Cassandra Henderson. I'm a maternal-fetal medicine practitioner at Garden OB/GYN in New York.

DR. CHOI: Thank you.

Dr. Hudak?

DR. HUDAK: Good morning. I'm Mark Hudak. I'm a neonatologist, and I'm professor and chair of pediatrics at the University of Florida College of Medicine in Jacksonville.

DR. CHOI: Thank you.

Dr. Kaimal?

DR. KAIMAL: Good morning. My name is Anjali Kaimal, and I'm a maternal-fetal medicine specialist, and I'm professor and vice chair of Clinical Operations for the Department of OB/GYN at University of South Florida.

DR. CHOI: Thank you.

Dr. McAdams-DeMarco?

DR. McADAMS-DeMARCO: Good morning. I'm Dr. Mara McAdams-DeMarco. I'm an associate professor and epidemiologist at the NYU Grossman School of Medicine in the Department of Surgery and Population Health. I'm also the associate vice chair for research in the Department of Surgery. Thank you.

DR. CHOI: Thank you.

Dr. Obican?

DR. OBICAN: Good morning. Sarah Obican, division chief of maternal-fetal medicine, University of South Florida.

DR. CHOI: Thank you.

Presentations by Public Participants

DR. WITTEN: Thank you, Dr. Choi.

This morning we'll proceed with the third grouping of presentations from public participants.

The FDA and this committee place great importance in the presentations by public speakers. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. Before you begin, please state your name and your affiliation, if relevant to this hearing.

The Food and Drug Administration believes that the agency and public benefit from a transparent process that helps ensure that advisory committee discussions and FDA decisions are based on information relevant to the presentations. If you have any financial interest relevant to this hearing, FDA encourages you to state the interest

as you begin. Such interest may include a company's or group's payments of your travel, or other expenses, or grant money that your organization receives from the sponsor or competitor. If you do not have any such interest, you may wish to state that for the record. If you prefer not to address financial interest, you may still give your comments.

We will begin the public presentations. As a reminder, the time allotted to each speaker varies based on the amount of time requested to speak. Our first speaker is Ms. Milena Berhane. You have 10 minutes. You may begin.

MS. BERHANE: Hello, and thank you for the opportunity to speak today. My name is Milena Berhane, and I'm the health policy associate at the National Consumers League. I'm here representing the Preterm Birth Prevention Alliance, a coalition of 15 maternal and women's health advocacy organizations that came together in 2021 with a shared concern about the state of preterm births in the U.S. and what the proposed withdrawal of Makena

and its generics could mean for women at risk.

Collectively, the Alliance seeks to improve preterm birth outcomes in the U.S. by maintaining access to safe, FDA-approved treatment and advocating for more diverse medical research that adequately represents the experiences of newborns and women of color.

Since convening as an alliance, our members have included the following pre-existing organizations with their own missions, leadership, and voices coming together to speak with one voice on this issue. These groups include: 1000 Days; 2020 Moms; the American Association of Birth Centers; Black Women's Health Imperative; Black Mamas Matter Alliance; Expecting Health; Healthy Mothers, Healthy Babies; HealthyWomen; Miracle Babies; the National Birth Equity Collaborative; the National Black Midwives Alliance; the National Consumers League; the National Partnership for Women and Families; Sidelines; and SisterReach.

Over the next few minutes, I will speak to why we believe it is unnecessary and potentially

detrimental to cut off access to this entire class of drugs, and I will address how removing 17P and its generics will not affect all women equally. For full transparency, the panel should be aware that COVIS Pharma, the sponsors of Makena, are one of more than a hundred funders who support the work of the National Consumers League. The company has provided some initial funding to support the Alliance, but is not involved in the strategic direction of the Alliance or its activities; and like all of NCL funders, it does not hold sway over our positions or our efforts.

As I'm sure you know, and will hear from many others, women of color have substantially higher rates of preterm birth than their white counterparts. According to the March of Dimes 2021 report card, while the U.S. preterm birth rate declined a fraction of a percent in recent years, from 10.2 percent in 2019 to 10.1 percent in 2020, rates of preterm births increased for Black and American Indian/Alaska Native women who continue to be up to 60 percent more likely to give birth

preterm compared to white women.

We at the Alliance believe that the removal of Makena and its generics would exacerbate these inequities and contribute to the already stark divide in maternal and infant health outcomes between Black, indigenous, and other women of color and their white counterparts.

For more than a decade, maternal-fetal medicine specialists have safely used 17P and its generics to help women with recurrent preterm birth carry their babies closer to term, improving the chances of a healthy birth and reducing the risk of long-term health issues for the infant. Taking it off of the market would mean cutting off access to the only safe and effective drugs for this indication, which would leave pregnant women and their providers without an affordable approved alternative.

The Alliance believes that the FDA should allow for additional studies to learn about which population 17P is most effective in treating, and we believe that this can and should happen while

maintaining access to 17P for women at high risk of adverse outcomes. Based on available evidence, maternal healthcare providers and their patients should have the opportunity to decide together whether 17P would be beneficial to them in their pregnancy.

I want to pause on this point of available evidence. All of the clinical trials and real-world evidence to date points to Makena and its generics being safe for women who have had a previous preterm birth. This makes keeping 17P on the market a question of efficacy and not safety. So why aren't we doing everything possible to understand which population 17P is most effective in treating before taking it off the market entirely?

Given the discrepancy and efficacy data between the original and confirmatory trials, it seems a logical next step would be to conduct additional efficacy studies in the population known to be at highest risk for recurrent preterm birth, which in the U.S. is Black and indigenous women;

yet the proposal to withdraw approval was based not on the original trial, Meis, which included nearly 60 percent African American and other women of color in the United States and found that 17P substantially reduced the rate of recurrent preterm birth delivery among women at high risk for preterm birth. Instead the proposal to withdraw seems to be based on the results of the confirmatory trial, PROLONG, which was conducted primarily outside of the U.S. among mostly white European women, and which found Makena to not have the same level of efficacy as in the Meis trial.

These trials studied two vastly different patient populations, one inclusive of women in the U.S. most vulnerable to preterm birth, and one not, so the fact that they had different outcomes is not surprising. What doesn't make sense is why the outcomes among white European women should hold more weight in decision making than the outcomes among women of color in the U.S. The Preterm Birth Prevention Alliance believes that evidence of efficacy for women of color in the U.S. should be

more determinative than the lack of demonstrated efficacy on white women in Europe.

In 2021, a meta-analysis study called EPPPIC, published in the Lancet, pooled data from 31 randomized trials in asymptomatic women at risk of preterm birth. It concluded that both 17P injections and vaginal progesterone reduced the risk of preterm birth before 34 weeks in high-risk women with singleton pregnancies. It also noted that shared decision making with women that have high-risk singleton pregnancies should discuss an individual's potential risks and benefits. However, despite this reinforcing conclusion about the efficacy of 17P, the agency made no change to its recommendation to remove.

To achieve birth equity and protect the physical, financial, and emotional well-being of mothers and infants, we cannot study pregnant women as a monolith. Instead, we must gain a better understanding of who can benefit most from treatments like 17P through more diverse studies that include adequate representation from the women

in this country who we know are most affected and are at the highest risk.

We believe that this research must explore the causes of disparate outcomes and risks of eliminating approved treatment options before a decision is made, and we believe that while these additional studies are conducted, 17P should absolutely remain available to patients and providers.

This last point is truly critical from the Alliance's perspective. Considering the proven life-impacting outcomes from the first clinical trials, years of anecdotal clinical data, and follow-up studies like EPPPIC, we believe that maintaining patient access to 17P while additional studies are conducted is key. The Alliance is fighting for a more inclusive healthcare system that gives every pregnant person an equal chance at having the best birth outcomes possible.

We do not believe that removing 17P from the market without understanding who could benefit most from its use is in the best interest of patients or

healthcare providers, especially without any other approved treatment options available. Women of color need a seat at the table. Thank you.

DR. WITTEN: Thank you.

The next speaker is Ms. Amy Romano.

Ms. Romano, you have 10 minutes.

MS. ROMANO: Good morning, and thank you for the opportunity to provide public comment today and for your work examining the science and regulatory issues around Makena in such depth. My name is Amy Romano. I'm a midwife whose work has spanned clinical practice; research; quality improvement; policy; payment reform; and care/delivery transformation. I'm a CEO of Primary Maternity Care, which I founded in early 2020 to help scale evidence-based, high-valued care models that improve birth outcomes and equity, and reduce cost.

We are an interdisciplinary service design and consulting firm with clients that include health systems, healthcare purchasers, independent providers, and non-profit advocacy organizations. We have no financial ties to Covis or Makena. I

was paid a consulting fee in 2020 from the Institute for Medicaid Innovation, a non-profit organization, to co-author an update to Medicaid managed-care organizations on progesterone for the prevention of preterm birth after the results of the PROLONG study were published.

My career has been devoted to understanding and disseminating strategies for primary prevention of poor birth outcomes. This passion was instilled in me from my own family history. My mother had given birth preterm two years before I was born. My sisters were born at what then was the edge of viability at 28 weeks. One of them, my sister Catherine [ph], survived and is healthy today. Her twin sister Frances died after a day and half. I was the next born baby after this high-risk pregnancy, and grew up understanding this as a significant trauma that had ripple effects across our family and community.

There are many important aspects to this decision, and there has been some robust discussion of ethics, safety, and uncertainty. I want to

focus my 10 minutes on a critical set of issues that have gotten much less attention so far during these hearings; namely that the cost of Makena is astronomical, and the string of companies that have owned it have a long history of unethical practice and profiteering, most notably when the original accelerated approval was granted, and the product entered the market at a cost 100 times higher than the generic formulations available in compounding pharmacies previously.

The cost has been driven by financial engineering and ruthless marketing, not by the real cost or value to society. This can be seen clearly if we zero in on the expenditures since Trial 003, or PROLONG, results became available. It is clear to me that Makena's private equity owners who acquired the drug within days of the previous FDA vote are maximizing their profits for whatever time remains, and that only the FDA can put a stop to it.

According to a review of the special drug evidence and coverage database at Tufts Medical

Center, commercial coverage from Makena has not changed in the last five years, with minimal or no restrictions to access beyond the FDA label. The evidence most commonly cited by health plans is the Meis trial, or Trial 002, which as we know is not the most up to date. A review of claims from a purchaser client of mine showed significant pricing distortions during this period. In the data set of claims from over 3,000 births between 2019 and 2021, the cost per patient for a course of Makena rose more than 200 percent, from less than 10,000 in 2019 to more than 20,000 in 2021.

A report last month from the Office of the Inspector General showed that from 2018 to 2021, Medicaid programs spent $700 million on Makena. Why are we spending $700 million on a drug that doesn't work? Even if we believe it works a little for some sliver or slice of a population, certainly the amount you're spending on it as a society, on this drug, should be going down, not up. The simple laws of supply and demand are enough to tell us that. Instead, Covis, through the close of PBM

contracts and private equity, is continuing to profit while the historic maternal and infant health emergency only worsens. This is not benign. There are so many ways we could have invested those 700 million Medicaid dollars and countless other healthcare dollars over the last three years.

In the time since Covis has earned these revenues, the rates of maternal mortality and stillbirth has increased and racial disparities have widened. According to a March of Dimes report issued just last week, 1 in 20 U.S. counties that had maternity care access in 2020 have lost it by 2021, and there are now people 2.2 million women of childbearing age and almost 150,000 babies affected by maternity deserts.

Although there are many worthy uses of such a substantial investment, I want to talk about one use in particular. In 2018, the full results of the federal Strong Start for Mothers and Newborns study became available. This study, funded and conducted by the Centers for Medicare and Medicaid Innovation, enrolled over 40,000 Medicaid members

and showed substantial benefits of the Midwifery-Led prenatal care model and free-standing birth centers.

The study authors concluded, "Women who received prenatal care in Strong Start birth centers had better birth outcomes and lower costs relative to similar Medicaid beneficiaries not enrolled in Strong Start." In particular, rates of preterm birth, low birth weight, and cesarean sections were lower among birth center participants, and costs were more than a few thousand dollars lower for mother-infant care during the birth and following year.

Despite this large federally funded study and similar research results previously conducted in the United States and abroad, showing a broad range of positive outcomes, it remains extremely challenging to scale the model because of low reimbursement. Although the model has been endorsed by the American College of Obstetricians and Gynecologists, the Institute for Medicaid Innovation, the National Partnership for Women and

Families, the March of Dimes, and countless other leading organizations, birth centers fail in community after community because of chronic disinvestment. Although the March of Dimes data show birth centers can provide critical primary maternity services in maternity deserts, they can't be sustained, especially in places with high rates of Medicaid insurance.

With $700 million we've spent on Makena since both the PROLONG and Strong Start results were available, we could have increased reimbursement to adequate rates to prevent birth center closures and still more than doubled the number of people accessing the models here in the United States.

I want to finish my remarks by returning to my personal experience. As I mentioned at the start of this, I was the next born baby after my mother gave birth preterm to my sister, one of whom died. That was a high-risk pregnancy in 1975. It wasn't until I started researching Makena because of these business practices, that it even occurred

to me to think about my own personal history, not my sister's and not my mother's, but mine.

When I was 6 weeks old, I was diagnosed with infantile hemangioma that affected my left eye. I had radiation therapy, I had two surgeries, I had cortisone treatments, and overall it took five years to complete the course of treatment for something that, until last week, literally, I thought was just a fluke. But as I talked to some of the doctors that we've heard from in these hearings and looked at the research, it finally occurred to me to Google can progesterone in pregnancies cause infantile hemangioma?

I'd never seen anything in my research on Makena about this, I'd never thought about it, really, ever at all, and what I found is that, yes, there's actually copious evidence that there's an association with progesterone given in pregnancy and infant hemangioma. It's the only modifiable risk factor that's known, or that I could find, in the evidence, and it happened to me.

So I really believe that we don't know what

we're messing with when we give hormones to people in pregnancy. I don't know, because it was 47 years ago, what my mother might have received, but we just found -- from hormones to hormones, to medical solution and pharmacologic solution to this problem -- what we know is a complex problem of preterm birth and optimizing birth outcomes. So I'm confident that my mom was given something. I know she was given IV alcohol at one point during her pregnancy with me to stop contractions, and we know, of course, we would never give that to people today.

So we learn new things, and we have to learn, and grow, and evolve from this knowledge, and we have to stop wasting money on some things that we know doesn't work when we have model after model. The birth center is just one, but I actually have given the same speech about 5, or 10, or 20 other things we could be spending this money on. So I'm passionate about this, I will leave it there, and I appreciate the time. Thank you.

DR. WITTEN: Thank you.

Our next speaker is Dr. Michael Carome.

Dr. Carome, you have 20 minutes.

DR. CAROME: Good morning. I'm Dr. Michael Carome, director of Public Citizen's Health Research Group. I have no financial conflict of interest.

Public Citizen strongly supports CDER's evidence-based proposal to withdraw approval of the NDA for Makena to reduce the risk of preterm birth in certain high-risk women with a singleton pregnancy. We requested such action in our October 2019 citizen petition to the FDA because evidence derived from the FDA mandated postmarket clinical trial for Makena failed to verify that the drug provides any clinical benefit. Moreover, the drug never should have been approved by the FDA because the single pivotal, premarket trial that was relied upon to establish efficacy was seriously flawed.

I will address three major topics. First, I will highlight the significant flaws and limitations of the premarket clinical trial

supporting approval of Makena that were identified by the FDA statistical reviewer and explain why it failed to provide substantial evidence of effectiveness. Second, I will address the failure of the postmarket trial of Makena, which was much larger and better designed than the premarket trial, to show any clinically meaningful benefit. Finally, I will discuss the risks of Makena and argue that it is unacceptable to continue to expose pregnant women to these risks, given the lack of evidence that the drug is effective.

The flawed premarket clinical trial; Makena's approval was based primarily on safety and efficacy data from a single clinical trial, hereafter Trial 002. Investigators at 19 clinical centers in the U.S. randomly assigned 463 pregnant women who had a history of spontaneous preterm birth to receive either weekly injections of hydroxyprogesterone -- 310 subjects -- or placebo -- 153 subjects -- starting between 16 weeks and 20 weeks 6 days of gestation, and continuing until delivery, or 36 weeks of

gestation.

The prespecified primary outcome was preterm delivery before 37 weeks of gestation. Of note, enrollment in the trial was halted early after a second planned interim analysis found that the boundary for the test of significance for the primary outcome had been crossed.

Regarding the primary efficacy endpoint, preterm delivery prior to 37 weeks of gestation occurred in 37.1 percent of subjects in the hydroxyprogesterone group compared with 54.9 percent of subjects in the placebo group, with a treatment difference of minus 17.8 percent and a 95 confidence interval, or CI, minus 28 percent to minus 7.4 percent, as shown in the table here.

Delivery prior to 35 weeks of gestation occurred in 21.3 percent of women in the hydroxyprogesterone group versus 30.7 percent of women in the placebo group, with a treatment difference of minus 9.4 percent and a 95 percent CI of minus 19 percent to minus 0.4 percent. Delivery prior to 32 weeks of gestation occurred in

11.9 percent of women in the hydroxyprogesterone group and 19.6 percent of women in the placebo group, with a treatment difference of minus 7.7 percent and a 95 percent CI of minus 16.1 percent to minus 0.3 percent. Trial 002 also provided absolutely no evidence that hydroxyprogesterone reduced fetal or neonatal morbidity or mortality.

Problems regarding the results of Trial 002 were readily apparent soon after they were published. For example, a New England Journal of Medicine editorial regarding Trial 002 noted the following, quote, "The 54.9 percent incidence of preterm delivery in the placebo group is so much higher than the rates reported in other risk cohorts that it calls into question whether these women are representative of the U.S. population at large," end quote.

In addition, the mean number of previous preterm deliveries was statistically significantly higher than the subjects assigned to the placebo group than in those assigned to the hydroxyprogesterone group, 1.6 plus or minus 0.9

versus 1.4 plus or minus 0.7, respectively, with a p-value of 0.007. Moreover, the proportion of subjects who had more than one preterm delivery prior to enrollment in the trial also was higher in the placebo group than in the hydroxyprogesterone group, 41.2 percent versus 27.7 percent. These differences may have biased the trial's efficacy results in favor of the hydroxyprogesterone group.

During the initial review of Makena NDA, which was submitted by Adeza Biomedical in 2006, the FDA statistical reviewer made the following overall conclusion, quote, "From a statistical perspective, the level of evidence from Trial 002 is not sufficient to support the effectiveness of hydroxyprogesterone. Without a second study, the generalizability of the study results to a larger population cannot be assessed," end quote.

The statistical reviewer enumerated numerous problems regarding the design, execution, and analysis of Trial 002 to support her conclusion that the trial was unsuitable for establishing the efficacy of hydroxyprogesterone for preventing

preterm births.

Problem 1: inadequate prespecified primary endpoint. The statistical reviewer explained that the prespecified primary outcome of the trial was not an appropriate endpoint to establish efficacy of the drug and support its approval, noting the following, quote, "Trial 002 was not designed for drug approval. FDA and the applicant did not have the usual meetings and discussions regarding the choice of endpoint needed to establish efficacy in a regulatory environment. As a result, the primary endpoint for the study -- delivery less than 37 weeks of gestation -- is not what the FDA would have advised," end quote.

On October 29, 2006, the FDA convened a meeting of its Advisory Committee for Reproductive Health Drugs to discuss the safety and efficacy of hydroxyprogesterone. A large majority of the committee, 16 of 21 members, agreed with the FDA that a reduction in preterm birth before 37 weeks of gestation was not an adequate surrogate for reduction in fetal and neonatal mortality or

morbidity. Nevertheless, the FDA based its eventual accelerated approval of the drug on this endpoint.

Problem 2: significant likelihood of false positive results based on appropriately adjusted analyses using the secondary endpoint of preterm delivery before 35 and 32 weeks of gestation. The FDA statistical reviewer stated that the FDA had determined that the clinical significance of preterm birth, with respect to neonatal mortality and morbidity, is most pronounced prior to 32 weeks of gestation, and therefore focused on this endpoint, as well as 35 weeks of gestation.

The fact that the study was stopped early made it more likely that any estimates of efficacy, based on the endpoints of preterm delivery, before 35 and 32 weeks of gestation overstated the drug's benefit. The FDA statistical reviewer emphasized that the upper bounds of the confidence intervals for the difference in the rates of preterm delivery before 35 and 32 weeks of gestation between the hydroxyprogesterone and placebo groups was very

close to zero.

The statistical reviewer concluded that the analyses of the data assessing the efficacy of hydroxyprogesterone, based on preterm deliveries before 35 and 32 weeks of gestation, were not convincing, noting, quote, "Although the results are statistically significant for delivery less than 35 weeks of gestation and delivery less than 32 weeks of gestation when accounting for interim analyses, the confidence intervals for the treatment effects are not convincing when considering that only one study was submitted to support the claims of effectiveness for the drug.

"When two studies are submitted, the chance of both studies yielding a false positive result is 1 in 1600. In the case of a single study, the results must be less than a nominal p-value of 0.00125 to ensure the same false positive rate. Deliveries at times earlier than 37 weeks of gestation were not statistically significant at 0.001. The results of the analyses of the 32- and 35-week endpoints suggest their false positive rate

could be as great as 1 in 40," end quote.

Problem 3: potential lack of generalizability: One site enrolled a disproportionate number of subjects. The statistical reviewer stated the following, quote, "FDA guidance on clinical evidence stresses the importance of a large multicenter study to establish the credibility of a single study submission. The guidance also noted the credibility of a single study is enhanced if no single center accounts for an unusually large proportion of the subjects, and that no single center is disproportionately responsible for the observed results," end quote.

However, of the 19 study sites in Trial 002, one site, the University of Alabama, enrolled 126 subjects, accounting for approximately 25 percent of total enrollment, which was about 3 times larger than the second largest site, and 44 percent of enrollment of subjects at 18 weeks of gestation earlier.

The statistical reviewer's analyses that

separated the data for the University of Alabama from the data for all other 18 study sites revealed that the disproportionately large representation of subjects from the University of Alabama influenced the significance of the overall results for delivery before 32 weeks of gestation, as shown in this table.

The statistical reviewer noted the following, quote, "The finding that is notable is the result of delivery less than 32 weeks of gestation among all other centers combined, which is not significant, p-value equals 0.197. Moreover, the results of the University of Alabama are statistically significant for this endpoint, p equals 0.034. This may suggest that the University of Alabama may be responsible for the overall finding of this endpoint," end quote.

Problem 4: additional analyses by the statistical reviewer further suggested apparent confounding of study site and gestational age at randomization.

In April 2008, the sponsor, then Cytyc

Corporation, submitted a complete response for the Makena NDA in response to the FDA's October 2006 approvable letter. The same FDA statistical reviewer highlighted the fact that the complete response did not contain, quote, "any additional efficacy data," end quote, to obviate the concerns and deficiencies noted during the review of the first NBA submission, and again voiced the following comment, indicating strong opposition to approval of the drug based on Trial 002 alone, quote, "From a statistical perspective, the effects of hydroxyprogesterone on preterm birth has not been established by adequate and well-controlled clinical trials. Although Trial 002 demonstrated statistically significant reductions in preterm deliveries, it is my position that the level of evidence from this single study is not sufficient to support the effectiveness of the drug," end quote.

Problem 5: the inconsistencies and treatment effects among groups defined by gestational age at randomization and by race.

In July 2010, the sponsor, then Hologic, Incorporated, submitted a second complete response to the FDA. Since the FDA at this time was contemplating approval of Makena under the accelerated approval pathway, based on reduction in preterm births before 37 weeks of gestation seen in Trial 002, the same FDA statistical reviewer conducted additional analyses related to this endpoint, which revealed the following:

1) The treatment effect at 37 weeks did not appear to be consistent among groups defined by gestational age at randomization. This finding may be confounded with race and study centers.

2) There was a lack of consistency of efficacy results among subgroups defined by race.

3) There was a lack of consistency of safety results at 24 weeks of gestation among subgroups defined by race; and

4) The doubling of the treatment effect from less than 35 weeks to less than 37 weeks of gestation, which was likely due to the increased number of deliveries among non-Black subjects

randomized to placebo.

The FDA statistical viewer reaffirmed her prior review that the data from Trial 002 failed to demonstrate the efficacy of the drug for the prevention of preterm delivery and concluded the following, quote, "From a statistical perspective, the information and data submitted by the applicant do not provide convincing evidence regarding the effectiveness of hydroxyprogesterone for the prevention of preterm deliveries among women with a history of at least one spontaneous preterm delivery."

The postmarket PROLONG trial. The postmarket PROLONG trial, or Trial 003, was well designed, well executed, and appropriately powered with 1708 subjects having been randomized. It did not suffer from the multiple flaws and deficiencies seen in Trial 002. The trial's co-primary efficacy endpoints were delivery prior to 35 weeks of gestation and a neonatal morbidity/mortality composite index.

Trial 003 did not demonstrate a treatment

benefit from Makena on reducing the neonatal composite index or the rate of spontaneous preterm birth prior to 35 weeks gestation, nor was there evidence of treatment benefit on the rate of spontaneous preterm birth prior to 37 weeks or 32 weeks of gestation, as shown in this table.

Furthermore, the FDA concluded that the unplanned exploratory subgroup analyses conducted by the sponsor, stratified by geographic region and race, did, quote, "not provide convincing evidence of efficacy over placebo in any subgroup, and there is no statistically significant interaction between Makena and any of these risk factors," end quote.

At the October 29, 2019 meeting of the FDA's Bone, Reproductive and Urologic Drugs Advisory Committee, when asked whether the findings from Trial 003 verified the clinical benefit of Makena on neonatal outcomes, the 16 voting members voted unanimously in the negative. When asked whether, based on the findings from Trial 002 and Trial 0003, there was substantial evidence of effectiveness of Makena in reducing risk of

recurrent preterm birth, the committee voted 3 yes and 13 no. A drug lacking substantial evidence of effectiveness does not meet the legal standard for approval and must not be allowed to be marketed.

The risk of the drug; Makena like all drugs can cause adverse effects. The FDA-approved product labeling for Makena provides warnings about thromboembolic disorders, allergic reactions, including angioedema, decreased glucose tolerance, fluid retention, depression, and hypertension. Many of these adverse effects are seen with other progestins.

The fact that there were no significant differences between the treatment in placebo arms in Trials 002 and 003 for any major maternal safety outcomes is not surprising, given the size of the trials and the expected frequency of adverse events due to hydroxyprogesterone, and the recent study by Murphy, et al., published in the American Journal of Obstetrics and Gynecology, found an association between the risk of in utero exposure to hydroxyprogesterone and the risk of cancer in the

offspring.

Despite its limitations, this study serves as a reminder that in utero exposure to the synthetic hormone hydroxyprogesterone may carry long-term risk for the offspring, in that the long-term safety of such exposure to the offspring remains uncertain.

My conclusion, many commenters have argued that Makena and generic equivalents must remain on the market because they are the only FDA-approved treatments available for pregnant women at risk of recurrent preterm birth. But the argument that having some drug treatment for a serious condition is better than no treatment is deeply flawed and dangerous, particularly for treatments for which there was a lack of evidence of effectiveness and clear evidence of potentially serious risk.

CDER's proposal to withdraw the approval of the NDA for Makena is evidence-based, whereas the sponsor's arguments opposing such an action are not. In the absence of evidence establishing that hydroxyprogesterone is effective for reducing the

risk of preterm labor, it is unacceptable to continue to expose women and their fetuses to the known and potential risk of the drug.

It is inconceivable that the FDA would have approved the Makena NDA if the efficacy data from the postmarket trial, showing no benefit, had been available prior to approval. The FDA itself stated that, quote, "If these conflicting findings of Trials 002 and 003 were submitted at the same time in an NDA seeking approval of Makena, we would conclude that there is not substantial evidence of effectiveness of Makena for reducing the risk of recurrent preterm birth," end quote.

Importantly, the proposal to withdraw approval of Makena was endorsed unanimously by CDER's Medical Policy and Program Review Council, the membership of which included the most senior and experienced leaders of the center. Makena should have been removed from the market soon after the results of the PROLONG trial were available. The yearslong delay in the FDA withdrawing approval of the NDA for Makena demonstrates fundamental

deficiencies in the current regulatory oversight for drugs approved under the accelerated approval pathway.

In closing, Public Citizen urges the FDA, as soon as possible, after the conclusion of this hearing, to withdraw approval of the NDA for Makena and for the abbreviated NDAs for all generic hydroxyprogesterone injection products for which Makena was the reference-listed drug. Failure to take such action would further erode the FDA's credibility and public confidence in the agency's accelerated approval process.

In addition, once approval of Makena is withdrawn, the FDA should add parenteral hydroxyprogesterone caproate for prevention of preterm birth to the list of drug products under 21 CFR Section 216.24 that were withdrawn or removed from the market for reasons of safety or effectiveness, and therefore may not be compounded under the exemptions provided by Sections 503A or 503B of the Food, Drug, and Cosmetic Act. Similar regulatory action has been taken to prevent

compounding of bromocriptine mesylate for prevention of physiological lactation. Thank you for your attention and the opportunity to comment.

DR. WITTEN: Thank you.

We will now move on to the next speaker, Ms. Tracy Hoogenboon. You have five minutes.

MS. HOOGENBOOM: Good morning from Southern California. My name is Tracy Hoogenboom, and I'm the director of Sidelines National Support Network. I have been with Sidelines since it was founded in 1991, over 31 years ago.

Sidelines is founded by my friend and women's advocate, Candace Hurley, who after infertility and two pregnancy losses -- and two high-risk risk pregnancies, found peer support through another patient at her doctor's office. I was also an infertility patient and high-risk mom, giving birth to premature triplets in 1989.

Sidelines' main mission is to support, encourage, and educate women and their families who are experiencing pregnancy complications, many of which had a prior preterm birth. We are a

non-profit group composed of mothers and fathers who volunteer to offer their services to other high-risk families free of charge. We are not being paid for our statement today and are strictly here representing our constituents.

Sidelines also partners with many businesses and groups to offer educational webinars to OB nurses on a variety of pregnancy-related topics. We've worked on bills to support funding for pregnancy loss; initiated letter writing campaigns to insurance companies asking for coverage of treatments, tests, and technologies; as well as presented to the FDA encouraging increased research and availability of other treatments, always taking the firm position that medical decisions should be left to the women and her healthcare provider.

We'd like to express our concerns about potential negative consequences of withdrawing Makena and progesterone during pregnancy. In the past three decades, Sidelines has supported tens of thousands of moms across the country, and hundreds have reported encouraging results in near- or

full-term babies following a previous preterm birth utilizing progesterone or Makena. We have many testimonials from women who will tell you this.

We at Sidelines are very concerned that the elimination of one of the only drugs currently available to treat preterm labor will be completely withdrawn, potentially causing harmful results, and will leave medical teams and expectant mothers with little or no treatment options.

We would be the ones receiving calls from desperate and disheartened moms if they were to learn from their physician that the one questionable study took away her only treatment option, and potentially her chance of a good birth outcome. What is the most terrifying thing you can tell any patient? There is nothing we can do.

We continue to be very concerned about the excessive high rate of preterm birth in the U.S. and extremely limited treatment options available for preterm labor. After many years of speaking to families and representing them on many issues, we're astonished and disappointed that more has not

been done in the areas of interventions, treatments, and technologies to improve the very poor 10 percent preterm birth rate and 10 percent low birth rate in the U.S.

Pulling the approval of the one drug approved for this purpose is a move in the wrong direction. Although antidotal, we have seen no evidence over three decades that this drug is in the same dangerous category as DES, or causes other problems such as autism, or that keeping it accessible would delay research in the areas of other preterm labor drugs.

In closing, we strongly encourage this committee to keep open access to Makena and progesterone in all its forms. We ask that you consider the many moms who have had successful pregnancy outcomes following a pregnancy loss or preterm birth, who deserve to have this class of drugs available while further research and studies are conducted. Thank you for giving me the opportunity to represent Sidelines National Support Network and the thousands of high-risk families we

represent at this important hearing.

DR. WITTEN: Thank you for your participation.

Our next speaker is Ms. Elise Erickson.

Ms. Erickson, you have five minutes.

DR. ERICKSON: Good morning. I am Dr. Elise Erickson. I'm an assistant professor at the University of Arizona. I have no financial disclosures. I conduct clinical maternal health research, in addition to serving families as a certified nurse midwife. My research centers on maternal morbidity and methods for understanding phenotypic differences in maternal health outcomes, including variability in clinical, genetic, and epigenetic features, as well as the study of social determinants of health.

We know that spontaneous birth as a whole includes births arising from many etiologies or triggers, including infection, placental insufficiency, external toxic exposures, including substances or chronic stress. We also know that some etiologies are isolated or not going to

reoccur in subsequent pregnancies because the unique features of the placenta and fetus, including their genetics in the first preterm birth, may not be present in the next pregnancy. Therefore, directing clinical providers to offer Makena with the sole indication of any spontaneous preterm birth is imprecise. We are likely to overtreat a significant proportion of the population of people who were not destined to have another preterm birth.

As a scientist, I see value and understanding in individual factors that will lead us to precision-based pharmacotherapy and build the evidence base, which would support tailoring our care to the patients who are most likely to benefit. As such, I would support future research to address the use of Makena to the kinds of spontaneous preterm births that will be most likely to be responsive. However, we don't clearly know yet which kind of spontaneous preterm birth that is, nor how to identify the person most likely to be affected by that etiology, however, I also

believe our first duty is to act ethically and with transparency.

I see there's been a call to continue Makena's approval because it would possibly address the burden of preterm births among Black populations in particular, however, this argument I believe sidesteps important conversations that are at the root of why disparities exist in the first place.

First, race is a social construct, not a biologically informed one, and likely describes a very diverse population who may or may not share any common ancestry. Secondly, despite this diversity within a racial group, we know individuals who are racialized as Black are exposed to both current pervasive prejudice, injustices, and social vulnerability, as well as the legacies of enslavement, Jim Crow, redlining, a failure to enact equitable Medicaid expansion, and the ongoing burden of toxic environmental exposures.

These factors are the backdrop to what is now in 2022 a lack of protection for comprehensive

reproductive health care, therefore, when we say Makena could be a treatment specifically for high-risk groups, and Black populations in particular, I think we need to dig much deeper into this proposal and consider how race is actually playing a role in this association. We also need to answer why we think exogenous hydroxyprogesterone is the best intervention to address these disparities; in short, we need more data.

Given all that's been shared in this hearing, ethically we should not continue with routine clinical use outside of the auspices of research. There's a lack of high-quality evidence for preterm birth prevention, and there are unanswered questions about newborn child development and the possibility for endocrine programming in the fetus. Black individuals have been subjected to experimentation without consent for centuries, particularly in obstetrics. The American College of Obstetrics and Gynecology outlines this history on its website.

Given what we know, if Makena use will continue, the bar needs to be higher than shared decision making. It needs to be done in the setting of written informed consent, as well as the establishment of a national tracking and monitoring system to study the long-term effects of this medication on postnatal maternal health, including depression, and the development of the offspring across social behavioral and biological domains.

In closing, our nation's most vulnerable communities deserve better from all of us than what is afforded to them by prior generations. Let's not make the mistake of ignoring history by assuming an exogenous hormone is innocuous to a fetus, particularly the ones that were never going to be born preterm, but also let's not assume it's universally effective because of one's race.

Studying this drug in high-risk communities can be done ethically, but people have to be told that they're being studied, and they have to have a choice not to participate. One of the speakers yesterday mentioned that women with prior preterm

births are often so traumatized by the first experience that they, quote, "would have done anything," unquote, to avoid it again. This is the definition of a vulnerable population, and we all have the duty to protect these people by ensuring that the principles of autonomy and justice are upheld. Thank you for your time and for your service on this issue.

DR. WITTEN: Thank you.

Our next speaker is Dr. Washington Hill.

Dr. Hill, you have 10 minutes.

DR. HILL: Good morning. I am Dr. Washington Hill, a fellow of ACOG, a member of the National Medical Association, and Society for Maternal-Fetal Medicine. I practice OB, GYN, and MFM in Sarasota, Florida at CenterPlace Health, a federally qualified health center. I have no conflict of interest and nothing to disclose or declare.

Good day, colleagues, members of the advisory committee, and FDA. I have practiced OB/GYN and MFM in one form or another for 57 years. I've delivered thousands of babies in this country

and Africa, many in preterm labor. Preterm birth is a significant problem in the U.S., especially in African American women who have as a group significant risk factors for preterm delivery called social determinants of health and a higher preterm delivery rate.

This is my independent opinion, view, and expert clinical perspective as an African American OB and MFM expert on the use of Makena in recurrent preterm birth prevention. The journey on use of Makena to decrease preterm birth and disparities follows a long and winding road, including accelerated approval based on the compelling NICHD-MFMU Meis Trial 002.

While normally Blacks can be underpresented in clinical trials with the given legacy of mistrust in the medical system, in 002, 59 percent, over half of the participants, were Black, some of whom I delivered. This landmark trial showed a robust decrease in preterm birth, concluding that weekly injections of 17P resulted in substantial reduction in the rate of recurrent preterm delivery

among women who were at particularly high risk for spontaneous preterm delivery, and a reduction in the likelihood of several complications in their newborns.

Studied carefully, this trial was not a fluke, or false positive, and was not flawed. I disagree with my colleagues, based on data, that Makena has shown no benefit and is ineffective. The landmark Meis study, 2019 positive meta-analysis, the EPPPIC meta-analysis, and over 17 years of positive clinical observational use has shown Makena's benefit, safety, and efficacy in reducing spontaneous preterm births.

As part of Makena's accelerated approval, a confirmatory trial, as you know, PROLONG 003, was required and did not meet the primary endpoint. Although 003 did not confirm the results of Meis, it also did not refute the findings but reported conflicting data. 003 was performed primarily outside of the U.S. and enrolled only 7 percent Blacks, far fewer than the Meis study that enrolled 59 percent. In 003, Blacks were less than half of

those represented than in Meis, 273 in Meis and only 113 in PROLONG; not enough of a robust diverse demographic to rule out ineffectiveness in Blacks.

Experts and clinicians, including myself, as you have heard and will hear today, believe that the differences in outcomes could very well have been due to the differences in study populations. Treatment, efficacy, and high risk, in especially Blacks, have not been excluded. There are inadequate data from a limited number of high-risk patients in 003 to remove Makena now. We are not at the point that Makena should be withdrawn. That would be premature and harmful to Blacks and other high-risk pregnant women at risk for preterm birth.

We are on the verge of losing access to the only FDA-approved medication for this indication, leaving no other well-studied safe option. These are important points to consider before removing this FDA-approved treatment, conducting additionally well-designed research, particularly within high-risk populations, which could help the clinician and the agency make the most informed

decision, advancing patient well-being and health equity.

There is no evidence whatsoever that this sponsor is practicing an inequitable or unethical corporate strategy mentioned. I read in the New England Journal a statement that resonates with me today. "When the majority of a population achieves little benefit from a drug, but a minority demographic group at greatest risk for a serious medical morbidity appears to obtain significant benefits, any decision that will ultimately make it impossible to obtain the drug should be undertaken cautiously." Thank you, Dr. Greene.

Leadership and members of the NMA OB/GYN section and NMA agree with ACOG and SMFM, and recognizing the study population differences, continue to support Makena use while gathering additional scientific data. Withdrawal can mean returning to the use of compounded formulations, which have potential safety issues and unreachable out-of-pocket costs. We have been down that road before. Treatment to prevent recurrent preterm

birth has gotten away from that with Makena as a safer option.

As a clinician, safety concerns expressed are without evidence. Makena is not DES. OB and maternal-fetal medicine agree to follow data so they can make the best shared decision with their patients. Let's not lose that opportunity by withholding the drug.

So where do we go from here? We need more scientific data and research on the effectiveness and safety of Makena in preventing preterm births in all women, but particularly in the high risk. That research analysis and investigation must be done; not doing that will be a mistake. Additional studies properly powered in high-risk women to see if they are optimal candidates for Makena therapy are needed. These may be the women who need the drug the most. Without that information, the drug should not be withdrawn. If it is, we will never know it.

Let's not eliminate Makena from clinical use without cautiously and systematically gathering

additional evidence and learned experiences from communities of color who are disproportionately impacted by preterm birth. Prevention, diagnosis, and treatment of recurrent preterm birth is complex and multifactorial. More data on which population this treatment is effective is needed. More data on the effectiveness in the Black mother with a history of spontaneous preterm birth is needed. We will not have that if the drug is withdrawn.

From the studies published, are we convinced Makena is not safe and effective, especially in Black and other vulnerable women with previous spontaneous births? I and other clinicians believe no. We have not answered that question. A well-designed randomized trial by the sponsor, which they are willing to do, needs to be done to answer this unanswered question.

Based on the totality of data today, withdrawal of Makena is not indicated. It would make doing further study more difficult, especially in Blacks. More data and study, as stated by the NAACP, NMA, and others you have heard from and will

today, is needed. Therefore, I strongly agree additional study be conducted while Makena remains on the market. Thank you very much for the opportunity to speak today and hearing us.

DR. WITTEN: Our next speaker is Patricia Bencivenga.

Ms. Bencivenga, you have seven minutes.

MS. BENCIVENGA: Good morning. My name is Patricia Bencivenga, and I represent PharmedOut, a Georgetown University Medical Center project that advances evidence-based prescribing. I have no conflicts of interest.

Makena is an ineffective, expensive, and unnecessary drug, and PharmedOut urges this committee to recommend the removal of Makena from the market. Covis and previous sponsors have marketed this drug to a particularly vulnerable population. For example, AMAG's 2020 bilingual flipbook, Dear Baby, this is what I will do for you, written in the first person and produced to look like a children's book states that, "because your brother came early, I am more likely to have

you early, too. I promise I will do everything I can to help you have the best start to life."

That best start, of course, includes Makena. The book also promotes their financial assistance program and the care managers at Makena Care Connection who work with me, my healthcare provider, my insurance company, and the pharmacy to make sure I get my medicine on time. We are a team.

It is unfortunate that the FDA does not require speakers at open public hearings to disclose financial conflicts of interest. Groups opposing the withdrawal of Makena have received support from Makena's manufacturer. For example, as mentioned earlier today, the National Consumers League accepted funding from AMAG in 2019 and 2020. Their annual report for 2021 is not available. The Preterm Birth Prevention Alliance, a project of the National Consumers League, is funded by Covis. HealthyWomen, Sidelines, the March of Dimes, Miracle Babies, and the Black Women's Health Imperative have all received support from Makena's

manufacturer. Dr. Hugh Miller from WOMB, who testified yesterday, received over 37,000 in consulting fees from AMAG.

These conflicted groups have argued that Makena should remain on the market because there is no other approved treatment for preventing preterm birth. Is there any unconflicted group that argues to keep Makena on the market? Arguments that more evidence is needed in women of color are also untenable. It's just not true that this drug is inadequately studied in Black women. Trial 002 and 003 had 387 Black women out of a total of 2,171 women. That is 17.8 percent Black women in the trials, higher than the 13.6 percent of the U.S. population that is Black.

We do need more research into preterm birth and health disparities, but Makena is a bad consolation prize for systemic inequities in health care. Giving Black women an ineffective drug is hardly a heroic act in the name of health equity. Drug manufacturers support consumer advocacy groups to support ineffective or dangerous drugs and to

buy their silence on drug harms and drug costs. This committee should ignore all of the conflicted groups and only trust unconflicted groups such as Public Citizen and the National Center for Health Research.

Randomized-controlled trials trump observational studies, and we have more than enough evidence from randomized-controlled trials that Makena doesn't work. There's no need for further studies. The case has been proven. It has been over a decade since this drug was approved under the accelerated approval pathway, and almost four years since its confirmatory trial failed to show a clinical benefit. Its claim that more studies are needed is a stalling tactic because every day that withdrawal is delayed is a day of more profit for Covis.

Makena exposes patients to harms for no benefit. Nobody needs a drug that doesn't work, even if it were free, and at more than $700 an injection, it's not. It bears noting that compounded products are about $15. It is the FDA's

responsibility to withdraw products granted accelerated approval from the market if they fail to show efficacy in confirmatory trials. Makena is ineffective.

We agree with the FDA that the continued marketing of Makena in the absence of demonstration of benefit incurs false hopes, and that keeping Makena on the market would be a disservice to patients and would undermine the accelerated approval pathway. We support the FDA's decision to remove Makena from the market. Thank you.

DR. WITTEN: Thank you.

Our next speaker, and the last speaker for this session, is Ms. Annie Dude.

Ms. Dude, you have three minutes.

DR. DUDE: Good morning. My name is Dr. Annie Dude. I thank you for the opportunity to speak today. I am a practicing high-risk maternal-fetal medicine doctor at the University of North Carolina Chapel Hill, although I speak for myself. I take care of a wide range of patients who see me for a history of spontaneous preterm

birth, and I have done so over the past ten years throughout my training, and then in clinical practice. I have no financial interest in Makena as a drug. I receive no fees and I have no conflicts of interest to report.

In addition to my clinical practice, which as I mentioned consists of many patients who have a high-risk of recurrent preterm births and who have come to rely on Makena as a treatment, I'm also a clinical researcher and conduct research on preterm birth prevention, and it is as a researcher that I wanted to speak today.

My main concern with using the PROLONG trial to justify the decision to remove Makena from the market has always come in the differences between the two studies and I think in a more fundamental inability to truly study the underlying question in a similar manner, as the environment, the clinical environment, in the United States that existed at the time of the Meis trial in 2003 no longer exists. As the study authors themselves note, patients who had a cerclage prior to study

enrollment or who currently use progesterone were not eligible for the study in the United States. This is the PROLONG study.

Given that such an FDA-approved treatment was available for the prevention of preterm birth, and patients were either overtly or subconsciously steered towards that treatment if they had a high risk of the outcome, do you not think we can claim that the state of equipoise existed at the time of the PROLONG study, and that truly the same environment existed as in 2003?

Many prior speakers have already noted the racial makeup differences between the two studies, so I will not reiterate that here. I am also concerned that the patients at highest risk of the outcome were not eligible for the study either because they were told or chose to use progesterone. As the authors themselves note, the PROLONG trial had a much lower underlying risk of the primary outcome, spontaneous preterm birth, and the study itself was underpowered to the point where they would have required more than twice as

many enrolled participants to show the difference in preterm births that they were looking for.

In addition to differences in their racial makeup, there were also lower rates of more than one prior spontaneous preterm birth, and much lower rates of a short cervix, which is a physiological condition that is likely on the causal pathway of recurrent preterm birth. The authors themselves admit that the risk profiles in the two studies were quite different. Furthermore, in the PROLONG trial, in the United States, the underlying risk of spontaneous preterm birth was higher even in the participants that were enrolled and that there was a trend towards efficacy.

As a researcher, I am bothered that a priori environments were very different in these two studies and that one study is being used to negate the effects of the other. This is not to say that the Meis study is the final word on using Makena to prevent spontaneous preterm birth, but I do not think it is justified to use the PROLONG trial to refute the outcomes of the Meis trial.

In terms of safety -- and I should note here that I am part of the Society for Maternal-Fetal Medicine publications committee that wrote the clinical directions after the PROLONG trial came out, noting that we recommend shared decision making with patients -- as a clinician, I strongly believe that patients can make decisions for themselves, and then having shared decision-making discussions regarding our safety data, our efficacy data, possible benefits in their particular situation, and taking into account the fact that over the past 10 years, many patients now themselves have lived experience of using Makena as a treatment. I strongly believe patients can make decisions in conjunction with their doctors for themselves.

While it is true that compounding pharmacies exist, and patients may be able to get either compounded Makena or vaginal progesterone for a much lower cost, my main concern with pulling FDA approval is even when these low-cost substitutions are available, without FDA approval, Medicaid may

no longer cover these medications, and there's a difference between even $15 and free in terms of patients who do not have resources themselves for medication. My concern is dropping FDA approval will lead to less Medicaid coverage, and this will lead to less access for patients, including patients who have successfully chosen to use this medication in the past and have seen for their own selves improved outcomes.

In terms of the long- and short-term safety effects, it is true that we do not have perfect information on long-term effects of progesterone in pregnancy. It is also true that any long-term effect in particular are going to be confounded by gestational age of delivery, as well as NICU treatment changes over time.

In summary, while I agree with prior speakers that the Meis study may not be the final word on using Makena to prevent preterm birth, and while more studies to see exactly which populations this drug may be most effective in, I do not think that using the PROLONG study to refute the results

of the Meis study is justified.

I think that as a clinician who takes care of patients who have had now over 10 years worth of experience of using this medication in their own lives to improve their birth outcomes, taking this away without better justification will lead to decreased equity for patients. I believe patients, in conjunction with their doctors, and using the data we already have, can make decisions for themselves regarding whether they want to pursue this treatment or not. I thank you for your time.

DR. WITTEN: Thank you.

I'd like to thank all the speakers for the presentations, and we'll now proceed with questions for this third group of public presenters from the advisory committee, the Center for Drug Evaluation and Research, Covis, and me.

Anyone wishing to ask a question of a public presenter must identify the specific presenter to which the question is being posed. As I did yesterday, I'll start by first providing CDER and Covis four minutes each to ask questions, and I

will return to them if there's time at the end of this questioning period if either group uses the raise-hand icon.

For the advisory committee members, please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the icon again after you've asked your question. When acknowledged, please state your name for the record before you speak and direct your question to a specific presenter. If you wish a specific slide to be displayed, let us know. Finally, it would be helpful to acknowledge the end of your question with, "Thank you; that's all I have for my questions," so we can move on to the next questioner.

I'll now turn things over to CDER for their four minutes to ask questions.

DR. STEIN: Thank you, Dr. Witten. This is Peter Stein, director --

DR. WITTEN: I can't hear. Sorry. Is there a problem with the volume?

DR. STEIN: Let me see if I can move this

even closer.

Can you hear now?

MR. KAWCZYNSKI: It's fine. I'll boost him up a little bit.

DR. STEIN: Okay. Thank you.

Thank you, Dr. Witten.

This is Dr. Peter Stein, director of Office of New Drugs, CDER. We don't have any specific questions, but once again, I would like to thank the presenters. We found the comments extremely useful and very helpful to our considerations. We want to thank them for taking the time to provide such detailed and thoughtful input. Thanks, and that's all.

DR. WITTEN: Thank you.

Covis?

DR. CHARI: Thank you. This is Raghav Chari at COVIS Pharma. Again, no questions from our side either, but wish to thank all of the speakers this morning for taking the time to be with us and sharing their important perspectives. Thank you.

DR. WITTEN: And are there any members -- I

see Annie Ellis. I will call on you for now.

MS. ELLIS: Good morning. I'd also like to thank all the speakers, especially moms who've experienced preterm labor. I do have a question for Dr. Dude, Annie Dude.

You had mentioned that the PROLONG trial lacked equipoise because of the availability of Makena, and also that more research is needed, so it's actually a two-part question.

In today's environment, would there be equipoise if Makena is available for some people in trials that are being run to get more data? You also mentioned a shorten cervix as being one of the indications of high risk for preterm labor. Are there any other conditions that you think should be highlighted in this future research that should be happening?

DR. DUDE: Can you hear me?

MS. ELLIS: Yes.

DR. DUDE: In terms of whether equipoise exists, I think it's really hard to go back to the world of 2003 before we had injectable

progesterone. I think as long as this treatment is available, whether on label or off label, it is going to be impossible to pretend it never existed, and the results of the Meis trial don't exist.

I think in terms of going forward, especially if this medication is only available under experimental premises, we could artificially, to some degree, return to equipoise, although you can never entirely eliminate the possibility. Patients can get it themselves from compounding pharmacies. I think in some ways achieving true equipoise is impossible. That is also why I strongly don't think the two trials should be compared head to head and state that one refutes the other.

I think as of now, Makena is also a hard drug to study in observational studies because it requires a lot of effort on patients to get Makena as a medication, and it requires weekly injections from 16 through 36 weeks, so any observational studies are likely confounded by those that are able to get 20-plus week's worth of injections and

are different than those who don't receive the full course of injections.

So I think, in some ways, future studies are always going to be hard to do. I think we can also -- taking what we have learned in almost 20 years since the Meis trial, we can look at different genetic profiles of patients to see if there are some that respond better than others, and in that we do have equipoise. We can look at some particular groups to see if they respond better than others, and in that we still have equipoise.

In terms of a short cervix, in clinical practice, we right now take a different path for patients who have a short cervix with no prior preterm birth, and we give those patients vaginal progesterone. With patients with a short cervix who have a prior preterm birth, we offer them an ultrasound indicated cerclage.

But based on from what I can tell from the PROLONG trial, if patients already had a short cervix, they would have been offered a cerclage and less likely not eligible for the trial. Those

patients, in theory, are already supposed to be on Makena, so it is a hard thing to disentangle exactly what is due to short cervix, exactly what is due to a cerclage, exactly what is due to progesterone. However, the fact that there were so few people who had a short cervix in the PROLONG trial I think lends credence to one of the limitations of a trial, which the authors freely admit, which is that the underlying risk of the outcome was much lower in this trial than it was in the Meis trial.

Does that answer your question in terms of can we ever go back to true equipoise? I think on some level that is impossible. And in terms of a short cervix, I think the fact that the rate of short cervix in the PROLONG trial is so low speaks to the fact that these are different and not the same populations.

MS. ELLIS: Thank you so much. I think it really gives us things to think about, and I really appreciate your insight. And again, I appreciate all the presentations by our public speakers as we

move forward. Thank you. I have nothing further.

DR. WITTEN: Thank you.

Are there other members of the advisory committee who have questions for this group of speakers?

(No response.)

DR. WITTEN: Seeing none, I don't have any questions, and I, too, would like to thank the speakers for coming and sharing their views with us today. We are now going to have a break, and we will resume at 10:30.

(Whereupon, at 10:32 a.m., a recess was taken.)

DR. WITTEN: We are now going to proceed with the affirmative presentation from Covis. I'm going to ask that each speaker introduce yourself before you speak, and now I'm turning it over to Covis.

Covis Presentation - Raghav Chari

DR. CHARI: Good morning. I'm Raghav Chari, chief innovation officer at COVIS Pharma. COVIS Pharma is dedicated to developing and bringing to

patients important therapies for severe and life-threatening conditions across several therapeutic areas. In my role at Covis, I oversee research and development, focused both on developing new products, as well as enhancing our understanding of our existing products, the new studies, and product line extensions.

Before we start, I want to thank this advisory committee for the time you spent, and will spend, considering the challenging topics and questions at hand. My colleagues and I are grateful for the opportunity to be here today to outline our proposed path forward. This approach is centered around preserving access to Makena for a small subset of patients at the highest risk of preterm birth while we conduct additional trials to reaffirm the benefit of this therapy.

By way of background, Covis acquired AMAG Pharmaceuticals in late 2020 and became the sponsor of Makena in March of 2021. This occurred after the 2019 BRUDAC meeting and following CDER's proposal to withdraw Makena from the market. We

became involved with Makena because we saw its critical importance in reducing the risk of preterm birth. We note that along with Makena, there are multiple generics on the market. Following Covis' acquisition of the product, Covis reduced the net price for private payer and state purchases, and under the Makena co-pay assistance programs, patients pay no more than $35 per injection.

While we will touch on the development history of the product, I want to emphasize the leadership team at Covis is independent from the prior sponsors. We are committed to executing a robust plan to address the outstanding questions and concerns, including conducting the necessary additional studies. We understand that you're being asked to weigh in on a difficult and complex situation. I'll therefore begin by highlighting some points I believe we can all agree on.

First, preterm birth has a negative impact on maternal child health. Reducing preterm birth is a public health priority and an area of unmet need in drug development. Second, preterm birth

impacts a substantial number of women in this country. In fact, the rate of premature births in the U.S. is higher than in other industrialized nations. Unfortunately, women who are Black, of the minority and are socioeconomically disadvantaged, have the highest rate of preterm birth.

Third, Makena and its generic equivalents are currently the only FDA-approved treatment for reducing the risk of preterm birth. And finally, while there is some debate about the general significance of early versus late preterm birth, in its briefing book, CDER explicitly states that gestational age of delivery is an intermediate clinical endpoint, which is itself a measure of therapeutic effect. Medical and scientific communities agree that gestational age of delivery is strongly correlated with neonatal health because it is related to the development of the fetus.

There are some additional common points of agreement regarding the clinical data we will discuss today, the Meis trial, a multisite,

double-blind, placebo-controlled clinical trial initiated by the National Institutes of Health, and included the world renowned Maternal-Fetal Medicine Unit, or MFMU Network. When approving Makena, CDER acknowledged this trial as adequate, well controlled, and very persuasive, and provided compelling evidence of clinical development.

The Meis trial met its primary endpoint and all prespecified secondary endpoints for preterm birth rate. It demonstrated that Makena significantly reduces the risk of preterm birth at less than 37 weeks of gestation compared with placebo. Following accelerated approval of Makena, the obstetrics field immediately recognized the drug as a major treatment advance.

Leading medical societies such as the American College of Obstetricians and Gynecologists, or ACOG, and the Society for Maternal-Fetal Medicine, or SMFM, issued statements endorsing Makena. Subsequently, Makena became widely used to reduce the risk of preterm birth in women with one or more previous occurrences of

spontaneous preterm births.

Looking at the PROLONG trial, there are again important areas of agreement. The sponsor and CDER agree that PROLONG did not verify the clinical benefit of Makena on neonatal morbidity and mortality, nor did it show an effect on reduction of preterm birth rate. The sponsor and CDER also agree that the populations in the Meis and PROLONG trials were different from each other, both in risk factors and the incidence of preterm birth. Both the sponsor and CDER agree that PROLONG confirmed the safety profile of Makena. As we will demonstrate today, these two studies evaluated two very different groups of women.

It is also important to remember that the Meis and PROLONG trials have already been evaluated by a prior advisory committee. Shortly after PROLONG was completed, BRUDAC met to consider the available evidence. After extensive discussion, the committee reached a divided conclusion; 9 members recommended withdrawing Makena approval and 7 members recommended leaving Makena on the

market with the requirement that new confirmatory data be generated.

I will now outline at a high level the path forward that Covis is proposing for your consideration.

Covis is committing to conducting an additional trial to confirm the clinical benefit of Makena while it remains available to a higher risk subset of patients. We're proposing a three-tiered approach to address the outstanding questions and concerns raised by the PROLONG trial, while at the same time continuing to meet the critical need of a higher risk group of patients.

First, we are willing to work with the agency on a plan to partially withdraw Makena. We're willing to narrow the labeling to use in a higher risk target population for whom a consistent benefit is observed in both the Meis and PROLONG trials. Today, we will share the data. characterizing this higher risk subset. We have also halted active promotion of Makena and are committed to continuing to do so. Our commercial

organization would focus solely on maintaining patient access.

Second, we agree with CDER that a randomized-controlled trial is the most appropriate way to confirm clinical benefit in this target population. Therefore, we're proposing to conduct a third trial to evaluate Makena's effect on an intermediate clinical endpoint in the identified target population. This study could be completed within a 4-to-6 year time frame.

Finally, we understand the importance of evaluating the impact of prolonged gestational age on neonatal morbidity and mortality. Therefore, we're also willing to conduct an observational study that will expand the breadth of data to address this issue. In our presentation today, we will present the details supporting the execution and feasibility of this plan. Here, I will briefly summarize the key points.

There is a higher risk population of patients who benefited from Makena in both the Meis and PROLONG trials. Because of this, we're willing

to work with the agency to narrow the current labeling to focus on the small subset of higher risk patients. This would effectively be a partial withdrawal of Makena. In addition to this, there may be other ways to limit the labeling that we will discuss later.

Higher risk in all our analyses and proposals today is defined as a woman with a recent prior spontaneous preterm birth before week 35, who has one or more additional risk factors such as prior spontaneous preterm birth before week 32; multiple preterm spontaneous births before week 37; the last pregnancy within 2 years; or women who have other social determinants of preterm birth.

As we will demonstrate today, a third randomized-controlled trial in the identified higher risk population is both feasible and necessary. Due to the conflicting results from the Meis and PROLONG trials, medical practice has changed since 2019. This was not only reflected in CDER's number of reports in the FAERS 2012 to 2022 backup slide that you saw yesterday, but in fact we

will show you later in this presentation data from surveys demonstrating that a sufficient proportion of practitioners would be willing to enroll patients in a third randomized-controlled trial for Makena and a similar proportion of patients who would be willing to participate. Importantly, these surveys highlight the feasibility of enrolling the study while Makena remains on market.

The proposed trial would enroll approximately 400 patients, specifically women with one or more prior spontaneous preterm births less than 35 weeks and one or more additional risk factors. Participants would be randomized 2 to 1 to receive either Makena or placebo, and we estimate that the proposed trial can be completed in 4 to 6 years at most.

We understand CDER's concerns regarding the feasibility of conducting a randomized-controlled trial while higher risk patients continue to have access to therapy. Given these concerns, we would also commit to study conduct criteria and to voluntarily withdrawing Makena if these criteria

are not achieved.

First, we plan to conduct an interim analysis for futility. If futile, we commit to withdrawing the product. We will also continue to not actively promote the product other than maintaining our existing patient adherence program. Second, we will track enrollment. If by 24 months after the initiation of patient screening, enrollment projections indicate that the trial cannot be completed within the desired 4-to-6 year time frame, we will work with the FDA to close the study and withdraw the product from the market. And finally, if the outcome of the proposed randomized-controlled trial is negative, we commit to withdrawing the product.

As a final step in our recommended path forward, we propose to conduct an observation study. The goal of this study would be to further characterize the relationship between gestational age and neonatal outcomes in treated versus untreated patients. This study would be designed to specifically demonstrate that pharmacological

prolongation of gestation with 17P accrued similar benefits to the neonate as is already seen with spontaneous births at corresponding gestational ages and will address the key concern you've heard highlighted in CDER's presentation.

Our presentation today will provide you with information to answer the key question. Should Makena remain on the market for the identified target population of higher risk patients while additional studies are conducted?

This is the critical question, and the data we will show today demonstrate that the answer must be yes. A complete withdrawal of the product would harm the patients at the highest risk for preterm birth. We're proposing a path forward that's best for women and their babies and contains multiple measures to address all of CDER's stated concerns.

Here's now the agenda for our presentation today. First, Becky Wood will discuss the legal framework surrounding the questions posed to the committee, then Dr. Lawson will provide a brief overview of preterm birth. Next, Dr. Sibai,

Dr. Blackwell, Dr. Greene will review the current body of evidence supporting the benefit-risk of Makena. Dr. Poggio will provide the description of the statistical analyses that we performed to develop our proposals, and Dr. Lawson will share her clinical perspectives before I conclude with an overview of our confirmatory study and our position on the questions being asked today.

Thank you. I will now turn the presentation over to Becky Wood.

Covis Presentation - Rebecca Wood

MS. WOOD: Thank you, Dr. Chari.

Good morning. My name is Rebecca Wood. I'm a partner at the law firm of Sidley Austin here in Washington, where I lead the FDA and healthcare group. I previously served as chief counsel in the Office of Chief Counsel at FDA. Sidley serves as outside legal counsel to Covis in this matter.

I want to focus briefly on why the governing legal standards support retaining Makena as an approved treatment option for preterm birth while Covis undertakes a new confirmatory study. I want

to focus on three main points. First, as we heard yesterday, the accelerated approval standard is designed to be flexible. Second, as we also talked about yesterday, withdrawal is not mandatory in the circumstances here. An important consideration is the background unmet medical need and the public health risk of alternatives. Third, both policy and precedent support keeping Makena on the market while additional study is undertaken. Let's begin with the regulatory flexibility built in to the accelerated approval framework.

The accelerated approval statute is intended to encourage FDA to utilize innovative and flexible approaches to assess therapies for patients with serious or life-threatening diseases or conditions and unmet medical needs. Similarly, FDA's regulations echo that drug approval demands flexibility.

I'm going to turn to the legal framework for the withdrawal of accelerated approval. The accelerated approval statute provides that 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. But even when one or more of these factors is met, that is the beginning of the analysis, and not the end.

It is critical to remember that the accelerated approval statute is permissive, as you heard yesterday. The statute says only that FDA may withdraw, and CDER acknowledges that CDER possesses various regulatory options when a confirmatory trial fails to verify clinical benefit. Accordingly, FDA has the authority to allow Makena to remain on the market while another trial is conducted.

There are a number of important legal limits on how FDA exercises its decision making, including considerations of policy and precedent. In FDA's response to GAO and public statements from senior agency officials, it's noted that when a confirmatory study fails, FDA should consider multiple factors. First, why did the trial fail?

Second, what options are available to patients? Leaving patients with no approved treatment may be unacceptable. Third, is there a subset of patients for whom the drug may be effective?

And just to illustrate a few examples, the director of FDA's Oncology Center of Excellence addressed the importance of considering why the trial failed, saying, quote, "There are many reasons that a trial fails. To remove the drug from the market or even an indication is a big deal and may not be in the public's best interest if you can understand why that trial failed. We have to have flexibility rather than just a draconian approach."

With respect to what options are available for patients, for example, the director of CDER's Office of Neuroscience recently stated that FDA must carefully evaluate all options available to patients and removing the drug may be unacceptable when patients are left with no approved treatments. FDA also considers the possibility that there could be a subset of patients for whom the drug is

effective, which you'll hear more about today.

I would like to focus on FDA's application of these factors. CDER's discussion of precedent yesterday did not mention ProAmatine, also called midodrine. Midodrine, which is used to treat hypotension, received accelerated approval in 1996. By 2007, confirmatory studies submitted in 2005 were determined by FDA to have failed to verify clinical benefit. In 2010, CDER issued a notice of opportunity for a hearing, NOOH, proposing to withdraw midodrine. In 2012, FDA agreed to hold that NOOH in abeyance.

In 2015, midodrine's sponsor submitted a supplement with the results of additional studies. This was 19 years after the original approval and 10 years after the first set of failed confirmatory studies were submitted to FDA, and midodrine remains on the market today. Now, the point here is not to suggest that any two decisions are identical. Rather it is to highlight the flexibility FDA has available to it and that it has used previously.

CDER's approach to Makena departs from how the agency considered the relevant factors with midodrine in at least two ways. First, with midodrine, the agency was careful not to withdraw the only approved treatment for a serious condition where there was an unmet medical need.

CDER recognized there, quote, "Midodrine is the only drug approved for the treatment of the serious condition at hand, and if marketing approval for midodrine is withdrawn at this time, patients with this condition will be left with no approved therapeutic options."

Second, with midodrine, even after its proposal to withdraw, CDER worked with the sponsor to design and conduct two additional studies. FDA said they are, quote, "FDA has two goals with respect to midodrine: to obtain high-quality data on the effectiveness of the medication and to maintain access for patients to the medication throughout this process."

Second, I want to say a few words about the legal status of other forms of 17P that may be

available even if Makena is withdrawn from the market. With respect to compounded 17P, as a matter of law, if FDA withdraws a drug from the market, its active ingredient is added to the list of withdrawn or removed drugs that may not be compounded. In practice, however, as we heard about yesterday, that process is uncertain and may take years. As a result, compounding is likely to continue for years following withdrawal, and as you heard yesterday, and as CDER has acknowledged on slide 107 of its presentation, 17P may be eligible for compounding if Makena were withdrawn.

Unlike Makena and its approved generics, compounded drugs are not FDA approved or labeled, and 503A compounding pharmacies are not subject to good manufacturing practices. And with respect to compounding generally, FDA has recognized that the unnecessary use of compounded drug unnecessarily exposes patients to potentially serious health risks.

Finally, I'd like to touch on the path forward. In the 30 years of the accelerated

approval program, 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. As the FDA Chief Scientist said in granting the sponsor's request for a hearing, "Covis has justified a hearing in this matter given the genuine and substantial issues of fact appropriate for a hearing."

In conclusion, FDA may and should exercise regulatory flexibility, here, where a confirmatory trial failed in light of the flexible accelerated approval standard, the permissive withdrawal standard, and FDA's approach to policy and precedent. Thank you. I will now turn the presentation over to Dr. Yolanda Lawson.

Covis Presentation - Yolanda Lawson

DR. LAWSON: Thank you, and good morning. My name is Yolanda Lawson. I'm a board certified OB/GYN, fellow of the American College of Obstetricians and Gynecologists, or ACOG, and founder and owner of MadeWell OB/GYN. I am also an

associate attending physician at Baylor University Medical Center and president-elect of the National Medical Association. We are the nation's oldest and largest organization, representing African American physicians, and our primary mission is to end healthcare disparities.

I have a passion for the physical, emotional, and overall health of women and have dedicated my time and energy to providing superior health care to women from all backgrounds. I understand CDER's position and what is at stake in this hearing. Today, I will provide my personal clinical perspective on why CDER should not withdraw Makena from the market, but instead allow clinicians to use their clinical judgment on the question of patient care. I am not being compensated for my time, and I have no financial interest in the outcome of this hearing. Covis is reimbursing my travel expenses with respect to this hearing today.

I will start here with a short overview of preterm birth, and later return to discuss my

experiences as a clinician, caring for women at risk of preterm birth. Let me give you some background on preterm birth. It is universally recognized that preterm birth is a serious medical condition associated with significant morbidity and mortality. In fact, in the United States, preterm birth and its short- and long-term complications are the leading cause of infant death.

There is a higher risk of death within the first 28 days of life for prematurely born infants. Babies born prematurely are often put on ventilators because their lungs are immature, their infection risk is high, and they are more likely to suffer brain damage or a brain bleed. While long-term complications are rare, they are profound and can be lifelong. These babies are at increased risk for learning difficulties, hearing and vision impairment, and chronic respiratory problems, including asthma.

While there is some debate about the general significance of early versus late preterm birth, the medical and scientific communities agree, the

risks associated with preterm birth lie on a continuum. In other words, as shown here, neonatal morbidity is highest when babies are born early preterm, which is less than 34 weeks gestation, and decreases proportionately to increasing gestational age; so 2 weeks of added gestational age before 35 weeks can significantly reduce the risk to the baby.

These statistics tell us, and I know from my own clinical experience, one of the most significant risk factors for preterm birth is a patient's history of spontaneous preterm birth. As shown in this table, earlier gestational age of the first preterm birth is generally associated with a higher risk of recurrence, therefore, a pregnancy after an early spontaneous preterm birth is generally considered high risk.

Preterm birth impacts a substantial number of women from all walks of life in the U.S. It is estimated that approximately 130,000 women per year in the United States have a history of prior singleton spontaneous preterm delivery. These are

women I treat every day in my practice. It is widely recognized that Black women, other minority groups, and the socioeconomically disadvantaged have the highest rate of preterm birth.

According to the March of Dimes 2021 report, the preterm birth rate among Black women is 14 percent, which is 51 percent higher than the rate among all other women in the United States, and it is important to keep in mind that these women would be most impacted if Makena was withdrawn from the market because clinicians like myself would lose an important treatment option.

I will discuss my role as a clinician and the impact of preterm birth on my patients later in the presentation. For now, I will turn over to Dr. Baha Sibai to discuss the Meis trial.

Covis Presentation - Baha Sibai

DR. SIBAI: Thank you, and good morning. I am Baha Sibai. I am a professor in the Department of Obstetrics, and Gynecology, and Reproductive Sciences at the McGovern Medical School, University of Texas, Houston. For the past 40 years, I have

taken care of pregnant women at high risk of preterm birth. I was involved in the design and conduct of several randomized trials on preterm birth. I served as the principal investigator, or the alternate principal investigator, in the Maternal-Fetal Medicine Network for more than 20 years. I was on the subcommittee that designed and completed the Meis trial, which led to the accelerated approval of Makena for the prevention of recurrent preterm birth.

I strongly disagree with CDER that the Meis trial was a proof-of-concept trial. Indeed, prior to initiation of this trial, there were at least five proof-of-concept randomized trials, comparing 17 hydroxyprogesterone to placebo or no treatment. These trials were published between 1964 and 1985, and one of these trials was published in the New England Journal of Medicine in 1975 by Dr. Jack Johnson. I am being compensated for my time here, but I have no financial interest in the outcome of this hearing. In addition, I receive no grant support from Covis.

I use Makena in preterm birth in women at risk on a weekly basis. Many of my patients are Black, minority, and socially disadvantaged, and have high risk factors for pregnancy. During the past two years, I have seen a significant increase in the number of women who are candidates for Makena and instead are receiving cervical cerclage. This is a highly unfortunate result of the widespread publicity questioning the efficacy of Makena. Cerclage is surgery. It can lead to preterm births when not indicated. It is costly, and it puts women at risk for more surgery in all subsequent pregnancies.

Let me now discuss the Meis trial results. The Meis trial provided clear and compelling evidence of a substantial clinical benefit in women at risk of preterm birth. Women with a documented history of singleton spontaneous preterm birth were enrolled at 19 sites in the United States. They were then randomly assigned in a 2 to 1 ratio to receive either Makena or placebo.

At the second planned interim analysis on

351 women, an independent data and safety monitoring committee determined the prespecified stopping criteria were met. To be clear, the efficacy was so robust that enrollment was stopped, however, women who were randomized up to that point remained on the trial until delivery. This resulted in a data set of 463 women, 92.6 percent of the planned sample size.

The primary outcome results showed that Makena reduced the risk of preterm birth prior to 37 weeks gestation by 34 percent, and reductions were also seen at earlier gestational ages compared to placebo. Makena reduced delivery at less than 35 weeks by 33 percent and introduced delivery at less than 32 weeks by 42 percent. This is the group at highest risk for both acute and long-term neonatal morbidity and mortality, and Meis showed highly statistically significant efficacy results across all major subgroups.

In CDER's own review of the trial itself, quote, "This treatment benefit appeared independent of risk, number of prior preterm deliveries, and

gestational age of the prior preterm birth." When approving Makena, CDER acknowledged the Meis trial was adequate, well controlled, and very persuasive, and provides compelling evidence of clinical benefit. CDER also stated that the Meis trial is sufficiently persuasive to support drug approval, based on the findings of a single adequate and well-controlled trial.

The Meis trial was immediately recognized as a major advance in the field of obstetrics and was published in the New England Journal of Medicine. The publication recognized the 18.6 percent absolute difference in preterm birth rates with Makena. This translated to a number needed to treat of 5.4 women to prevent one preterm birth.

Shortly thereafter, leading medical societies weighed in. They recommended progesterone supplementation to reduce the risk of recurrent preterm birth in women with a history of spontaneous preterm birth. The American College of Obstetricians and Gynecologists issued a committee opinion seen on this slide. The group stated that

this treatment should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth.

I want to take a moment to discuss the speculation that the Meis trial is an outlier or a false positive. This is not the case. First, as previously discussed, the Meis results were so compelling, the efficacy so robust, that an independent data and safety monitoring committee recommended stopping the trial early. This decision was based on 351 randomized patients. Women randomized up to the point remained in the trial until delivery. This resulted in a data set of 463 women, or 92.6 percent, of the planned sample size.

Second, I will address the concerns around generalizability of the data. We conducted multiple subgroup analyses associated with spontaneous preterm birth. We looked at a number of planned spontaneous preterm births, race, marital status, smoking, or substance abuse. These analyses consistently demonstrate that Makena

reduces preterm birth, and that the results were generalizable to a wide range of women with previous spontaneous preterm birth.

Finally, the preterm birth rate in the Meis trial was not unexpected given the high risk population enrolled. This included a high proportion of patients who were Black and had more than one prior spontaneous preterm birth, including one at an earlier gestational age.

It is important to emphasize that the placebo rate of preterm births at less than 35 weeks in the Meis trial was not abnormally high. In fact, it was similar to that of another international randomized trial, which compared vaginal progesterone to placebo and enrolled 64 percent of its populations in the United States. Many of the centers in the Maternal-Fetal Medicine Network were a part of this trial.

Let me further put the rate of preterm births and the 17P arm and the Meis trial in context. Here, I am comparing Meis to the Omega-3 trial, another multicenter study conducted by the

Maternal-Fetal Medicine Network, which was published in 2010. Omega-3 studied whether giving an omega-3 fatty acid supplement to women with at least one prior preterm birth would reduce their risk of another.

All patients in the Omega-3 received weekly injections of 17P. As you can see, while the patients enrolled in the Meis were at higher risk, the rate of preterm births in the 17P groups was generally comparable. These data support that the rate of preterm births in the Meis trial was not unexpected. Thus, the results should not be viewed as a false positive.

CDER has also raised concerns about the generalizability of the Meis trial due to high enrollment at 20 U.S. sites. I conducted an analysis of the Meis trial results. It was peer reviewed. From this analysis, I can tell you that 27 percent of women enrolled from one site does not undermine the trial.

For decades, preterm birth rates have been higher in the southeast compared with other U.S.

regions. Thus, it is not unexpected that one site in that region would have the highest enrollment rate. Nevertheless, this institution did not bias the results. In fact, Makena demonstrated a significant reduction in preterm births at other sites with a relative risk of 0.70. Therefore, the trial results remain significant even when all the women from the southeast site were excluded from the analysis. Further, the p-value of 0.82 from an interaction term in a logistic regression analysis indicates the southeast site results were not significantly different from the other sites.

Thank you. I will now turn the presentation over to Dr. Blackwell.

Covis Presentation - Sean Blackwell

DR. BLACKWELL: Thank you.

My name is Sean Blackwell, and I'm the department chair and a professor at the McGovern Medical School in Houston, Texas, where I specialize in maternal-fetal medicine, with a focus on the treatment of women with preterm births. Like Dr. Sibai, I am a former principal

investigator with the Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. While Dr. Sibai was an active co-investigator and co-author for the Meis trial, I was a Maternal-Fetal Medicine Fellow and junior faculty, who screened, and recruited, and cared for women while they were in the trial, while working in Detroit, Michigan at Wayne State University. I'm also a past president of the Society for Maternal-Fetal Medicine, which is the professional society for high-risk pregnancy specialists.

For disclosure purposes, I have no financial interest in Covis, and Covis is not compensating me for my time. Covis is reimbursing me for travel and logistical expenses only.

I was the lead author of the PROLONG publication, and I am here to provide background regarding PROLONG and explain why its results were so different than the Meis trial. PROLONG stands for progestin's role in optimizing neonatal gestation. Between 2008 to 2009, the then sponsors negotiated with the FDA to plan this trial, which

was originally referred to as Study 003 and later called PROLONG. It would have the same eligibility criteria, screening and recruitment, and operational protocol as Meis.

One issue that will be discussed in more detail by Dr. Greene is that in the planning of PROLONG, the rate of preterm births chosen for sample size and power calculation was entirely based on Meis, with an assumed preterm birth rate less than 35 weeks of 30 percent in the placebo group, with a proposed effect size of 30 percent.

There were several differences between the design elements of PROLONG and Meis. PROLONG had different primary outcomes. These were co-primary efficacy endpoints of a preterm birth less than 35 weeks and a neonatal composite morbidity index, while Meis had a singular primary outcome rate, or outcome measure, of preterm birth less than 37 weeks and was not powered to assess for neonatal outcomes.

Also, PROLONG had a much larger planned sample size. It would be over 3 times larger with

the intent to provide better assessment of any potential harm related to concerns of early pregnancy loss or stillbirth. And finally, PROLONG had a planned 2-year follow-up of newborn outcomes, including neurodevelopmental assessment.

Since completion of PROLONG was a requirement of accelerated approval, there was intentionally no plan for any interim analyses related to efficacy. The DSMC conducted and reported safety monitoring as its main focus. Due to the overwhelming positive findings of the Meis trial, such that all patient subgroups had benefit, the study was stopped early due to efficacy, preterm birth experts, academic, and private physicians, and patients were all eager to start treatment as part of routine clinical care.

The New England Journal published the Meis trial in 2003, and in that same year, SMFM and ACOG, our major professional societies, authored a new statement advocating use of progestogens. Academic medical centers with the highest risk patients, including those who participated in Meis,

were not willing to enroll their patients into a confirmatory trial at that time. When PROLONG began in 2009, neither Dr. Sibai, who was faculty at the University of Cincinnati, nor me, at UT Houston, enrolled patients. It was acknowledged and planned by the sponsor and the FDA that the bulk of recruitment for PROLONG would occur outside the United States.

The PROLONG protocol, like Meis, required starting study medication early in pregnancy and having prenatal care infrastructure to facilitate weekly therapy until delivery. It required a setting with advanced obstetrical care to manage preterm birth and NICU services to care for newborns as early as 24 weeks. This requirement led to the sponsor utilizing a contract research organization, also called a CRO, with infrastructure and relationships in Eastern Europe, where routine progestogen therapy had not started.

This graph shows PROLONG enrollment from 2009 to 2018. As part of the contingent approval of Makena, FDA required at least 10 percent of

PROLONG patients be enrolled from North America. After a key milestone was reached for recruitment in the United States, Makena received approval in 2011. After 2011, the sponsor and the CRO focused enrollment on locations outside the United States to achieve the required overall sample size.

This next table shows the final PROLONG recruitment by country. Overall, 61 percent of women were from Russia or Ukraine, while 23 percent were from the United States. This next table describes the rate of preterm birth less than 35 weeks for both study groups for the top recruitment sites in the United States. There were 391 women enrolled in the United States; 95, or 24.2 percent, were from Department of Defense locations, and the remaining were from the civilian locations. Overall, the DoD sites had a preterm birth rate of 9.5 percent versus 13 percent per Makena versus placebo, which you can see in the top row. As a reminder, and to set a context, the Meis trial placebo group had a preterm birth rate of less than 35 weeks of approximately 30 percent.

Due to the need to recruit from Department of Defense locations and not include major academic medical centers, the U.S. PROLONG patients had a different clinical characteristics set and a preterm birth risk profile than Meis, and I will show this data in upcoming slides.

Between 2009 and 2018, Russia and Ukraine were the major enrollment locations outside the United States, and this resulted in even more dissimilar patient characteristics and even lower risk profile than planned and than the Meis study.

So what is the evidence that PROLONG, with identical eligibility criteria of a prior spontaneous preterm birth, had substantively different patient characteristics on a preterm birth risk profile? These two graphs demonstrate the co-primary outcome rate for PROLONG preterm birth less than 35 weeks and the neonatal composite morbidity index. In the overall trial, the study group had an 11 percent rate of preterm births less than 35 weeks and an 11.5 percent rate in the placebo arm.

This next graph illustrates preterm birth risk profiles for three randomized-controlled trials, using preterm birth less than 35 weeks in the placebo arm as a proxy for a baseline risk of preterm birth. The three trials are Meis, O'Brien, and PROLONG. The O'Brien trial, which was discussed by Dr. Sibai earlier, was an international placebo-controlled trial of women with a prior spontaneous preterm birth; 64 percent of women were recruited in the United States.

Now, this graph not only highlights the differences in baseline risk between the Meis trial and PROLONG, but also the differences between women recruited in the United States versus outside the United States for PROLONG.

Another way to compare the risk profile of women in Meis and PROLONG is to compare them based on the frequency and number of early prior spontaneous preterm births. This is important, as the earlier the prior spontaneous preterm birth, the greater the risk of recurrent preterm birth. Women in PROLONG-US had a lower frequency of early

spontaneous preterm birth and a much lower rate of having two or more early spontaneous preterm births.

This next table demonstrates key patient characteristics and compares Meis, PROLONG outside the United States, and PROLONG-US. In the Meis trial, 59 percent of women were Black or African American, while less than 1 percent of PROLONG subjects outside the United States were Black or African American, and in PROLONG-US, 29 percent were Black.

This table also demonstrates the differences in socioeconomic markers or social determinants of health. In the last three rows, the frequency of being unmarried, having a highest educational level less than or equal to 12 years, and any substance abuse are compared and described.

One final piece of evidence is the frequency of a short cervix in women who were enrolled in to PROLONG. Cervical length was not standard practice when Meis was conducted and was not collected as part of the study protocol, so its frequency is

unknown. When PROLONG started in 2009, it was then a standard practice to measure the cervical length by ultrasound in women with a prior spontaneous preterm birth in order to assess the potential need for a cervical cerclage.

For our purposes, a short cervix is defined as a cervical length less than 25 millimeters. 1.4 percent, or under 2 percent, of women in PROLONG had a sonographically short cervix, which was much lower than what would have been planned and what would be expected for a high-risk patient profile.

I will now compare this to data from other studies published in the United States. In a multicenter trial of high-risk women with a prior spontaneous preterm birth, who were randomized to cerclage versus no cerclage, the rate of a short cervix was 31.4 percent. This was published in 2009 and reported by Owen and colleagues in the American Journal of Obstetrics and Gynecology.

In a multicenter trial of high-risk women with a prior spontaneous preterm birth less than

32 weeks, the rate of a short cervix was 29 percent. This was published in 2001 and reported by Owen and colleagues in a different study published in the Journal for the American Medical Association.

In other published observational studies, the frequency of a short cervix in high-risk women, with a prior spontaneous preterm birth less than 37 weeks, ranged from 4.5 percent to 9.1 percent. This includes data from the MFMU PreTerm Prediction Study, as well as data from a universal screening program in Houston, Texas.

It is uncommon for a trialist to argue that a study she or he was heavily involved in is, quote, "flawed"; however, it is my opinion while there was strong internal validity of the trial and the trial successfully mirrored the protocol of Meis, we enrolled a much lower risk patient cohort, with preterm birth event rates substantively lower than what was planned and modeled after Meis.

I have shared with you that the data for PROLONG's preterm birth rate was nearly two-thirds

lower than what was planned. We planned a baseline rate of 30 percent with a planned 30 percent effect size, and the actual rate of preterm birth less than 35 weeks was 11 percent. For these reasons, I believe PROLONG results are not informative for assessing the efficacy of Makena in a high-risk patient population.

As the chair of our department, I lead a faculty of over 175 OB/GYN faculty, fellows, and residents. Our team delivers nearly 10,000 women per year. My primary hospital is a level 4 academic medical center with an overall preterm birth rate of 26 percent.

Since the publication of PROLONG and the prior FDA advisory meeting, I continue to utilize Makena for my patients, as do many other MFM physicians across the United States. However, other physicians have stopped prescribing Makena, and certainly there is a major difference in practice after publication of the PROLONG trial and communication of the FDA advisory meeting in 2019.

While I continue to utilize Makena for my

high-risk patients and advocate for its use, I recognize there is a lack of clarity due to conflicting trial results, and there is lack of consensus from various experts and stakeholders. I support the need for another placebo-controlled clinical trial in the United States.

Thank you. I will now turn the presentation over to Dr. Greene.

Covis Presentation - Michael Greene

DR. GREENE: Thank you, and good morning. I'm Michael Greene. I'm professor emeritus of Obstetrics, Gynecology, and Reproductive Biology at Harvard Medical School. I practiced maternal-fetal medicine for 39 years in Boston at Brigham and Women's Hospital and at Massachusetts General Hospital. I've been an associate editor of New England Journal of Medicine for more than 25 years, and I am a former member and chair of the FDA's Advisory Committee on Reproductive and Urologic Drugs.

I am not being compensated for my time, and I have no financial interest in the outcome of this

meeting. I am here today to discuss why, in my opinion, the totality of the evidence continues to support the conclusion that Makena is safe and effective for use in a high-risk subset of patients.

I'd like to start by emphasizing three important points. First, Makena is not indicated to be used in the general population and is indicated only for use in women who have a history of spontaneous preterm birth. This is a critical limitation, as history of spontaneous preterm birth is a significant risk factor for recurrent preterm birth.

Studies that evaluate different potential risk factors such as HIV infection are not helpful in evaluating whether Makena is effective for its intended use. This is particularly true if the study in question specifically excluded Makena's intended patient population; that is women with a history of spontaneous preterm birth.

Second, Makena is indicated only for use during singleton pregnancies. The labeling for

Makena includes an explicit limitation against its use in women with multiple gestations. Therefore, studies in these patients are also not helpful in evaluating whether Makena is effective for its intended use in singleton pregnancies.

Third, CDER has taken the position that there are, quote, "inherent limitations to observational studies for externally-controlled trials, whether retrospective or prospective." I agree with CDER's position and do not think observational studies have much to contribute to the discussion of Makena's efficacy.

Applying these principles, we can see that CDER's effort to paint Meis as a, quote, "outlier," unquote, is undermined by a careful examination of the individual studies in this forest plot. The Hakim, Wang, and Massa studies, cited here in CDER's forest plot, are all observational and, as CDER has said and I agree, are not by their design sufficiently persuasive to be considered.

The studies performed by Dwight Rouse and Steve Caritis evaluated women carrying twins and

triplets, respectively; therefore, the results from these two very different populations are not relevant to women with singleton pregnancies. The Price trial, cited by CDER, evaluated women with HIV and specifically excluded women with a history of preterm birth. Furthermore, the rate of preterm birth in the placebo arm was 9 percent, approximately what it is for the U.S. population in general. This is not a high-risk population.

What's left is just Meis and PROLONG. This is important because only randomized-controlled trials conducted in Makena's target population are truly relevant to our consideration of Makena's efficacy here today and because there are only two such trials, it is not appropriate for CDER to characterize the Meis trial as an outlier. I must also note that after providing this figure, CDER provided a second similar figure with seven more randomized-controlled trials added, for a total of 15. Those trials recruited women with twins, triplets, arrested preterm labor, and sonographic short cervices, none of whom met the enrollment

criteria for either Meis or PROLONG.

I want next to address how I evaluate Meis and PROLONG. As was explained earlier by Dr. Sibai, there's no real question that Meis was a successful trial. As Dr. Blackwell explained, there's no real question that PROLONG failed to confirm the effects seen in Meis. As FDA officials have recognized, when there are conflicting results, we have an obligation to try to reconcile the two trials and to understand why the second trial failed to confirm the first.

In my opinion, understanding why PROLONG failed to confirm the Meis trial can be explained by a careful examination of the data. Fundamentally, PROLONG failed to enroll a population at similarly high risk for preterm birth as was enrolled in the Meis trial. Recurrent preterm birth is a common complex disorder with no singular cause. The causes are likely multifactorial and difficult to measure. They undoubtedly include genetic, environmental, and behavioral factors.

That said, there are several well known risk factors that we routinely use as very imperfect proxies for the risk of recurrent preterm birth. This slide, which you have seen before, lists various factors recognizing the literature as correlating with a higher risk for recurrent preterm birth. As you can see, with the exception of substance use among the U.S. women enrolled in PROLONG, the majority of the women enrolled in PROLONG were at significantly lower risk for recurrent preterm birth than the women enrolled in Meis.

Recognizing the classic risk factors are imperfect proxies, the most important difference between the two populations is best shown in the actual observed rates of preterm birth in the placebo groups in both trials. In the Meis trial, the rate of preterm birth less than 35 weeks in the placebo group was 31 percent, whereas in the PROLONG trial, it was 9.7 percent outside of the U.S., 18 percent in patients enrolled in the U.S., for an overall rate of 11.5 percent, clearly

demonstrating that the placebo-treated patients were substantially different between the two trials.

It is also important to note, and as Dr. Blackwell mentioned, that the 31 percent number in the Meis trial were births at less than 35 weeks was the number used to calculate the sample size for the PROLONG trial.

In its briefing book, CDER repeatedly refers to PROLONG as a, quote, "negative," unquote study. CDER also asserts that PROLONG excluded or ruled out any treatment effect. And CDER also asserts that PROLONG conclusively establishes a lack of substantial evidence that Meis is a false positive.

I do not think these are fair assertions. PROLONG failed to confirm Meis, but it is not a, quote, "negative" study. PROLONG failed to enroll a sufficiently high-risk population, resulting in a study without adequate power to warrant a statistically robust inference of a null effect. In my opinion, Meis remains substantial evidence of effectiveness in women who are at high risk of

recurrent birth, while the PROLONG trial do not overturn the results of Meis. They are, unfortunately, irrelevant to Meis.

Given where we are, I believe an adequately powered further RCT is necessary, but we should not simply repeat PROLONG. We should instead learn from that experience and design a better trial that evaluates a truly high-risk population. I agree with the sponsor that this is likely to require additional enrollment criteria beyond those used in PROLONG and Meis. I also think it is worth considering the use of more sensitive outcome measures related to gestational age.

I understand working through those details of study design are not today's task. They should be worked out by the sponsor and CDER in a collaborative manner. You do have to vote today, however, on whether Makena should remain available while the new trial is conducted. I have previously written that it would be a mistake to withdraw Makena from the market, given the drug is safe for its intended use. I would add, though,

that it would make sense to update the labeling to reflect the target population of the new trial.

I know that FDA will ask you to discuss and vote upon several questions at this meeting. I want to leave you with what I think are two important questions. First, given what we know about risk factors for recurrent preterm birth, were the populations enrolled in Meis and PROLONG efficiently similar to allow for a meaningful comparison?

Second, are the observed rates of preterm birth in the placebo arms of the two trials, of 30.7 percent in Meis and 11.5 percent in PROLONG, efficiently similar that they can be confidently said to represent two populations at similar risk for recurrent preterm birth?

I submit the answer to both questions is no. Prior speakers have quoted portions of my editorials in the New England Journal of Medicine out of context. That can be done by anyone for their own purposes. In keeping with the title of this presentation, quote, "Totality of the

Evidence," I would encourage anyone who is interested to read those editorials for themselves in their entirety. I stand by them. Thank you, and I turn the podium over to Dr. Poggio.

Covis Presentation - Eugene Poggio

DR. POGGIO: Thank you, Dr. Greene.

Good morning. I'm Gene Poggio, president and chief biostatistician at Biostatistical Consulting. For the last 37 years, I've been involved in the design and analysis of hundreds of clinical trials for drugs, biologics, and medical devices in a wide variety of therapeutic areas for numerous sponsors. I'm a paid consultant to sponsor, but I have no financial interest in the outcome of this hearing.

In this presentation, we'll examine risk factors for recurrent preterm births with the goal of identifying a higher risk patient population for which 17P shows evidence of efficacy in the PROLONG trial, as well as in the Meis trial. As you've seen, the results for Meis and PROLONG differed substantially. In Meis, the primary endpoint in

the preterm birth -- secondary endpoints were met. In PROLONG, neither co-primary endpoint was met. As you have also seen, the two studies enrolled vastly different populations. In particular, there were large differences in underlying risk factors, with subjects in Meis being at greater risk. Covis believes the difference in results in the two studies is due primarily to the differences in risk.

We investigated risk factors for recurrent preterm birth using data from a medical records database for obstetrics called Dorsata, as well as from data from Meis and PROLONG. The Dorsata database included about 1700 pregnancies with confirmed preterm birth. In the analysis of this database, we excluded subjects treated with 17P so as not to confound the analyses. For the same reason, in the analysis using Meis and PROLONG data, we included only placebo subjects.

We investigated risk factors in these three databases using logistic regression models with delivery less than 34 weeks as a dependent

variable. Potential risk factors considered included demographic characteristics, medical history, obstetrical history, and substance use. Obstetrical history factors were consistently the most important predictor of preterm birth.

Most important of all were mean gestational age of all prior spontaneous deliveries and gestational age of most recent spontaneous delivery. Also important were at least one prior spontaneous delivery less than 32 weeks and more than one prior spontaneous delivery less than 37 weeks. Additional risk factors identified included race, inter-pregnancy interval, and smoking.

Both the Meis and PROLONG studies used dichotomous primary endpoints. Meis used preterm birth less than 37 weeks and PROLONG used preterm birth less than 35 weeks, as well as the neonatal composite index. In order to increase sensitivity to be able to detect treatment effects, most of the post hoc analyses we conducted used a continuous endpoint, specifically time from randomization to

delivery. This was capped at 35 weeks based on clinical input so that increases prior to 35 weeks are considered to be more meaningful clinically.

Generally, the analyses were conducted using linear regression with time from randomization to delivery as a dependent variable, and treatment; gestational age at random; and either mean gestational age at prior deliveries or gestational age at most recent delivery, as predictor variables.

FDA noted in its review of the Meis trial that there appeared to be little evidence of a treatment effect for patients randomized after 20 weeks gestation. Covis agrees with this observation. Accordingly, in all the analyses that I will be presenting, we have excluded subjects randomized after 20 weeks.

As you know, the PROLONG trial enrolled patients both in the U.S. and outside the U.S. We believe the U.S. subpopulation of PROLONG is more representative of the relevant population for FDA decision making. The ex-US patients represent a

somewhat different population under different healthcare systems. In particular, they represent a lower risk population. Further, the number of patients in the U.S. subpopulation is sufficient for our purposes here. Accordingly, all the subsequent analyses presented for PROLONG are for U.S. patients only.

Before presenting the results of these analyses, I'd like to point out some important caveats. First, all of these analyses are post hoc. They were not prespecified. Second, there are substantial multiple comparison issues. In the post hoc analyses, we examined multiple subgroups and multiple endpoints. Thus, the results shown should be considered hypothesis generating.

This figure shows results for PROLONG-US for time from randomization to delivery capped at 35 weeks by the category of gestational age at most recent prior spontaneous delivery. The latter is shown on the X-axis. The Y-axis shows the estimated treatment effect expressed as weeks

gained; that is the increase in time to delivery for 17P-treated patients as compared to placebo-treated patients. The error bars represent 95 percent confidence intervals.

One readily sees the estimated treatment effect increases almost monotonically, from one week on the right-hand side of the figure for gestational ages less than 37 weeks to 3.3 weeks on the left-hand side for gestational ages less than 28 weeks. CDER has presented a slide analogous to this, based on Meis, that does not show such a trend, but there are other results for Meis that show evidence of a trend, though somewhat weaker than that shown here. We would be happy to discuss these results in the Q&A, if you wish.

This next figure is also for PROLONG-US and is analogous to the prior figure, except that here the X-axis is the category of mean gestational age of all prior spontaneous deliveries. Here, too, we see the estimated treatment effect increases almost monotonically with risk and increases from one-half week for mean gestational ages less than 37 weeks

on the right to 3.5 weeks for mean gestational ages less than 28 weeks on the left. Thus, we see greater treatment effects with greater risks. Specifically, we see increases in weeks gained with 17P treatment from about 1 week to more than 3 weeks as the category of risk increases based on either gestational age of most recent spontaneous delivery or mean gestational age of all prior spontaneous deliveries.

Based principally on these results, but also taking published literature into account, we identified the following four risk groups for analysis. Specifically first, women with at least one recent spontaneous preterm birth less than 32 weeks, with recent being defined as within the last 5 years; second, women with at least one recent spontaneous preterm birth less than 35 weeks and multiple spontaneous preterm births less than 37 weeks; third, women with at least one recent spontaneous birth less than 35 weeks and an interval between the current pregnancy and the prior pregnancy less than 2 years; and finally,

Black women with at least one recent spontaneous preterm birth less than 35 weeks.

This next slide presents the estimated weeks gained capped at 35 weeks in PROLONG-US for each of these four high-risk groups. As you can see, the estimates range from 0.8 to 1.9 weeks. These compared to an estimate for the overall PROLONG-US population of 0.7 weeks. These results are all for patients randomized prior to 20 weeks gestation. The overall result, including those randomized with a gestation of at least 20 weeks, is 0.5 weeks.

Based on these analyses, we are proposing the combination of these four high-risk groups as our higher risk target patient population, specifically women with a prior spontaneous preterm birth before week 35 who have at least one of the following additional risk factors: a prior spontaneous preterm birth before week 32; multiple spontaneous preterm births before week 37; a short inter-pregnancy interval; or being of Black race.

Here we see the overall results for the continuous endpoint of time from randomization to

delivery capped at 35 weeks for the proposed higher risk target population for both PROLONG-US and Meis. For PROLONG, the estimate is 1.86 weeks or about 13 days, and the result is nominally statistically significant, as can be seen based on the confidence interval. For Meis, the estimate is 1.33 weeks or about 9 days. Here, too, the result is nominally statistically significant.

On this next slide, we see results for the proposed higher risk target patient population for the dichotomous endpoints of spontaneous preterm birth less than 37 weeks, less than 35 weeks, and less than 32 weeks. For PROLONG, we have point estimates of odds ratios ranging from 0.69 to 0.36. For Meis, we have point estimates of odds ratios ranging from 0.24 to 0.35. Each of these is nominally statistically significant. You'll note that the upper limits of the 95 percent confidence intervals in the Meis trial are all well below 1.0, ranging from 0.48 to 0.70.

In summary, we have identified a higher risk target patient population for which the new

continuous endpoint of weeks from randomization to delivery, capped at 35 weeks, is nominally statistically significant in both Meis and PROLONG-US; and the old dichotomous primary endpoints are preterm birth less than 35 weeks and less than 37 weeks, as well as the secondary endpoint of preterm birth less than 32 weeks, are nominally statistically significant in Meis and have favorable point estimates in PROLONG-US.

Thank you. I will now turn the presentation back to Dr. Chari.

Covis Presentation - Raghav Chari

DR. CHARI: Thank you, Dr. Poggio.

To reinforce the clinical trial evidence being discussed today, I'd like to briefly summarize some of the additional evidence generated since the approval of Makena, which further supports the efficacy and safety profile.

EPPPIC is the largest existing individual patient data meta-analysis of progestogen used to prevent preterm birth. These include vaginal progesterone, intramuscular Makena, and oral

progesterone. The meta-analysis includes participant level data from 31 trials: more than 11,000 women, and 16,000 offspring, and 5 randomized trials for intramuscular Makena.

EPPPIC is the first individual patient data meta-analysis in Makena in singleton gestation pregnancies. The meta-analysis found that 17-OHPC reduced the relative risk of early preterm birth in high-risk singleton pregnancies before 34 weeks, with the relative risk of 0.83. Favorable reductions are also seen before 28 weeks and 37 weeks, and they indicated potential reductions in serious neonatal complications and incidence of low birth-weight infants.

Yesterday we heard CDER's description of the evidence from all the observational studies is negative. One of these observational studies cited by CDER is at Bastek, et al. We feel it may be useful to probe the findings from the study a bit further by way of example.

The authors compared the preterm birth rate and gestational age distribution at the delivery

and delivery among women at their urban medical center, at two different time periods, before and after 17P became available. The time periods were chosen due to a local policy change in 2006, which established 17P as the standard of care. Thus, it was prescribed to all eligible women as defined by the product label.

The authors concluded that 17P was associated with a meaningful delay in preterm birth. While the overall birth rate of preterm births less than 37 weeks did not differ between the two time periods, the authors did observe a shift towards late preterm births among patients treated with 17P.

As shown here, when looking at the two time periods, there was significantly fewer preterm births between 21 weeks and 33 weeks 6 days among the 17P group and more preterm births during the late preterm period. These findings are clinically relevant because outcomes in babies born late preterm are generally improved compared to those of early gestational ages. As the authors explained,

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

This was also the finding from the time from randomization analysis for PROLONG-US, that 17-OHPC is associated with prolongation of gestational age prior to week 35, while not overall shifting the incidence of preterm births before week 35 or 37, that Dr. Poggio just shared with you.

The odds of having a preterm birth during each prespecified gestational age period was also calculated. Women were 2.3-fold more likely to deliver a preterm infant during the late preterm period after 17P when compared to the time period prior to 17P availability, while being correspondingly less likely to deliver at earlier gestational ages. Despite these findings, CDER focuses only on the fact that there was no difference in the institution's rate of preterm birth less than 37 weeks. This is unfortunate, as it omits a very meaningful finding that has a

direct impact on public health outcomes.

Turning now to the data supporting Makena's positive safety profile, the safety of Makena for pregnant women and their babies has been demonstrated by the Meis and PROLONG trials. The Meis trial demonstrated the positive safety profile of Makena, and in CDER's own words, "There were no safety findings," as noted in the center's review of the trial at the time. The most common type of adverse event reported was injection site reactions, which is not unexpected, as patients received weekly intramuscular injections.

There was a non-statistically significant trend toward an increase in the second trimester miscarriage rate and stillbirth rate in the Makena arm. Conversely, however, the incidence of neonatal deaths was reduced in the Makena group, and the overall incidence of combined fetal and neonatal mortality, from the treatment onset to delivery, was similar in both groups.

The follow-up study, which examined outcome data at 2 years of age or greater on the children

born to women treated in the Meis trial also revealed no 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 versus Makena. The authors of the follow-up study therefore concluded this study provides reassurance that Makena is safe for the fetus when administered in the second and third trimesters.

While PROLONG was unable to confirm the benefits observed in Meis, it did not reveal any unexpected or new safety concerns. It reaffirmed Makena's overall favorable safety profile. In addition, PROLONG showed consistent, favorable maternal and fetal safety outcomes comparable to control. The rate of fetal or early infant death was low in both treatment groups, 1.7 percent in the Makena group and 1.9 percent in the placebo group, with a relative risk of 0.87.

Given that the upper bound of the 95 percent confidence interval was less than 2.0, doubling in

the risk of fetal or early infant death was excluded. Thus, the primary safety objective was achieved for PROLONG. The rate of miscarriage was also low for Makena compared to placebo, with a relative risk of 0.28. With regard to stillbirth, 1.1 percent and 0.5 percent of patients in the Makena and placebo groups, respectively, experienced an event with a relative risk of 2.07.

There is no known biological hypothesis indicating Makena would increase the risk of stillbirth. Moreover, Dr. Baja Sibai conducted a blinded review of the clinical study report narratives for each of the 12 stillbirth cases. He found that the level of these 12 cases had identified underlying contributing factors distinct from Makena, including infection, abruption, and placental infarcts. Indeed, CDER itself acknowledged during the October 2019 presentation the number of fetal or neonatal deaths were low, but was similar between the groups, and the study met the prespecified endpoint of excluding a doubling of the risk of fetal or early infant

deaths for Makena.

Moreover, a recent publication by Sibai, et al. in the Journal of Perinatology explains the integrated safety data for Meis and PROLONG trials demonstrate a favorable safety profile comparable to placebo maternal and fetal risks. This table contains a relevant obstetrical outcome or events in 3 percent or more of women in the Makena group.

The incidence of pregnancy complications such as preeclampsia, gestational diabetes, or clinical chorioamnionitis, as well as the incidence of serious adverse events, was not different between Makena and the placebo arms. Overall, the adverse events in the integrated data set were low and comparable between Makena and placebo.

In addition to the Meis trial and PROLONG, more than a decade of real-world use supports the positive safety profile of Makena. More than 350,000 women have been treated with Makena, and no new safety signals, concerns, or signals of risks have been identified. The known potential risk of Makena are already described in its labeling. In

the next slide, you will see the number of reported adverse events for each of these known risks within the last decade. The reported adverse event rates in real-world use are consistent with the as-labeled safety profile of the product.

Presented here are the number of reported adverse events for each of these known risks within the last decade. Of women exposed to Makena, the reported adverse events are consistent with the as-labeled safety profile of the product. For example, during the past decade of Makena use, 36 of 356,000 patients, or 0.01 percent, have reported thromboembolic events. While we acknowledge the reported adverse events tend to be lower than the incidence rate seen in controlled clinical trials, we can note that the observed real-world evidence is entirely consistent with the product label.

Finally, CDER recently closed a newly identified safety signal, or NISS, for Makena with respect to the risk of cancer in offspring of women who took hydroxyprogesterone caproate during

pregnancy. CDER has acknowledged the NISS was based solely on an article published by Murphy, et al. The Murphy article is not relevant to considerations of the safety of efficacy of Makena, first, because it's not about Makena; rather, it's about Delalutin, a different drug that is not indicated for prevention of preterm pregnancy. While both contain the ingredients 17P, they differ not only in the indication for use, but also in the timing and frequency of administration.

The study described in the Murphy article also has a number of methodological flaws that make it difficult to interpret and inconclusive not only in regard to Makena. Because of this, two expert statisticians have submitted declarations pointing to various deficiencies in study design and analysis that undermine the validity of the study's conclusions. ACOG has also said that the study's findings are not conclusive and should not influence practice. CDER's own internal documents also acknowledge the study's numerous flaws.

Here are some key quotes from CDER's

internal document that Covis requested and obtained for this proceeding. Based on this information, there are significant limitations in the Murphy article, which limit the ability to draw any conclusions from this study.

Finally, in terms of compounded versions of 17P, which may remain available to some patients if Makena were withdrawn, we are concerned about the serious public health risks associated with the compounded version. It is important to highlight that compounded drugs are not labeled, nor are compounding pharmacies held to the same good manufacturing practice standards that apply to approved drug products, so patients may face significant risk for serious injury and death as a result of poor drug quality and unsanitary conditions in compounding facilities. These issues are even more serious for injectable drugs.

We all know that compounding has a troubled history in the U.S. As of 2017, FDA had sent compounders more than 130 warning letters regarding significant violations of federal law and have

overseen more than 100 recalls of compounded drugs. In some cases, the consequences have been dire. Looking more specifically at compounded 17P, from 2013 to 2019, a period of just seven years, there were 26 recalls involving compounded 17P. Several of the recalls were for lack of sterility assurance, as well as recalls related to product contamination and adverse events from bacteria and fungi in product suspension fluid.

Thank you. I will now turn it over to Dr. Lawson.

Covis Presentation - Yolanda Lawson

DR. LAWSON: Thank you, Dr. Chari

I would now like to provide my personal clinical perspective on CDER's recommendations to remove Makena from the market and share statements from leading medical organizations on the importance of having Makena available as a treatment option. I'd like to begin by answering a question that is key to our discussion today.

Why does Makena matter to clinicians? As I discussed earlier, preterm birth is a serious

medical condition associated with significant morbidity and mortality. The lower the gestational age of delivery, the greater the risk to the baby. Even 2 weeks of added gestational age before 35 weeks can significantly reduce this risk.

The impact of preterm labor and birth goes beyond medical statistics. Preterm birth has an enormous impact on the emotional, economic well-being of the women I treat. Women whose babies are born prematurely can experience emotional trauma, postpartum depression, and other negative effects on their health and well-being, and you can only imagine the exponential psychological impact if the baby does not survive due to complications of prematurity.

Conversely, I could share with you many examples where Makena made a difference, and instead of extreme psychological distress and grief, these mothers experienced the joy of giving birth to a healthy baby. If Makena is no longer available, the implications to high-risk women could be dire. It is my clinical perspective that

Makena remains an important treatment option for higher risk patients and should remain available to these women.

What would be my treatment alternative if Makena were withdrawn from the market? As a clinician, I am very familiar with the use of compounded drugs where an approved product is not available. In fact, in a 2022 survey of approximately 400 OB/GYNs and maternal-fetal medicine specialists, conducted by Covis, more than a quarter of physicians answered that they are very likely to recommend compounded medications if there are no FDA-approved alternatives, however, compounded 17P is an imperfect alternative.

I want to be clear. Prior to Makena's approval, I prescribed compounded medications to prevent preterm birth; however, in my clinical experience, you have to be very careful with compounded drugs because there are significant variations in purity, consistency of active ingredients, and quality. This is particularly the case with injectable drugs, and many communities

don't have access to reputable compounding pharmacies. Therefore, a compounded drug may not be available. This creates a health equity issue. For all these reasons, I prefer to use an FDA-approved drug rather than a compounded version.

I also want to comment briefly on safety from a clinician's perspective. In addition to data from the studies discussed in this hearing, there is a lot of real-world evidence from use of Makena over the last decade, and yet there have been no new safety concerns, signals, or risks identified.

To date, CDER has pointed mainly to known potential risks of Makena already described in its labeling. Specifically, they highlight injection site reactions as a major concern and a reason to withdraw Makena from the market. Balanced against the overwhelming burden associated with preterm birth, this seems like a minimal risk, and not a substantial reason to withdraw the product. Many in the medical community and my specialty society continue to support 17P as an important treatment

option, even after CDER issued its proposal to withdraw Makena.

As shown here, ACOG stated their recommendations remain unchanged, and that consideration for offering 17P 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. The Society for Maternal-Fetal Medicine echoed this position. They issued a statement reaffirming their support for 17P and made clear their recommendations also remain unchanged.

Finally, I want to note that many other organizations, including those that specifically represent minority populations, also support Makena remaining available as a treatment option. They include the NAACP, the Black Women's Health Imperative, and the National Birth Equity Collaborative. These organizations have spoken out about issues, including the burden of preterm birth particularly for Black and minority women, and have

expressed concern that withdrawal would leave women in need without an important treatment option.

To conclude, I feel strongly that the FDA should keep Makena available while research continues into the appropriate patient population. It is important for Makena to remain a treatment option to support clinical decision making. The FDA should do what is best for our patients, which is to keep this medication available to those of us who manage these very high-risk patients every single day. Thank you. I will now turn the presentation back over to Dr. Chari.

Covis Presentation - Raghav Chari

DR. CHARI: Thank you, Dr. Lawson.

I will conclude the presentation by summarizing our proposed path forward and by reviewing the feasibility data, supporting our ability to execute on this plan while Makena remains on the market.

As described earlier, we propose to undertake a three-tiered approach to address the outstanding questions and concerns raised by the

PROLONG trial, while at the same time continuing to meet the critical needs of a higher risk group of patients. This includes a partial withdrawal of Makena specifically to limit use to a higher risk target patient population or other labeling changes; a randomized control trial to confirm Makena's effect on an intermediate clinical endpoint and for further discussion; and an observational study to validate the benefit of prolonging gestational age on neonatal morbidity and mortality with 17P treatment.

In terms of the higher risk patient population, as Dr. Poggio explained earlier, our post hoc exploratory analysis indicate women with a prior spontaneous preterm birth before week 35, who have one or more additional factors, achieved a consistent benefit with Makena in both the Meis and PROLONG trials. Therefore, we're willing to narrow the labeling to this higher risk subset. Further, it may be appropriate to align the labeling to initiating therapy prior to gestational age of 20 weeks.

In the alternative, we are also open, for example, to modifying the limitations section of the label, or modifying the clinical study section of the label, a version of which was proposed to CDER by the prior sponsor in September 2019, and to sending a Dear Health Care Provider Letter, limiting the use of the target population to high-risk patients.

We are also proposing to conduct a third randomized-controlled trial in women with one or more spontaneous preterm births less than 35 weeks, who have one or more additional risk factors. We're proposing to randomize approximately 200 patients in a 2 to 1 ratio between Makena and placebo. The primary endpoint will evaluate the increase in time from randomization to birth for Makena-treated patients compared to placebo. We're proposing the primary endpoint be capped at 35 weeks gestation, which will ensure that the measure of time gained on 17P is clinically relevant with respect to neonatal development.

The endpoint we have proposed is designed to

measure prolongation of gestation up to week 35 of gestation. This proposal is based on the reported decline in week-on-week benefit in neonatal morbidity and mortality. This figure from Manuck, et al.'s analysis of an obstetric cohort of more than 115,000 women and their neonates demonstrates that incidence rates of death, major neonatal morbidity, and minor neonatal morbidity declined significantly with each advancing week of gestation, with the biggest decline in risk occurring up to 35 weeks. We will also shortly address the question on whether pharmacological prolongation of gestation with 17P is equivalent to moving a neonate further to the right in this picture.

Throughout the presentation, we've also highlighted the importance of selecting high-risk patients who achieve the greatest benefit of Makena. To address some of the enrollment concerns identified in the PROLONG trial, Covis proposes to refine the inclusion criteria for the proposed randomized-controlled trial. First, the previous

singleton qualifying spontaneous preterm birth less than 35 weeks must have occurred within the last 5 years since randomization, and patients must also have one or more additional risk factors. In addition, there must be a documented medical history of first trimester ultrasound measurement to calculate the gestational age of the qualifying delivery.

Presented here are the estimated sample sizes for the proposed randomized-controlled trial, based on the endpoint of time from randomization to delivery, capped at 35 weeks gestation. A sample size of approximately 400 patients is sufficient to detect a difference of one week between the mean gestational age of the arms. We should note that we are anticipating, based on our analysis of the highest population of PROLONG-US, or weeks gained of approximately 2 weeks, for conservatively powering this study to detect a smaller mean difference.

These estimates were made with a standard deviation of 3.0 weeks, which is based on the

overall PROLONG-US population. The standard deviation is higher for the high-risk subgroup, but even with that higher standard deviation, a sample size of around 400 is sufficient to detect a difference of 1.5 weeks.

Based on our feasibility assessments, we're also confident this trial can be conducted in the U.S. and completed in 4 to 6 years at most. To describe some of the work that we've done in more details, first, I'd like to invite back Dr. Blackwell to share the results from a recent survey that he conducted to evaluate the willingness of practitioners to participate in a third randomized-controlled trial.

Covis Presentation - Sean Blackwell

DR. BLACKWELL: Thank you, Dr. Chari.

Since publication of the PROLONG trial, I have spoken to many different stakeholders regarding the findings and implications. I have participated in panels, debates, lectures, and think tanks that deconstruct this trial. As part of the process for deciding what should we do next,

I recently conducted an anonymous survey of investigators from the current Eunice Kennedy Shriver NICHD-MFMU network sites.

The MFMU is currently the largest obstetric clinical trials network in the United States. It includes 12 academic medical center clinical sites and has an obstetrical delivery network of over 120,000 births per year. Both Drs. Sibai and I are former principal investigators, and are still quite involved in the network. The network has done over 30 multicenter, phase 3, randomized-controlled trials, including the Meis trial. I sent a series of survey questions to gain their insights regarding a potential trial, future trial, for Makena.

Question number 1: What is your level of interest in participating in another 17-OHPC trial? It would be done in the United States, placebo controlled, and involve women with a singleton pregnancy and a prior spontaneous preterm birth. Of the 12 investigators who responded, 11 indicated interest in participating in a new trial, and one

suggested that a new trial is not warranted because of Meis.

Question number 2: If another RCT is conducted in women with a prior spontaneous preterm birth, in your opinion, how important is the following study design issue? After randomization, a short cervix develops, and the protocol allows for cervical cerclage placement. These investigators overwhelmingly felt that any protocol today would need to include some aspect of a rescue for women presenting or developing a shortened cervix post-randomization, with the option to perform a cerclage after enrollment.

We also asked these investigators about their opinion on the best qualifying gestational age, in weeks, entry threshold.

Question number 3: In order to increase the risk profile of women eligible for the trial, having a lower gestational age threshold for a qualifying spontaneous preterm birth has been discussed. In both Meis and PROLONG, women had a qualifying preterm birth of less than 37 weeks.

One-third recommended another threshold of less than 37 weeks, one-half recommended less than 34 weeks, and 17 percent, or the remainder, recommended a 32-week threshold.

Finally, we queried them on their views of the type of weeks gained analysis that Dr. Poggio presented earlier.

Question number 4: What is your opinion regarding evaluating the primary outcome in a different manner? Would you consider a delay in delivery that had clinical meaning? This delay in delivery could be a continuous outcome or reviewed as a time-to-event metric. Half of the respondents indicated interest in this kind of analysis as the primary outcome for a future randomized-controlled trial.

Since we are very early in the process for designing a clinical trial and specific details would have to be negotiated with the FDA, this survey and my back-and-forth discussions with other investigators and clinicians is truly big picture only by necessity, but my take-home message from

this exercise and other discussions is that experts in preterm birth clinical trials would be willing and open to be involved in another well-designed, placebo-controlled trial.

As I previously mentioned, I've been very active in the area of what to do next, and before I turn back the podium, I want to spend a few minutes talking about the feasibility of a future trial, as this is a major issue of concern.

Number 1: Since PROLONG was published three years ago and has undergone its, quote, "autopsy," much has changed. The positive findings of the Meis trial remain highly influential to many, but as we have heard from CDER's critique, and others, there is clearly not consensus about whether or not Makena should be used.

There is data to suggest that the use of Makena in the United States has significantly dropped over the past three years, however, SMFM and ACOG have not recommended a practice change against the use of progestogen, including Makena.

Number 2: As a trialist, I believe another

study is warranted to settle the clinical question for the multiple reasons I've provided PROLONG did not address the key question. This would be a third trial. I do not see this as an outlier situation because it often requires multiple trials to answer an important clinical question.

Other important obstetrical interventions have required multiple trials to address treatment questions. Some were negative, some were inconclusive, despite an ultimate overall positive benefit in the literature. Examples include magnesium sulfate for neuroprotection and antenatal corticosteroids in preterm populations; and in fact, there are probably many more.

Number 3: It was mentioned that a new study would be too difficult to recruit, based on the PROLONG experience. Just to clarify, once U.S. enrollment targets were achieved in PROLONG, emphasis shifted to the larger recruitment sites outside the United States. So the fact that the U.S. numbers tailed off at the end of the time period in PROLONG was not a specific recruitment

problem, and in my opinion does not forecast for a future trial.

Number 4: Another potential hurdle that has been raised is the regulatory issue related to IRB approval and informed consent, specifically related to the placebo aspect of a randomized-controlled trial. Even though Makena was approved in 2011, IRBs continued approval for PROLONG despite Makena's FDA approval, and now in 2022 and beyond, given the current lack of consensus about efficacy, I do not believe IRBs would object to another trial, including the use of a placebo.

Number 5: There are more data on safety after PROLONG related to pregnancy loss and short- and long-term neonatal outcomes, which was much less known prior to PROLONG. In addition, the EPPPIC meta-analysis provides robust information on other maternal safety outcomes. Thus, it's currently more favorable for communicating the risks versus benefits of being in a trial with a focus question about efficacy, with less concern or unknown about incremental risk related to safety.

Number 6: There remain no other evidence-based treatment options for this population. Vaginal progesterone, cervical cerclage, and cervical pessary have all been tested and found ineffective. Thus, there are no other routine care interventions that would interfere with this proposed trial.

Number 7: I believe it is better for a potential trial for a medication to not be, quote, "withdrawn from the market" and then be offered back in a research trial. In my opinion, withdrawal of the drug would have a major negative impact on the willingness to participate from both patients and clinicians. This move would stigmatize the medication and challenge our recruitment.

For these reasons, I believe a trial in the U.S. is feasible, and if well designed and well planned, there would be adequate buy-in from referring physicians and patients. A lot of hard work and back-and-forth efforts would need to be done between the sponsor, clinical, and trial

experts, and the FDA, but I believe it is accomplishable in the reasonable time period.

Thank you. I will turn the presentation back over to Dr. Chari.

Covis Presentation - Raghav Chari

DR. CHARI: Thank you, Dr. Blackwell

Feasibility assessments of non-academic sites also support the possibility of enrolling another RCT. Based on our outreach, we anticipate a formal RCT could enroll approximately 60 patients per year across the U.S. sites, and at this point, we do not see the need to enroll subjects from OUS sites.

We've also conducted a survey within the Dorsata practice network, and responses indicate a willingness to participate in a placebo-controlled RCT with Makena. In the consenting practices, there are about 1200 patients per year who've had pregnancies and who have had a prior spontaneous preterm birth before week 34. We estimate another 60 to 180 patients per year from this network.

In addition, we've conducted surveys to

evaluate the use of progesterone medication in clinical practice and the willingness of physicians to contribute patients. The results show that the use of progesterone by injection has declined since 2019. In fact, among physicians who recommend progesterone for patients at risk for spontaneous preterm birth, only 40 percent recommend 17-OHPC injection. This number is consistent with the decline in volumes that we have seen for 17-OHPC since the 2019 advisory committee meeting. This supports our view that there is a return to equipoise in the community.

The same survey also supports a higher willingness of providers to contribute patients to a trial with an approved product compared to a trial of an unapproved product. In fact, while 80 percent of respondents expressed interest in participating in a placebo-controlled trial of an approved product, only 39 percent said they would enroll patients if the product was unapproved, and an even smaller percentage, 15 percent, indicated interest in enrolling patients if the product had

its marketing authorization withdrawn.

This survey was designed to be representative of U.S. prescribers who treat pregnant women at high risk for preterm birth, and the findings give us assurance, on the one hand, that we will be able to recruit for an RCT if the product remains on the market, and conversely highlights for us serious potential concerns with recruitment if the product were withdrawn from the market.

We also conducted a survey of 325 patients with a history of spontaneous preterm birth that supports the willingness of these patients to consent to such a trial. Among patients at risk for preterm birth, almost all, 95 percent, say it is important that treatment options to reduce the risk of another preterm birth be approved by FDA. Given their history of spontaneous preterm birth, 68 percent of respondents reported they're likely to participate in the clinical trial and take an approved prescription drug while pregnant if it was designed to study treatment options to reduce the

risk of preterm birth, however, only 37 percent of patients reported they would be willing to participate if the drug was not FDA approved.

These findings reinforce the views in our ability to recruit pregnant patients to a placebo-controlled RCT if the product were to remain on market and, conversely, the challenges we would face if the product's approval were withdrawn.

Given CDER's concerns regarding the feasibility of conducting a randomized-controlled trial, we would also commit to study conduct criteria and to voluntarily withdrawing Makena's criteria not achieved. These checkpoints would come during an interim efficacy analysis of utility at a 24-month check on enrollment projections and based on the final outcome of the study.

In all cases, if any of these indicate that prespecified goals cannot or have not been achieved, we will work with the FDA to withdraw the product from the market.

As a final step in our path forward, we're

open to conducting an observational study. The goal of this study would be to establish the relationship between gestational age and neonatal outcomes in treated versus untreated patients to validate the benefit of weeks gained on 17P. This approach is based on our review of the available literature on the association of neonatal morbidity and mortality with gestational age.

Overall, there is a consistent picture of significant benefit that you see in prolongation of gestation from week 30 to week 36. In our mind, one residual question that remains is, does treatment with Makena change that pattern in some fashion?

We contemplate designing a study to compare the incidence of neonatal morbidity and mortality for each week, from week 20th onwards, of gestational age at birth in 17P-treated versus untreated women who have a preterm delivery. Demonstration of comparability of outcomes in each gestational age group would rule out the potential adverse impact of prolongation of gestation; for

example, in the example cited by CDER, whether there is a toxic uterine environment or the impact of other pharmacologically induced neonatal adverse outcomes in 17-OHPC treated women.

These results would confirm or refute the conclusion that the benefits of pharmacological prolongation of gestation are equivalent to currently available neonatal morbidity and mortality gestational age outcomes from untreated preterm birth in the general population.

To conclude, I'd like to take a moment to share our position to the questions posed to this committee. First, do the findings from Trial 003, PROLONG, verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

The findings from PROLONG do not verify the clinical benefit of Makena on neonatal morbidity and mortality in the study population. However, it is our position that when a confirmatory trial fails to provide additional confirmation of clinical benefit, that's the beginning, not the

end, of the required analysis.

Next, you will be asked to discuss and vote on whether the available evidence demonstrates that Makena is effective for its approved indication of reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

We stand by the significant outcomes observed in the Meis trial. As Dr. Sibai described earlier, Makena demonstrated statistically significant reductions in preterm births across all prespecified endpoints in all key subgroups, but we recognize the questions and concerns that were raised by the PROLONG trial.

In our view, and as described earlier in this presentation, the PROLONG trial enrolled a lower risk population compared to Meis; therefore, PROLONG was not capable of confirming the benefits of Makena in a population of patients similar to those enrolled in the Meis trial.

So the question remains, what now? Based on extensive post hoc exploratory analyses, we've

identified a higher risk target population of women who achieved a consistent benefit with Makena in both the Meis and PROLONG trials. Therefore, we are asking to work with the agency to partially withdraw Makena so that the labeled indication is aligned with this higher risk subgroup of patients who remain at the highest risk of preterm birth.

While CDER has challenged the results of the PROLONG trial specifically with regard to the benefit in a subgroup of patients, in the proposed target population of high-risk patients, we do see a consistent benefit of Makena.

Here we see the overall results for the continuous endpoint of time from randomization to delivery capped at 35 weeks for the proposed high-risk target population for both PROLONG-US and Meis. For PROLONG, the estimate is 1.86 weeks, or about 13 days, and the result is nominally statistically significant, as can be seen, based on the 95 percent confidence interval. For Meis, the estimate is 1.33 weeks, or about 9 days, and here, too, the result is nominally statistically

significant.

We see a consistent effect on the proposed target population for the dichotomous endpoint of preterm birth less than 37 weeks, less than 35 weeks, and 32 weeks. I also note the confidence intervals for the less than 35 and less than 32 weeks for the Meis subgroup, which speaks to the strength of the efficacy signal seen in this population.

To summarize our position on the second question, the available evidence demonstrates that Makena is effective for a higher risk subset of patients at greatest risk of preterm birth. We also want to point out that the sample sizes of these groups speak to the difference in the risk levels of PROLONG-US versus Meis. The target population is less than a quarter of the total enrolled population in PROLONG-US.

With over three-quarters of the population being lower in risk, how can these results of PROLONG-US negate the overall findings of the Meis study? Therefore, we are willing to limit the use

of Makena to patients who are at highest risk and need access to the therapy while we execute on our path to address the outstanding questions and concerns.

To summarize our position on the second question, the Meis trial remains substantial evidence of Makena's efficacy. Additionally, post hoc analyses of PROLONG-US support that Makena is effective in a higher risk subset of patients at greatest risk of preterm birth. Therefore, we are willing to limit the use of Makena to patients who are at higher risk and need access to the therapy while we execute on our path to address the outstanding questions and concerns.

Next, the committee will be asked whether Makena should remain on the market, and importantly, whether or not FDA should allow Makena to remain on the market while an appropriate confirmatory study is designed and conducted. We urge this committee to recommend that Makena remain on the market for at least this subset of high-risk patients while we collect additional evidence to

reaffirm its benefit. Our proposed path forward will address the outstanding questions and concerns raised by the PROLONG trial, while at the same time continuing to meet the critical needs of patients at the highest risk for preterm births.

Therefore, for all of the reasons discussed today, it is our position that the agency should not withdraw the only FDA-approved therapy for reducing the risk of preterm birth. Covis respectfully requests that its proposal receive proper review and consideration by the agency as we continue to welcome a cooperative path forward in the best interest of patient care. Thank you.

DR. WITTEN: Thank you, Covis, for your presentation.

We're going to move to a break, but I'm going to turn it over to Mike K. to give us instructions about the break.

(Whereupon, at 12:33 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:30 p.m.)

DR. WITTEN: We will now proceed with questions for Covis by three representatives from the Center for Drug Evaluation and Research. For this portion of the hearing, I will turn things over to CDER to begin with their first question to Covis.

Questioners should identify themselves before asking their first question. If a questioner from CDER wishes to ask a question of a specific presenter from Covis, they should so indicate. Once a question has been asked, one or more representatives from Covis will answer the question. Representatives answering the question for Covis should indicate when the answer is concluded, if possible, then we will turn things back to CDER for the next question. If the questioner or answerer wants a specific slide displayed, please let us know the slide number, if possible.

I'm turning it over to CDER now.

Questions for Covis by CDER

DR. NGUYEN: Hi. Good afternoon. If I may have Covis' slide number 4, please?

Thank you very much. I'm referring to point number 4 on this slide, where you state gestational age of delivery is an intermediate clinical endpoint, which is itself a measurement of a therapeutic effect that strongly is correlated with neonatal health, and this is a point of agreement.

I'd like to confirm that you agree with CDER that this endpoint is reasonably likely to predict, not known to predict neonatal outcomes; correct?

DR. CHARI: It is our position that it is likely to predict -- at least in the case of spontaneous untreated births, we agree with CDER that the question on whether 17P changes that picture in some fashion is not established.

DR. NGUYEN: Thank you very much.

DR. STEIN: I'm going to follow up on, I think, a discussion from, I believe, Dr. Poggio earlier, and this is on some of the post hoc non-prespecified analyses that were shown for

Trial 003.

I wonder if you could pull up our slide, CDER's slide 255 from the deck. I think we presented the analysis that we did yesterday on Trial 002. Thanks.

You presented I think the data on the right from this slide, which is looking at Trial 003 with the risk factors that were identified post hoc, so this is the subset of subset analysis that you indicated predicted a differential response. We conducted, as we showed yesterday, the same analysis in 002.

I wonder if you could confirm that the analysis that was seen suggesting this trend in 003 was not seen in 002. If anything, it looks like it's going slightly in the other direction.

Do you agree that these risk factors are not consistent in predicting response between the two trials?

DR. CHARI: I'd like to ask Dr. Poggio to help answer that question.

DR. POGGIO: Thank you. Gene Poggio.

Let me show you a few slides here. This is from the Meis study, and this has I would call a weak suggestion of increased treatment effect with increase in risk, and this is based on mean gestational age of prior deliveries on the X-axis. And you see on the left side, again, it's just a weak suggestion of a trend, but it goes from 1.4 weeks to 1.5, whereas on the right it's in the 0.8 to 1.1. So this is mean gestational age, prior deliveries, based on a prior spontaneous delivery.

Let me show you one more slide here.

DR. STEIN: If I could just clarify, so this is not the same analysis that I showed on the prior slide; is that correct, Dr. Poggio?

DR. POGGIO: Right.

DR. STEIN: So if you could go back just quickly to slide 255, I just want to make sure, because we're switching between analysis. So here we're looking at MRP gestational age and you changed to mean gestational age; because I want to just make sure -- because the question I asked, and I just wanted to make sure we're all aligned. The

analysis that I'm showing here shows, if anything, the opposite trend of what was seen in 003 in 002, and I just wanted to see would you concur with that; that in fact these two analyses don't show consistency.

Then I perfectly appreciate if you want to go on to the analysis that you were showing. I just want to make sure that we're clear about what this shows between 002 and 003.

DR. POGGIO: Yes. Essentially, these were done --

DR. WITTEN: Excuse me. Can everyone state your name before you speak?

DR. STEIN: Oh, my apologies. Peter Stein, Office of New Drugs, CDER.

DR. POGGIO: Gene Poggio again.

So all these analyses were done in pairs, if you will, where we did the X-axis. In some cases it was mean gestational age, categories of mean gestational age, and other times it was categories of most recent prior spontaneous delivery. So we sort of have the full set here. One of them, I

only have in table format rather than graph. But I think maybe if I can do this one --

Screen share, please.

So on this one, again, apologies it's not a graph, but this is based on mean gestational age from Meis, and this is just in Blacks, and we see here, one, a big increase in the numbers in absolute sense, but also see a clear trend with the higher risk group less than 28, 2.81, whereas for the lower risk group down to 1.4; so essentially a factor of 2.

So in a way, we've got two things going on here. You can see the increase in the Black population and you can see the trend of increase in treatment effect with higher risk.

DR. STEIN: Well, thank you. But again, I do want to emphasize that on the prior slide you showed was not the analysis that you had shown previously or that we had presented yesterday. You went from the most recent to mean, and now you're looking at another subset of a subset, which is in Black patients.

I just wanted to point out that these are not -- the results across these various analyses are not consistent, and I guess what I'm asking is would you agree that the results across these risk factor analyses, trying to predict responders, are inconsistent as you go from different analyses?

All of these, of course, are post hoc, but I just wanted to see if you would confirm that there's not really a consistency of response. Each one of these has a slightly different pattern; some of them a fairly markedly different pattern.

DR. POGGIO: I would respectfully like to disagree. I think the clear consistent effect is with increased risk, we see bigger treatment effects. What I showed previously in the presentation was for the PROLONG study, we looked at two different -- we looked at it by mean gestational age and most recent pregnancy, and saw clear increases in treatment effect with bigger risks, and on the slides we've just looked at, we see increases when we go from the total population to Blacks. And the increase is understated because

one is everybody, including Blacks, and the other is just Blacks. And then in the slide in front of you now, in the Black population, in Meis, we see clear increases in treatment effect with increased risk based on the mean gestational age.

I would also just conclude with, if you will, for me at least, the proof is in the pudding, if you will. All these analyses have trends, but really just to identify risk factors for preterm birth -- and keep in mind, those analyses were all done just using the placebo group, so we're looking to see what the treatment effect is, and then taking the variables. We use those variables to pick predictors of risk factor and identify the population, and then did the analyses based on that.

So what matters, from our point of view, is what is the performance of that high risk, in that high-risk group? And as you saw on this slide, we saw clear improvements that were nominally significant in both groups, 1.86 in PROLONG-US and 1.33 in Meis. And as you also saw, point estimates

for the dichotomous endpoints of preterm birth were also all in the right direction and are nominally significant in one of the studies.

Does that answer your question?

DR. STEIN: It does.

If we could bring slide 255 up again. But again, I do take your point, and I appreciate the clarification, but I think you continue to indicate that it was consistent, and I guess we'll have to agree to disagree because when we look at the analysis that you refer to in Trial 003, we'd say that the results in Trial 002 are actually not consistent with that. So these analyses are inconsistent between the trials, so again, the patterns differ, which is not surprising. These are exploratory post hoc, not prespecified analysis.

Thank you very much. We can go on to the next question.

DR. CHARI: Can I just clarify a couple of additional points?

DR. WITTEN: Please state your name for the

transcriptionist.

DR. CHARI: Yes. I beg your pardon. This is Raghav Chari at Covis.

Dr. Stein, I'd like to just make a couple of additional clarifications, and I think they drive what we as well found as a surprising result. When we analyzed the PROLONG data and we saw the strong signal, we were somewhat surprised as well to see this type of pattern that you are looking at with the Meis data.

In our view, there are at least three contributing factors, and I fully understand that these are all post hoc analyses, so you go looking for explanations and development of hypotheses, but I think there are three contributing factors for why the data look this way.

Let's start first with the fact that, in general, the Meis population had multiple risk factors, whereas typically in the PROLONG population, you had there, risk factor behavior driven predominantly with one risk factor; not surprising to us, therefore, that a univariate risk

model like this single dimension does describe, in some kind of monotonic or almost monotonic fashion, the pattern that you see in the PROLONG study, but however, the fact is that when you have multiple risk factors and you're accounting for only one, you expect that at some level, that monotonicity will be abolished, and that's indeed what you do see.

The second factor that really pulls down the results for the Meis study is -- and we talked a little bit about this yesterday when we had the question and answer session on the Meis study, where we look at the non-Black subjects who all largely gave birth in the placebo arm, as well as the active arm after week 35.

I remind you that this is an analysis that could deliberately cap or censor the 35-week gain, so about 40 percent of the population literally drops out of the numerator in terms of its ability to contribute, but stays with the denominator, and that substantially pulls the numbers down in the Meis analysis, which is part of why when Dr. Poggio

shows the analysis in the Black population, that population actually was giving birth before week 35 in the placebo arm. So you are able to actually measure the weeks gained, whereas the non-Black population simply cannot contribute to this analysis in the numerator. So qualitatively speaking, I think that that's a second reason why.

Then the third, if you go back to -- and I'll remind folks who know the Meis data pretty well, one of the concerns in the active arm of 17P was a slew of early births that happened almost immediately after randomization, and I'm happy to have Dr. Sibai talk more about it if it's of interest.

But the point was that it was determined after careful analysis that that slew of early births had nothing to do with the pharmacological intervention, but there were other factors involved. Nevertheless, the vast majority of all of those early births, within days of randomization, were disproportionately in the 17P arm.

So when you look at this kind of weeks gained analysis, it really weighs down the results because you're getting zero weeks gained, or close to zero weeks gained, from time of randomization in those 12 subjects, and when you look at the kind of sample sizes we're talking about, it starts to obscure the trend.

When you --

DR. STEIN: Thank you very --

DR. CHARI: I just --

DR. STEIN: I do think we need to move on, but I appreciate your response. I guess my point was that the results are inconsistent, but also I think you've given some very interesting hypothesis, and I suppose that was the point I was making, is that these types of analyses are hypothesis generating, and I think you've just discussed three very reasonable hypothesis that might explain post hoc findings. But at the end of the day, we're still left with inconsistent findings between the two studies, but thank you very much.

DR. CHARI: Absolutely.

DR. NGUYEN: Thank you. Christine Nguyen, OND, CDER.

Mike, is there any way I can show side by side Covis' slide 37 and Covis slide 69?

MR. KAWCZYNSKI: What number did you want, 67?

DR. NGUYEN: I'm sorry. Covis' slide 37 alongside with Covis' slide 69.

It's Covis' 69, not CDER's.

MR. KAWCZYNSKI: Oh. I can't show Covis. Covis has to do theirs.

DR. NGUYEN: Okay. That's fine.

If I may have slide 37 up first, and then I'll ask for slide 69 from Covis. Thank you.

This slide shows a similar magnitude of treatment effect by relative risk, if we look on the right side, in those with greater than one versus only one spontaneous preterm birth; Black versus non-Black; unmarried versus married; smoking versus no smoking; education, 12 years or less or greater than 12 years. So to me, when I look at

this slide, these risk factors didn't change how a person would respond to Makena.

Would you agree with that?

DR. CHARI: Well, the preterm birth less than 37 endpoint, we would agree.

DR. NGUYEN: Great. Thank you.

May I have Covis slide 69 up, please?

Here, you've indicated that PROLONG has failed to enroll a high enough risk patient population to show that Makena had a benefit on the gestational age looked at, including less than 37 weeks, and here, I'm seeing the same risk factors.

In Trial 002, you've indicated these risk factors wouldn't change how a woman would respond to Makena, but the opposite argument is made here, that having these risk factors are not -- would make a difference in her response to Makena; is that correct?

DR. CHARI: We are making that argument of less than 35 endpoint, yes.

DR. NGUYEN: I guess I'm still not

understanding because these are very different conclusions. On the one hand, we're saying these risk factors shouldn't make a difference on whether or not you respond, but on the other hand, you're saying that 003 is flawed, it can't demonstrate Makena's effect, when in fact we're having women who really are in the same Venn diagram as the one in the Meis trial, at least for these risk factors.

DR. CHARI: So I'll attempt to provide a reconciliation. The big difference I think is the choice of the endpoint, less than 35 versus less than 37. As we've pointed out, particularly when you look at the less than 35 endpoint -- and this is reflected in table 22 of CDER's from the 2019 briefing book -- you do see marked differences in response rate across all of these subgroups, and I think that's part of the point.

The other point I would make is that particularly when we are looking at comparing like-to-like populations, i.e., ones that are pertinent to the U.S. patients, that you see substantially fewer patients who are represented

within each of those subgroups within the U.S. PROLONG population, and those risk factors are substantially less.

As you saw in the Meis data as well, you do see different response rates for the less than 35 group, which is the primary endpoint, or one of the two primary endpoints for the PROLONG study. So that's how we would reconcile those two pictures. Then certainly we've spoken at length about that slew of premature births that takes place between 35 and 37 weeks. That tends to obscure, I think, some of the differences clinically that are there in the different populations.

DR. NGUYEN: Thank you.

Would you expect that we should be able to see a drug effect on the less than 37-weeks endpoint as well? Because certainly this trial was adequately powered to look at that endpoint, even down to very small clinically magnitude effects, as shown in Dr. Johnson's slides yesterday.

DR. CHARI: So I think I would like to

address that in two different ways. One is when we try to do the same power calculation -- and if I can have a slide share, please, Mike? Thank you.

When we run the same calculation that you did, and you showed in your slides for the less than 37-week endpoint, the less than 35-week endpoint has less than 60 percent power to be able to detect a 30 percent reduction. So I think that's the first place I would say with respect to the power considerations, and this is looking at the overall PROLONG trial.

It is our view that given the overall very low risk and very low level of events associated with the ex-US portion of PROLONG, when we focus on the U.S. subpopulation, that power is substantially less. Just by way of example, the high-risk subgroup that Dr. Poggio talks about, in the post hoc analysis that we've done, it's 87 subjects in the PROLONG-US sample, and with 87 subjects, that's less than a quarter of the total PROLONG-US group. So we do think that there is a lack of ability to really discriminate.

Where I think you're going with your question is, should you not have seen an effect, and I think that we would view both of these studies as, generally speaking, well-run studies, and that it's actually possible for the results of both studies to be reflective of reality. In the one hand, what we're saying is the high-risk patients are probably responding, and our post hoc analyses support that, whereas the general lower risk population may not be great candidates for 17P intervention, which is one of the reasons why we're proposing to narrow the label.

DR. NGUYEN: Great. Thank you. I think we're on the same page that certainly both 002 and 003 are valuable. Again, I think what we're still left with is, on one hand, we're saying there are no modifying effects of these major risk factors. I mean, we all understand that being Black or having one prior preterm birth and whathaveyou still increases a woman's chance of having a recurrent preterm birth. So that was shown in 02 but in 03 we're seeing the opposite trend. So I

think that is a big question mark, but I agree with you, both trials are certainly of high value and that 003 shouldn't be ignored.

You brought up a really --

DR. CHARI: I'm sorry. This is Raghav Chari again. Could I just ask Dr. Poggio to that last point? Because I do feel like we have a different point of view on the fact that there are no risk modifiers, because I want to share particularly the view when looking at it from a Kaplan-Meier perspective. I think that it's important to specifically look at the data this way because it highlights important differences.

DR. POGGIO: Gene Poggio again. Share the screen, please.

I should clarify, I think in Dr. Johnson's presentation, she mentioned an interaction between Blacks in treatment in Meis, and it wasn't significant, and I'd just like to say that that was -- and we provided that figure, so I think we own that. But it was based on a Cox proportional hazard model, which assumes that there's

proportionality of the hazards, and that isn't true, as one can actually see looking at these slides.

If you look at these two slides, on the left is the Black population, on the right is the non-Black population, and you see a separation on the left, a treatment effect beginning at about week 25 on the left, and on the right you only see it after about 35. If one does a log-rank test and censor it at 34, on the left you see a statistically significant difference between the two, so a treatment effect in Blacks if you just go up through 34. If you do the same on the right, you see no evidence of a treatment effect. If you censor at 37 on the other hand, then they're both statistically significant, but you can see that it's clearly a difference in what's going on with the treatment between Blacks non-Blacks here.

So I hope that helps clarify. Depending on the particular endpoint and how you define treatment effect, with some definition, there clearly is an effect modification with race here.

DR. NGUYEN: Christine Nguyen, OND, CDER. Thank you. I think when we last [indiscernible], you had mentioned your proposal for a narrow indication.

If I may have Covis' slide 139 up, please?

Great. You proposed to narrow Makena's indication to what is shown here, and to approve an indication, we must have strong persuasive evidence of benefit, and that is across all indications that we approve at the FDA. The data you generated to support this proposal was conducted as part of multiple analyses, multiple cuts, and all conducted post hoc; is that correct?

DR. CHARI: That's right.

DR. NGUYEN: Thank you.

And would you agree that the scientific community would believe that these types of analyses are only to generate hypotheses, as they do on your slide 139?

DR. CHARI: Yes.

DR. NGUYEN: Great.

What we're seeing is that your proposed now

indication is based on hypothesis-generating data, and in fact it's the same population for which you are proposing a new trial to test to see if Makena is indeed effective in that population.

So are we having to consider putting an indication for use that is still under investigation?

DR. CHARI: If I can just clarify, and then I'm going to ask Becky Wood also to provide a more legal perspective on the proposals that we're making with respect to label modification. But yes, we have shown the analyses, and admittedly they're post hoc, but the results nominally are very strong when you look at the subgroup for this particular subgroup, where we're using the analysis on Black patients as a proxy for other determinants of preterm birth.

But nevertheless, when you look at that subpopulation, not only do the hazard ratios improve substantially with respect to the overall Meis population, but also the upper bound of the 95 percent confidence interval dropped

substantially below 1, which is a feature that you did not have with the original Meis data, based on the discussions that we've heard both yesterday, as well as today. So we do feel that the Meis data does describe very strong efficacy for this population.

Secondly, I would remark that, generally speaking, the clinical community that treats high-risk patients would be in agreement with the fact that it is some combination of multiple risk factors that are really driving their concern around this population, and this proposal tries to address that as well.

But with that said, let me bring on Becky Wood to offer some additional thoughts.

DR. NGUYEN: I'm sorry. Christine Nguyen again. If I could make a comment before Ms. Wood speaks.

So you are proposing a new RCT to investigate the efficacy of Makena. Again, we're going to have a placebo control, in the same, or very similar -- it sounds like it's really the same

proposed indication in the drug label, correct? You're proposing a new RCT to investigate Makena's effect.

DR. CHARI: That is correct, and I want to draw your attention to the fact that we would obviously like to sit down and discuss this in detail with CDER to see to what extent there might be a different view on what would be the additional risk factors that we would include, and there might be others that we would want to add to this list as well. So that's something that we would really be looking forward to after these hearings are over, assuming that there's a path forward.

DR. NGUYEN: Okay.

My one last comment is, the fact that we're investigating this use in that population, certainly the question remains whether or not the drug works in the narrow population, so it will be hard for us to conclude there is already persuasive compelling evidence that this drug works in this narrow population. That's just a comment. You don't need to respond. Thank you very much.

MS. WOOD: Thank you, Dr. Nguyen, and just a brief comment. Obviously, the sponsor's position is that Meis continues to provide substantial evidence of efficacy for Makena. We're not necessarily proposing a new indication. There are a number of potential authorities that FDA could consider using to adjust the labeling. For example, there could be a further limitation of use. There could be additions to other aspects of the label, including the clinical trial section. There could be a Dear Health Care Provider Letter.

I think what Covis is trying to show to the agency is the work that it's done to really focus on this high-risk group, and we've certainly seen in other precedents by the agency, for example, in the Iressa context, where there was a sense that a subgroup was benefiting, that there was an ability to make a change to labeling. Obviously, that's premature to decide at this moment exactly what that would look like.

Really the sponsor wants to show to the agency its willingness to work with the agency to

adjust the labeling in a manner that would be appropriate for public health.

DR. NGUYEN: Great. Thank you very much. I have another question.

In your brief, you stated data on the gestational age of the prior preterm birth, particularly in women from Russia and Ukraine, was unreliable because there was no requirement for first trimester dating. You suggested because of these reliability issues, that the prior preterm birth in these women were perhaps not even preterm, or even much further along than what was recorded.

But isn't it true that the average birth weights of the babies born in the prior preterm birth to mothers in Russia and Ukraine were similar to, if not slightly lower than those from other countries?

DR. CHARI: We have not run that calculation, but we assume, and we take CDER's word for it, that if that's what it appears that the analysis shows, then we would accept that that analysis has been conducted.

DR. NGUYEN: Great. Thank you.

We did run those analyses to test the hypothesis, and because of the results we found, it really did not show evidence that the babies born to these mothers in Russia and Ukraine could have likely been systematically further along in gestation. Thank you.

DR. CHARI: Yes. If I can provide some context behind why we looked at those issues, we've been struggling to understand why the data from every single possible cut that we could look at in the ex-US population, particularly the data from Russia and Ukraine, looked so uniform. And by uniform, what I mean is that when we look at it in terms of weeks gained relative to the most recent prior gestation -- so you just think about it as a change from baseline, which is one of the different analyses that we did -- you see a phenomenal improvement of the entire placebo group, all the way from wherever that prior gestational age is to pass 37 weeks. That's one example. When we look at the neonatal index as well, the neonatal index

looks very much like that of an almost completely healthy population.

Then of course, third, you've got the overall incidence of the preterm births, and while that's slightly adjusted, we couldn't wrap our heads around why is it that that data looks the way it did. I think what you saw was us looking at clinical practice in those countries and seeing that there aren't established standards in terms of how they do those measures; and then secondly, the fact that this just looked like a very healthy population, which was not reflective, at least in terms of risk factors, of what we are trying to study, which is the American population that's at risk.

So that's the backdrop behind those analyses. We take CDER's point and note it very carefully, but that's also, for us, the reason why we've been focusing on the U.S. PROLONG population, where at least we've been able to see some degree of correlation between risk factors and outcomes.

DR. NGUYEN: Thank you. We appreciate your

extensive search into potential reasons why the PROLONG data differ from 002.

If I may move on -- I apologize. Christine Nguyen, OND, CDER again. May I have Covis' slide 49 up, please?

Just to confirm, subjects outside the U.S., certainly including those from Russia, were enrolled near the start of Trial 003 in 2009. Do you agree that Trial 003 was designed as an international trial; that it was not intended to be a US-only trial because of concerns of recruitment for a trial this size after Makena would have been approved?

DR. CHARI: Yes. Since it was part of the work with the prior sponsor, I'm going to ask Dr. Sean Blackwell to help answer those questions about PROLONG.

DR. BLACKWELL: Thank you. This is Sean Blackwell. The short answer is yes.

DR. NGUYEN: Great. Thank you so much. And actually, Dr. Blackwell, if I may ask, are you aware of any evidence that preterm birth in a woman

outside the U.S., certainly in Russia or Ukraine, would have different biological reasons than women in the U.S.?

DR. BLACKWELL: Thank you for that question. Again, it's Sean Blackwell answering.

I think one of the challenging aspects of preterm birth is that it's really a syndrome. It's not singular disorder. It's a multifaceted, multi-pathway syndrome. Clearly, there are differences in the rates in the severity of preterm birth between different countries and different populations that will be seen in multiple trials related to progesterone, both related to 17-OHP, as well as vaginal progesterone.

So I think that the biological mechanism to explain the differences in Russia and Ukraine versus the United States are very challenging, to give a detailed answer.

DR. NGUYEN: Great. Thank you. I appreciate that.

Along the way, are you aware of any pharmacological differences in response to Makena

in women outside the U.S. versus those in the U.S.?

DR. BLACKWELL: Sean Blackwell answering. Again, I would say that it's very challenging to give specific scientific answers to that given the lack of clarity related to the causes and the mechanism of preterm birth as it relates to the preterm birth syndrome, and a similar answer related to the questions about the frequency.

DR. NGUYEN: Great. Thank you.

I'd like to actually focus in on the U.S. cohort at this time. We noted that Trial 003 enrolled 391 subjects, and compared to Trial 002, that's 85 percent. As I've discussed, we talk about the risk factor, at least the major risk factors in one trial showing that it didn't matter, and another trial, it seems Covis indicates that it does matter.

So putting that aside, would you agree that there was no treatment effect in the U.S. subgroup in 003, despite the fact that we did almost have 400 subjects?

DR. BLACKWELL: Sean Blackwell. I think

this is an important issue, and I'm going to give a little bit longer comment, again, coming back to the idea that preterm birth is not a singular condition or a singular disorder, and when we prophylax against it, or whether we treat it acutely, we're treating a syndrome with multiple pathways related to the development of prematurity.

The other comment that I would make is these risk factors are not all or none, and they're very different. The risk factor of -- the two strongest risk factors that exist for the development of preterm birth are a prior history of preterm birth, and number two would be a sonographically short cervix.

When we look at these other risk factors, most likely the next most powerful risk factor is being African American or Black in the United States. These other risk factors related to social determinants of condition, of determinants, certainly have weaker signals but positive signals. So I'm cautious to equate African American race in the same way that I may equate smoking, or

substance, or lower socioeconomic status. Clearly, although these risk factors are present in the U.S. cohort of PROLONG, their frequency in their nature is much different than what was in Meis.

To come back to your question, I would agree that there's not statistically significant treatment effects that were identified in the PROLONG-US cohort, and certainly I think one of the drivers for that is the much lower frequency of the primary outcomes that we saw in the U.S. population compared to the Meis.

DR. NGUYEN: Great. Thank you.

I think what I'm hearing is that we don't really -- granted that preterm birth is a syndrome, so it's complicated, to say the least, but certainly there is no known biological or pharmacological reasons for the different responses that we saw in women outside the U.S., and even women inside the United States for Trial 003, we're not seeing a treatment effect there either. Thank you so much.

DR. BLACKWELL: Thank you.

DR. STEIN: Thanks. Peter Stein, OND, CDER. I have a question. I wanted to come back to comment that was made earlier about Bastek, et al. It's probably just worth clarifying just one or two points.

First of all, I just wanted to clarify that in Bastek, we talked yesterday a little bit about the availability of information on utilization of HPC or Makena in some of the real-world evidence studies and the limitations, but I wanted to just confirm that in the Bastek study, there was no information whatsoever as to whether the women did or did not receive HPC or Makena; is that correct, in that study?

DR. CHARI: That's right.

DR. STEIN: You also commented that CDER focused on the overall population rather than the analysis that you showed. I just wanted to clarify, and perhaps you could confirm, we did so, but that was actually the prespecified analysis; it was the pre/post in the overall population. So the intended objective of the study was what we focused

on.

I wonder if you'd just confirm that because you, I think, were looking at some of the exploratory analyses that they showed, but I did want to just confirm that the primary analysis was what we referred to, the overall pre/post introduction of Makena into the institution.

DR. CHARI: Yes, we would agree.

DR. STEIN: Okay. Thank you.

I just wanted to also come back to something that was mentioned earlier, which really relates to the therapeutic intent of Makena. Obviously, we have drugs that are focused on treatment, where all patients receiving the drug -- hopefully all patients receiving the drug -- have the disease and might potentially benefit from it versus a preventative mode for treatment, where many of the people who will receive the drug might not end up with the condition.

So in this case, this is a drug that's used in a preventative mode, so in fact most women who would receive Makena would not go on to a preterm

birth. Even if they had a prior preterm birth, the occurrence of another preterm birth is actually relatively smaller in that population. I think it was earlier noted that if we accept the Meis data and applied that, that more than 5 women would be treated for one woman who would have prevention of preterm birth.

I just wanted to confirm that we're both looking at this as a treatment for prevention of, clearly, a serious condition with an unmet need versus in a treatment mode. Would you agree with that characterization?

DR. CHARI: Absolutely.

DR. STEIN: Thank you.

DR. NGUYEN: Thank you. Christine Nguyen, OND, CDER. Actually, this question is for Dr. Blackwell.

DR. CHARI: Sean, may we have you come up? Thank you, Dr. Blackwell.

DR. NGUYEN: Thank you.

Hi, Dr. Blackwell. I was actually listening with great interest when you were describing the

incident of short cervix in a woman considered high risk, and certainly I agree with you, within the last 20 years or so in the practice of obstetrics, that has evolved quite a bit.

I was just curious. In your discussion, were you implying that Makena would work in these women, number one? And number two, if Makena were to be withdrawn, that cervical cerclage would be an acceptable alternative in women who otherwise would receive Makena? I just want to clarify my understanding. Thank you.

DR. BLACKWELL: Alright. Well, thank you for those questions. This is Sean Blackwell again, answering.

If Makena were withdrawn -- I'll start there -- cervical cerclage certainly may be used for women with a prior spontaneous preterm birth, however, right now, based on trial data and other information, that would be not evidence-based. The only proven role, at least in my opinion, for the role of a cerclage are in two situations, one of them dealing more specifically with this

population.

If a woman with a prior spontaneous preterm birth starts out on Makena, or some other therapy, and then later on develops a shortened cervix, defined as less than 25 millimeters, then she would be a candidate for a cervical cerclage due to a shortening in the presence of a prior preterm birth.

The other situation whenever we see cervical cerclage is being used, with adequate data to support it, are in women with a prior history consistent with cervical insufficiency, which would be painless cervical dilatation, or cervical change, or cervical dilatation with exposure of membranes earlier on in pregnancy, perhaps less than 20 weeks, but certainly it could be after that in some certain situations, or in women who in an asymptomatic standpoint present with cervical dilatation with or without a prior preterm birth.

Those would be the situations where, at least under my opinion, a cervical cerclage would have evidence to support its use. Now certainly

there is a range of patient conditions, and patient requests, and physician decision making along with patients on the risk-benefit of a cerclage.

To come back around to, I think, one of the questions, Dr. Sibai mentioned earlier that he's concerned that if Makena is removed from the market, more and more patients will just have a cervical cerclage used instead of any other pharmacologic therapy, and that would increase surgical risks and other potential complications, especially in the setting of the lack of evidence and what we know about cervical cerclages.

I think the other question that you asked me -- and again, let me know, and when I finish if I didn't adequately answer the first question. The other question that you asked --

DR. NGUYEN: Actually, may I ask a clarifying question from what you just said, just to make sure I understand this well?

In one situation, if a woman had a painless delivery certainly early in the trimester, that would be very suspicious for a cervical

insufficiency, and that woman would receive cervical cerclage probably pretty early on, 12-14 weeks or so. So those women would not be the indicated population for Makena.

Am I understanding that correctly?

DR. BLACKWELL: That is --

DR. NGUYEN: And the second situation -- okay, thank you.

The second situation is, if you are monitoring a woman's cervix -- and let's say it's second trimester or 20 weeks or so, it's less than 25 weeks -- you can put a stitch in her. Now, whether or not she's been on Makena, you would do that, right? Just the fact that her cervix is short. So it's not like if you didn't have her on Makena, you would put a stitch in her. I mean, she has to have cervical reasons to have that stitch, right?

DR. BLACKWELL: So that would be the management approach that I would argue is the most evidence-based.

DR. NGUYEN: Okay.

DR. BLACKWELL: The concern I think of any people in this space, what Dr. Sibai was mentioning, that people would, without adequate support from our professional societies or clinical trials, start prophylactically putting cerclages in just because of the prior history, and that would increase the number of surgeries that would be done without evidence, and potentially increase the risks associated with that.

DR. NGUYEN: So you're saying prescribers, surgeons, would put in a stitch when there's no reason to do so. Her cervix is fine. Sure, she may have a prior preterm birth. Her cervix is fine, and someone's going to do that without evidence to do so? I would be concerned if that was happening. That's the part where I'm trying to be clear on if that's a reasonable clinical practice, for people to put in cerclages just because Makena is not around, and there's no cervical reason to do so.

DR. BLACKWELL: Well, clinical judgment can be a challenging thing. Not all patients are the

same. Certainly not all prior histories are the same. But at a professional level as a maternal-fetal medicine consultant, I certainly see a range of practice in the real world -- I certainly do see a large number of providers, and patients, choosing this method and this clinical approach, and I think it's a real concern. I share Dr. Sibai's opinion that if Makena is removed from the market, and doctors and patients don't have that as a choice for prophylaxis, the cerclage will be chosen as a prophylaxis instead.

DR. NGUYEN: I just wanted to confirm that Trial 002 and 003, which evaluated Makena's efficacy, excluded women who either had a cerclage in place or who planned to have a cerclage in place. So we don't have any, really, evidence of Makena's effect regarding women who may be candidates for cerclages.

DR. BLACKWELL: That's correct. That is correct, but just to clarify, I don't think that's what Dr. Sibai or I are arguing related to the effectiveness of Makena. It's the concern of a

cervical cerclage being the replacement for Makena in women with this indication that we're talking about.

DR. NGUYEN: Right, and I think that's the argument I'm trying to make. We're arguing that physicians are thinking if Makena's around, the cerclage would take the treatment place for Makena. I just want to point out the fact that we have no evidence of efficacy in Makena as it relates to cervical reasons for a cerclage. They actually are pretty distinct. That's all. Thank you.

DR. STEIN: Thanks. This is Peter Stein, Office of New Drug, CDER. I think that concludes our questions unless -- Dr. Nguyen, any other questions from you?

DR. NGUYEN: No, I don't have any questions, and I would like to thank Covis and all of your consultants who have helped us understand our questions better. Thank you.

DR. STEIN: Thank you. That's all.

DR. CHARI: Thank you, and we really appreciate the questions and the opportunity to

clarify our thinking with you.

DR. WITTEN: Thank you.

We're now about to take a break. Committee members are reminded that there should be no discussion of the hearing topic with other committee members during the break, but I'm going to turn it over to Mike who maybe has some instructions for us. Thank you.

(Whereupon, at 2:24 p.m., a recess was taken.)

Questions for Covis by the Presiding Officer and Advisory Committee

DR. WITTEN: We'll now proceed during this session with questions for Covis by the advisory committee members and me.

Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If

you wish for a specific slide to be displayed, please let us know the slide number, if possible. And finally, it would be helpful to acknowledge the end of your question with, "Thank you; that's all I have for my questions," so we can move on to the next question.

This is a session for questions from the advisory committee members to Covis, so I'll open it up to questions from the advisory committee.

(No response.)

DR. WITTEN: So I don't see any questions to kick it off, and I'll start with one, which is, in Study 003, the study failed on the conventional endpoints, but then you showed a continuous endpoint on which the study succeeded in this analysis, and I'm wondering if you can give a clinical interpretation of those two disparate results for that study.

DR. CHARI: I'd be happy to try to do that.

DR. WITTEN: Yes, state your name, please.

DR. CHARI: I beg your pardon. This is Raghav Chari from Covis.

DR. WITTEN: Thank you.

DR. CHARI: I'd be happy to try to provide that explanation.

I think most of us recognize that the continuous endpoints are more sensitive and are able to more sensitively detect treatment effects. In fact, putting aside the fact that we do see a favorable odds ratio as a point estimate in the high-risk subgroup that we showed, what appears to be happening is that you are getting an extension of prolongation of a subset of patients in terms of the gestational age, but not sufficiently pushing enough of them across the hurdle on the 35-week point, which is why you're not seeing a treatment difference on the 35-week endpoint.

As we've looked at the individual lines of the patient data, which we've spent a lot of time analyzing for the 391 subjects in the U.S. PROLONG data set, it seems consistent with the mild signal that is seen in the overall PROLONG-US population for the less than 32 endpoint. But of course, Dr. Witten, all of these are post hoc observations,

but the idea that you're pushing patients past week 32 with this prolongation of gestation, particularly in the more severe birth history subjects, but perhaps not getting them all the way past 35, and which is why you're not seeing your marked different in the event rates, in the conventional prespecified endpoint.

DR. WITTEN: Thank you.

Next is Cassandra Henderson.

DR. HENDERSON: Thank you. Cassandra Henderson in New York.

Dr. Chari, I'd like to ask a question.

MR. KAWCZYNSKI: Cassandra, please hold your microphone by your mouth.

DR. HENDERSON: Thank you. Thank you. Okay. Can you hear me now?

MR. KAWCZYNSKI: Yes, ma'am.

DR. CHARI: Yes, she's fine

DR. HENDERSON: Thank you. Cassandra Henderson in New York.

Dr. Chari, I'd like to ask, if you are allowed to do this third trial, what are you going

to do to mitigate what we've heard was a problem with the PROLONG, that individuals who are really high risk, or practitioners who had patients who were high risk did not want to put them in a trial where they would actually have to risk having placebo?

How are you going to mitigate against having a group that's not going to be very high risk because the really high risk are going to self-select to get Makena?

DR. CHARI: That's a really good question, Dr. Henderson, and I'd like to ask Dr. Blackwell to help us with that question given his clinical expertise and also role in the previous study.

DR. BLACKWELL: Alright. Thank you. This is Sean Blackwell answering.

I think this is an important issue, and it's not a trivial one. Certainly going forward, the regulatory bodies, the IRBs, referring doctors, the people that would be principal investigators for a trial have to be locations that believe in the clinical equipoise that exists, and then need to be

able to have a process to be able to communicate that, and I think that's a lot of the important work that will be done in preparation for a trial.

Certainly, I think critics have argued that there's insufficient data to suggest that Makena is effective across all gestational ages, and I would be arguing that I think there is the greatest need to identify efficacy at higher risk patients, and however it is that it gets defined in a future trial. I think that good patient information, good informed consent processes, and then communication of a trial through different methods is going to be really important.

In general, when you look at most large trials involving pregnant women, consent rates are about 50 percent, whether the intervention is a surgery, or a medication, or some other healthcare intervention. So regardless of what we're studying, there's always going to be some people that are either excluded or, for whatever reason, declined. But I definitely think that this is something that's going to require a lot of effort

and thoughtfulness in anticipation of that aspect.

DR. HENDERSON: But what have you thought about trying to not get a group that was self-selected for not really high risk because they believe they're going to treat themselves with the drug?

DR. BLACKWELL: Well, I think the exact eligibility for a future trial, beyond the history of a prior spontaneous preterm birth, I think has to be negotiated and determined in collaboration with the FDA, and the sponsor, and others, so I can't necessarily get too detailed because I don't know what that population is. Certainly it's got to be a population where there is enough clinical equipoise for people to feel comfortable randomizing these patients to a placebo.

There are many people that would be comfortable with women -- if we just looked at very early gestational ages, that they'd be comfortable with the equipoise out there to be able to offer this intervention to patients.

DR. HENDERSON: Thank you very much.

DR. BLACKWELL: Thank you.

DR. HENDERSON: No more questions. I'm done. Thank you.

DR. CHARI: This is Raghav Chari again. If I could just offer a quick clarification for Dr. Henderson's question, one other related point, Dr. Henderson, to your question, is this notion of clinical equipoise.

I would argue that especially after the presentations that you've heard in this hearing I think coming from CDER's vantage point, where they have summarized their position as no benefit, all risk -- and that is coming from the authority on drugs -- and then of course the point of view that we have shared, we think, if anything, coming out of these hearings for the product to even stay on the market, that there will be many more clinicians who are in that middle group of undecided, who would certainly be willing to enroll the high-risk population because they are not clear in their minds that there is a definitive benefit.

DR. WITTEN: Thank you.

I'm going to call on Kristine Shields.

DR. SHIELDS: Hi. This is Kris Shields. I'm the community representative, and I have kind of a follow-on question on the same topic.

If you could explain, you had mentioned, Dr. Chari, that you would be limiting the use of Makena to high-risk patients, patients who are at high risk for having preterm birth. But isn't it true that if Makena stays on the market, then any physician could use it in any population, whereas if it's removed from the market, then its use would be truly limited to high-risk patients in the clinical trials? And those are the people for whom it may be effective.

Would you have a population of pregnant women who are not in a high-risk category, who are being provided Makena?

DR. CHARI: Thank you for that question. Raghav Chari again.

The fall-off in the use of Makena since the 2019 advisory committee, or around that time to now, has been quite substantial, and I would say,

the most stark representation of that was a graph that CDER showed yesterday on the FAERS adverse event reporting, which, as you would imagine, is proportional to the market use. I think that the lines are showing something around 40 percent of the overall numbers that you saw a few years back, and that's consistent with the decline that we have seen in prescription volumes.

It's our sense, actually, that today where the drug is being used, it's being used in a conservative fashion for high-risk patients already, and that this additional clarification around whatever form of limitation appears to be regulatorily feasible. I'm not a regulatory lawyer, so we've proposed multiple mechanisms, including amending the label and the indication statement, including the data in the clinical trial section, putting in other limitations, which FDA has done previously in studies, to make it very clear. Then I think that the organizations that manage the use of these, including the FAERS, have it also in their ability to make sure that there's

some guardrails that would align the utilization of this product with it. So I think that there are a lot of tools to add to the fact that the earlier observation, that it's our belief that it's primarily being used in higher risk patients today.

DR. SHIELDS: Okay. Thank you very much.

DR. WITTEN: Next, I'm going to call on Susan Ellenberg.

DR. ELLENBERG: Thank you. I'd like to thank the sponsor for their detailed presentation. I was interested in your thoughtful proposal for a follow-on study that you believe, based on your thorough analysis of the studies that have already been done, that might clearly demonstrate, more clearly demonstrate, the effect of the drug.

You have talked about doing this study in a context of having Makena still on the market, and my question to you is, is this the study that you would propose if, in fact, the marketing approval is withdrawn? Would you go forward with this study, or would you go forward with a different study, or would you not go forward with any steps?

DR. CHARI: Thank you for that question, Dr. Ellenberg. Raghav Chari again.

We are convinced, based on our market research and our discussions with practicing clinicians, that we are able to do the study in the advertised time frame of 4 to 6 years, and complete if the product stays on the market. Unfortunately, from the market research that we have done, and I think also amplified by the approach to withdrawal that CDER has suggested -- again, really saying that this is a product with no benefit, only risk -- and our market research with both physicians and patients, highlights that the ability to recruit a clinical study, if the product is withdrawn, is not at all clear to us today.

That's where it becomes hard to answer the last part of your question, which is can we commit to a clinical study of this nature if the product is coming off the market? And I think it would require a lot more work on our part to understand exactly what that means, so it's not clear. I can't give you a clear answer on that today.

DR. ELLENBERG: Okay. I don't hear CDER saying that there's clearly no benefit. What I hear CDER saying is that benefit has not been established. So I think it's not quite as strong as what you said.

DR. CHARI: I take that point, and I do think that it would be important to nuance that. But certainly our research was done prior to the presentation by CDER, and even with the less direct message about the lack of benefit that CDER talked about, the feedback from the survey for both physicians and patients was that they will be less likely to recommend patients for the clinical study.

I think this is stemming from the psychology of what does it mean for FDA to withdraw approval for the product, what is it saying about the product, and do I as a patient want to participate in that clinical study? And at least our research seems to be telling us that they're less likely to participate in the study if that were the case.

DR. ELLENBERG: Okay. If I just might make

one comment. The description of the survey said that people were less likely to participate if the product was not FDA approved, but of course any new product that's being studied is something that's not FDA approved. So I guess I have to wonder exactly how that question was worded because I suspect that they were promising a new drug, a different drug, for this indication that was placebo controlled, that was being studied for FDA approval. I would be surprised if people said, oh no, they wouldn't be interested because it isn't FDA approved already.

DR. CHARI: Right. I'll make a couple of clarifications on that, Dr. Ellenberg.

First is, we had two rounds of surveys. The first round of surveys, based on feedback from our counsel, we were asked not to make it specific to the withdrawal of the product because of the public knowledge of the ongoing proceeding, which is why we phrased the question that we did, particularly to patients.

We then followed up with physicians with a

second survey, and that second survey was very specific about the question in the preterm birth space, so I think those physicians would have probably also read between the lines and known what this question was about.

But we specifically asked them the question about their likelihood of participating or recommending a patient into a clinical trial if the approval was withdrawn. In that situation, the responses were 80 percent yes, if the product was still on the market; I think 39 percent or something like that if the product were not approved; and if approval was withdrawn, it was all the way down at 15 percent.

So there was this gradation, and we asked that question directly to physicians who would be either recommending patients or performing informed consent, and that is where in the second follow-up survey we got a very clear answer to that question, which is based on the specific scenario.

DR. ELLENBERG: Thank you.

DR. WITTEN: Okay. Thank you.

The next questioner is Sarah Obican.

DR. OBICAN: Hi, Dr. Chari. Thank you very much for your time today. I just have a few follow-up questions, if I may. I believe this was on your slide 139. It was regarding the potential future study that would potentially be done in terms of the indications for that.

Could you pull up that slide?

DR. CHARI: Thank you. Can we have slide 139?

DR. OBICAN: Thank you.

On there it says, "other social determinants of preterm birth." Since there are a few social determinants for preterm birth, what do you think those would include? I know the decision would not only come from you, and it would be a joint decision, but my question would be, what would your interest be in terms of the social determinants for preterm birth that you would include, and why?

DR. CHARI: Right. I will start answering that question, and then also perhaps ask our clinicians to provide some additional insights on

that.

I'll start off by remarking that when we did our analyses, our post hoc analyses, we focused on Black as a proxy for high risk and as a proxy for social determinants of preterm birth, and that is what guided us to it. We are acutely aware of the challenges with how you write this label, which is why it would need to be a collaborative effort with CDER.

As we looked at the various risk factors, certainly there are other factors including alcohol use, substance abuse, smoking during pregnancy, that are additional risk factors--the last not necessarily being a social determinant--then also income levels and so forth. So I think that there needs to be a real conversation about exactly how to prespecify these in a label.

But with that said, also in our conversations with clinicians, it appears that they have a much better idea of exactly what these factors involve in terms of contributing to a patient's potential risk, and it's also sometimes

very geography specific.

With that, maybe I will ask Dr. Blackwell to speak a couple of minutes to just expand on the concept of social determinants.

DR. BLACKWELL: Well, thank you for that question. This is Sean Blackwell again.

I'm going to apologize up-front for my answer because I'm not going to be able to give you a detailed answer for what's the right trial. I'll first start out by saying one of the challenges that we have here is there's the regulatory aspect about labeling, which I'm going to stay as far away as possible because that's well out of my expertise and interest, and then there's the other aspect related to a clinical trial and what I do as a clinician. I do think that, from the clinician side, in order to make sure that we don't have mission creep, inappropriate treatment, and be able to provide the therapy for the best patient, we have to be really clear. That's number one.

Number two, it's the same on a clinical trial. You've got to have very clear eligibility

for a proposed trial. To decide what that population should be requires a lot more work than what we have now and, fortunately, we weren't tasked with designing a trial at this advisory board meeting.

I think the way I look at it, it's the concept that a trial could be done and what would be some potential aspects of a trial. Certainly, many of these risk factors, given their frequency and their predictive value, would be reasonable choices to look at eligibility criteria for a trial, but I think deciding who are the right patients to benefit or to test a treatment benefit is going to require much more information, identifying the clarity of who these patients were, and then there are baseline risks, and that takes, I think, a lot more work than the information that we have.

Do we want to target a population that has a risk of 50 percent of recurrent preterm birth, or would it be appropriate to target a patient profile that has a 30 percent recurrent risk?

So again, I'm going to apologize for my lack of an answer, but it's a little bit more complicated. Perhaps somebody else can give something that's a different perspective or more thoughtful, but I think that's, unfortunately, the best I can give you at this time.

DR. OBICAN: Thank you, Dr. Blackwell.

I just want to ask permission from my colleagues. I have two more questions, but I want to be cognizant about my colleagues who may have other questions, too.

Is it ok to ask another question or two, or should I wait till others have an opportunity as well?

DR. WITTEN: Why don't you go ahead with a question or two, and then we'll go on to the others --

DR. OBICAN: Okay. Thank you very much.

DR. WITTEN: -- but we have time.

DR. OBICAN: Thank you.

I'm happy for anybody to answer the question, but this is probably for Ms. Wood. My

question would be that during the hearing, I had heard there's a precedent, and through the reading as well, that CDER can decide to keep the drug on the market or not.

My question is, is there a precedent of a drug being removed and still being indicated for a partial withdrawal? So in other words, having it be available for a more honed or different subpopulation in the past.

DR. CHARI: Thank you for that question, Dr. Obican. I will have Rebecca Wood answer that question for you.

MS. WOOD: Thank you. May I share my screen, please?

This is an example that I had mentioned earlier, the Iressa example. Slide up. This is an example that I mentioned --

DR. OBICAN: I'm sorry. I still have the 139 slide, the Analyses Support for Higher Risk Population. I'm so sorry. I'm not seeing your particular slide.

MR. KAWCZYNSKI: It's up, Sarah. That may

just be your bandwidth. It's up.

DR. OBICAN: Okay. I can't see it.

MS. WOOD: I will describe it to you, then.

DR. OBICAN: Thank you.

MS. WOOD: I mentioned the Iressa example when I was talking about a circumstance in which the agency looked to see whether there might be a subgroup that benefited. In that example -- and I'm displaying the change to the label -- the indication was changed to patients, quote, "who, in the opinion of their treating physician, are currently benefiting or have previously benefited from this treatment."

But they literally redlined the label to add that word, "who are benefiting or who have benfited from the treatment," in light of some data that was believed to have helped those particular patients. So that's one precedent that I pointed to.

Again, our position is the sponsor is wanting to show our willingness to work with the agency,As aggressive as doing a partial withdrawal. We're willing to do things that are less aggressive

as well, including some of the labeling changes that I mentioned, to get additional data into the hands of physicians, and obviously would look forward to working with the agency to that appropriate public health path forward.

DR. OBICAN: Thank you very much, Ms. Wood.

My last question that I have for right now is, I understand that there was the time frame that was proposed. For the next trial to be done, it would take about 4 to 6 years, or at least this is what the thought is currently from your end.

My question is, before the first patient is enrolled, considering the difficulty of performing the trial from you or another site like this, what do you anticipate -- and I know this is a hard question. What would you anticipate would be the time frame until that first patient is enrolled, until we can start that 4-to-6 year clock, please?

DR. CHARI: Raghav Chari. Thank you for that question, Dr. Obican.

At this point, let's just assume that we're marking the time from the point where there is

agreement with CDER on a path forward. From that point forward, it will take some time to work out the exact protocol with CDER, and then once we have that in place, we would probably anticipate about 6 months to get the study up and running to the point where there's IRB approval and the ability of those individual sites to begin screening patients, which is why, given our own uncertainty with respect to how long this whole process is going to play out, we suggested that from the point where patient screening starts, we would agree to study conduct milestones, including from 24 months from that point, if we are not on track with respect to our enrollment targets, that we would work with CDER to wind down the study, and take the product off the market.

DR. OBICAN: Thank you. Yes, I appreciate that point. And just to be clear, the 4 to 6 years was in regards to the end of the patients that would be in the trial, so that would be the actual trial and not the time to take the trial to its fruition, to its, at least, beginning.

DR. CHARI: The 4 to 6 years would be from beginning to end, including all of the analyses and reports, at least to the conclusion of the clinical study.

DR. OBICAN: I understand. Thank you very much for your time. That's all for me.

DR. WITTEN: Thank you.

Next, I'm going to call on Mark Hudak.

DR. HUDAK: Yes. Thank you. I also have several questions, so please let me know when I need to defer to somebody else.

DR. CHARI: Yes, Doctor.

DR. HUDAK: First of all, this is really an exceedingly important clinical issue. I think everyone knows that. We have not solved the problem of prematurity. It has a lot of effects on the mother, and the baby, and the family, and the healthcare community. In this country, it's a huge problem because we have a rate of prematurity; 2019 pre-COVID, it was 10 and a half percent, and I suspect that COVID only has increased the rate of prematurity in our liveborns.

So it is a huge problem, and I think everybody is struggling with this, and everybody is sensitive to the fact that we really do need to have an effective therapy. I won't say how many years I've been doing neonatology. There's always been something sort of around the corner that's going to be the magic bullet, and it hasn't happened, so we are worse now than we were 40 years ago.

In retrospect, certainly, as I telegraphed yesterday, I think it's clear that the primary efficacy endpoint that was chosen really could have been different, and had been more meaningful, and provided more insight. I think some of the ways that the FDA and Covis have tried to represent the data have been very helpful to us in trying to understand that; however, I think I and -- I'll speak for myself, and I wouldn't be surprised if others on the committee are also a bit confused.

Essentially, we had the presentation of the 002 study, which is a very positive basis for the accelerated entry of Makena into the marketplace.

There were weaknesses and anomalies in that study, we all understood, but as it stands on its own, it was a very positive study.

When CDER presented the PROLONG study, 003, to us yesterday, looking at the entire population, looking at different subgroups, there was absolutely no signal of any benefit, in any way, in any slide, at any point. Then you presented information today, where you looked at different things, and came up with some pretty persuasive looking graphs on prolongation of pregnancy by the last pregnancy gestational age and so forth.

Some of this may be apples and oranges, but I guess the question I have is, looking at the information the FDA presented on their slide 50 to 52 yesterday, where they looked at high-risk groups and different risk factors, and then looking at your slides 84 and 85, where you sort of showed those two graphs of the increasing duration of pregnancy, especially at the lower gestational ages, it doesn't compute to me.

So I guess the first question I have is,

what at the end of the day now, between Covis -- and I'd like a response from you and also from CDER. What are your current points of commonality in terms of what is there in the 002 trial and 003 trial that have harmony in terms of the data?

DR. CHARI: Right. Thank you for --

DR. HUDAK: Are there any things that there is harmony with respect to subanalyses, or whatever, that we can sort of take home and think about overnight?

DR. CHARI: Yes. Thank you for that question, Dr. Hudak.

Our perspective -- and we shared some of this in Dr. Poggio's presentation, as well as mine -- is that certainly there is a subgroup within PROLONG, which shows a favorable hazard ratio. The size of that subgroup is small, so the confidence intervals are not going to be below 1 for any of those three categorical endpoints.

I think it speaks to the challenge of being able to find true high-risk subjects within the

PROLONG population. As an example, if we look at the incidence rate of preterm birth overall within PROLONG for less than 35 weeks, it's 18 percent; yet however, when you look at the Black population within PROLONG-US, it's 20 percent. So there's really no appreciable difference between the risks of these populations.

I think when we talked with the investigators, the Black population that was in PROLONG was a very different kind of risk factor. Perhaps Dr. Blackwell has talked about the DoD patients that we enrolled, and those patients had a very low risk rate overall with a preterm birth rate of 9 percent, for example, perhaps because of the excellence of the health care that is being provided within that system.

So I think that becomes a real challenge, and for us, when we look at the Meis data, particularly when we look at less than 35 weeks, we see all of these different proxies for risks. And it's clear to us the majority of the population, when you just look at the step-up in the placebo

rates in those corresponding risk factors, there isn't an appreciable step-up. So that's telling us that we need to do a better job to define those high-risk patients, which is where we are focusing on multiple risk factors, and then when we start looking at patients with multiple risk factors is when we start to see the benefits from that weeks-gained analysis.

The size of that data set within PROLONG-US is only 87 subjects, so it's not much to really hang your hat on when it comes to these categorical endpoints because you need a much larger sample size to see something statistically significant.

DR. HUDAK: And if you were to do that same analysis in 002, do you come up with the same result?

DR. CHARI: Yes.

If I can have slide up on the -- could I have screen share, please, Mike?

This is the 002 population that we analyzed for that same high-risk population, and if you look at Meis, just to remind you or orient you on the

values, the overall Meis had hazard ratios or odds ratios around the 0.7 range. These are markedly improved relative to that. And again, if you recall the conversation that was had on the less than 35 and less than 32 endpoint, that upper bound of the confidence interval is very close to 1 in the overall 002 population. But here you're seeing a clear separation with the upper bound being of about 0.7 in both the less than 35 and less than 32 endpoint for the Meis population.

Of course, it's a --

(Crosstalk.)

DR. HUDAK: I remember this slide, but did you have a slide that showed for the Meis population the graphs of the weeks gained by gestational age of the last pregnancy compared to the Covis analysis?

DR. CHARI: Sure.

Yes. Just have them pull that slide for a moment. Slide up. This is the overall treatment effect in the Meis population, which is 1.33 weeks for Meis, and surprisingly to us, it's a stronger

overall effect in PROLONG-US when you look at the weeks gained.

DR. HUDAK: Okay. Yes. I'd like to see these data displayed in the same way as you did for PROLONG because this is --

DR. CHARI: So --

DR. HUDAK: -- but that's ok; that's ok. I understand you can deduce that.

DR. CHARI: Yes.

DR. HUDAK: Does CDER have any response to my question about whether you see any commonality between the two studies now?

DR. WITTEN: Well, I'll ask them maybe to address that in their --

DR. HUDAK: Their closing thing?

DR. WITTEN: -- in their closing remarks tomorrow.

DR. HUDAK: Okay.

DR. WITTEN: We should proceed with asking Covis.

DR. HUDAK: Alright. Well, thank you. Those are my questions.

DR. CHARI: Dr. Hudak, I just wanted to clarify one additional point, and I think we went into this a little bit in the conversations that we had with CDER in terms of the impact of risk factors, as well as the reasons why we did not see as clear a trend relative to CDER's analysis on the Meis population.

If I can have slide up, please? Screen share, Mike. Here we go.

This is an example of what happens with risk, and I think the key point we want to emphasize here is the risk. As you step up in risk, what you're seeing here is as you add additional conditions to the baseline inclusion criteria of, in this case mrpGA -- which is most recent pregnancy, gestational age less than 35 -- you're starting to see an increasing effect on the weeks gained in this population. So as you layer on incremental risk, we're seeing this.

I think the key takeaway message that we want to say is that the more likely you are to have very early -- or I would say an earlier preterm

birth, the more there seems to be a suggestion that 17P appears to be helping push these patients further along, and in some cases, in rather clinically significant ways, in terms of the total numbers of weeks being gained relative to placebo.

DR. HUDAK: Right. But I guess I'll go back to FDA slides 50, 51, and 52, so maybe you can pull those up. These are the slides that they tried to find out, in 003 PROLONG, whether or not if you added risk factors, you saw any greater evidence of efficacy. And at least looking at this slide 50, 51, and 52, sort of running through those, it did not suggest that there's an increased efficacy.

Now, maybe the risk factors they pulled out were different; I don't know. Look at the bottom, it looks like there's somewhat similar history, more than one preterm birth, Black, et cetera, but their risk factors were different than the risk factors you used.

DR. CHARI: Yes. That's a very fair question, and certainly the analysis of the data that we have suggested, that even though we may

be --

(Crosstalk.)

DR. CHARI: -- of gestation to these patients, you may not necessarily be getting them across the line at 35. So the question is, if you've got somebody who's likely to have given birth at 31 or 32, and you're pushing them to 34 or 34 and a half, is that a clinically meaningful gain, even if you're not getting them to 35?

I think that's how we see this because we actually see the relevance of adding weeks in the earlier period of gestation, whether or not you're actually getting all the way to 35.

DR. HUDAK: I agree with you. I think that the categorical of less than 35 weeks or not is not a very good endpoint, and I understand that's why there's a difference in interpretation, I guess, of some of the Blacks data with respect to use of the Cox proportional hazard model, which is not appropriate looking at that particular categorical outcome. Thank you.

DR. CHARI: Thanks, Dr. Hudak.

DR. WITTEN: Okay. We're going to move on to questions from Annie Ellis.

MS. ELLIS: Hi. Thank you so much for your presentation and the hard work that has gone into everything. I especially appreciate hearing from Drs. Sibai and Blackwell on conducting the trials, and the insights, and what they have brought, as well as Dr. Lawson's presentation on preterm birth and the problem itself. I also appreciate that you sought patient perspectives through your market research, and I do have a couple of questions about that. I'm not sure who's appropriate to answer them.

My first question is, were demographics collected with that survey, such as is the person currently pregnant or how much high risk, and if they had prior use of strategies to prolong pregnancy including Makena?

DR. CHARI: The way this survey was designed -- again, I'll try my best to answer that question. The way this survey was designed, it recruited women who had had prior spontaneous

preterm births. We collected demographic information on race and geography, and a few other factors. But particularly we did not probe on prior birth history, so we don't have a way of stratifying the analysis based on severity of the prior preterm birth and those types of concerns.

But based on the overall distributions of our data, for the different demographic factors, I would say that our data appears to be normally distributed, so I have no reason to expect that there isn't a representation of the spectrum of use and spectrum of histories in that population.

MS. ELLIS: Yes. Part of the reason why I asked is, as a clinical trial participant in the oncology space, not in this space, I think how we would answer a question, retrospectively, as well as what would we do in the moment as far as participation, may be different things. So I was just curious if anybody was currently pregnant or if you had that information during a survey, and it appears no.

DR. CHARI: I do believe that information

was collected in terms of whether or not they were currently pregnant, but I don't have, off the top of my head, the percentage of currently pregnant.

MS. ELLIS: Yes. I would just be curious to know that.

Also, I understand your process for using your counsel to help design the survey. Was the question asked if the mothers or the patients would consent to randomization? Was that part of the survey?

DR. CHARI: We explained to the subjects what a placebo-controlled study was, and that part of the process of enrolling in a placebo study was that they would not know whether or not they received the active treatment or the placebo, so that was explained to them.

MS. ELLIS: Was 2 to 1 randomization also included when you described what placebo control was, that they would have a greater chance of getting --

DR. CHARI: No, we did not. We did not explain that.

MS. ELLIS: Would you be considering using your advocates from the maternal group network to help you with your participant education materials to perhaps increase accrual?

DR. CHARI: We haven't thought through strategy at that level, and at this point, we would start to really roll up our sleeves on that if we knew there was a path forward.

MS. ELLIS: Alright. Thank you. I don't have any other questions.

DR. WITTEN: Thank you.

We'll now call an Esther Ellenberg -- sorry, Eisenberg.

DR. EISENBERG: Hi. I want to also express my thanks for your thorough presentations. They're very helpful.

My question has to do with, if you are able to go forward with a randomized placebo-controlled trial, have you thought about having a separate arm of women who were approached and qualified for the study but chose not to participate, and get them to agree, with informed consent, to have their data

collected so that whether they choose Makena or choose not to use Makena, their data can be collected as well?

DR. CHARI: It's a really interesting thought, Dr. Eisenberg, and we would certainly welcome yours, as well as other folks' thoughts on that particular question. We propose something very traditional with respect to the designs, but certainly we would be open to other suggestions on how we may enrich the data set and make it more robust so that it aids clinical decision making down the road.

DR. EISENBERG: In my experience, working with the Reproductive Medicine Network on infertility, this has been a way to accrue additional information. Clearly, it's not as pure as a randomized-controlled trial, but as you mentioned, it may be very difficult to get the high-risk patients that you need in order to show a difference, and sometimes this is a way to get that population, and you have other ways to try to assess the data. Thank you so much.

DR. CHARI: Thank you.

DR. WITTEN: I'll now call on Mara McAdams-DeMarco.

DR. McADAMS-DeMARCO: Thank you so much. I really appreciate the thorough presentation that you've given on the post hoc data analyses and your proposed future RCTs and cohort studies.

We all know that race is not a biological trait. What then is the sponsor's justification for using race as either a trial entrance criteria or potential indication for this medication, as was pointed out so eloquently by our public participants? We saw that there was no effect measured modification for prespecified endpoints in either the 002 or 003 trial comparing participants by race, as was also pointed out by Dr. Nguyen.

So why then do we think that this drug would have a differential effect based on a non-biological factor like race? I recognize that there is a precedent with BiDil, but the field of medicine and public health has moved away from racialized medicine. So what is the biological

basis for using race in the manner that's been described today

DR. CHARI: I will clarify. Thank you for that question, Dr. McAdams.

I'll clarify that we used race as a proxy within the various data sets for risk. Just to remind you, the modeling work that we did looked at all kinds of different factors that could be distinct, including race and prior birth history, and a whole host of other factors. We modeled the placebo response rate -- I should say the placebo outcome rate in the Dorsata data base, as well as the PROLONG-US and the Meis data set.

So we tried to get an objective perspective by looking at the placebo groups within these different data sets to understand what seems to drive preterm birth rate. What was clear from our analysis is that there appears to be a correlation of treatment effect that's more detectable in higher risk patients who would otherwise have a tendency to give birth early. I think it's really an important nuance question in terms of how do you

write a label that then describes that higher risk patient?

I think, for us, the starting point is something around prior birth history, which is some kind of cutoff as we proposed less than 35, less than 34 prior spontaneous preterm birth rate, and then additional risk factors so that it's a patient that's coming in with multiple risk factors.

That's what, for us, is kind of the baseline concept, and then I think we really need to sit down with FDA and figure out how do you describe that in an effective manner that is practical from a labeling perspective, is instructive to clinicians, and allows for clear decision making in clinical use, as well as clear decision making in terms of inclusion criteria for a subsequent study. I want to emphasize that we're really looking, at this point, at prior birth history plus multiple risk factors, and those risk factors could be many.

DR. McADAMS-DeMARCO: Yes. But again, race is not a risk factor. Racism, structural racism, those are the inherent risk factors. So I would

just challenge you to think whether you're talking on a social epi standpoint when you're characterizing race, or whether you're talking about biological differences between populations. Thank you.

DR. CHARI: Thank you so much for that suggestion, yes.

DR. WITTEN: Thank you.

Any more questions?

DR. McADAMS-DeMARCO: No, thank you.

DR. WITTEN: No.

We'll move on. Next is Aaron Caughey.

DR. CAUGHEY: Hi. Thank you so much for this presentation. Go to slide 83.

I appreciated that it was probably quite surprising when you finished PROLONG, and there was no difference. And as was shown by CDER yesterday, no matter how you slice it, again as was mentioned earlier, there was no difference. So then you started looking at this increase in gestational age.

In this figure, first of all, I'll point out

that this is just the U.S. patients, so you --

DR. CHARI: Correct.

DR. CAUGHEY: -- [inaudible] --

DR. CHARI: Correct.

DR. CAUGHEY: And each of these models, each of these estimates is a model that predicts weeks gained for this group of patients for the prior preterm birth under this gestational age, 28, 29, 30, which means that the N equals 37 patients at less than 28 weeks are also included in the 29, 30, and 31; is that not correct?

DR. CHARI: That's correct.

DR. CAUGHEY: So did you do it where you would actually do it by the week; in other words just those at 37 -- or those dosed at 36, just over the 35 [indiscernible], because it looks to me -- both on this slide, and if you go to the next slide, you see the same effect, if you go to 84 -- that there's likely to be very little benefit with the prior preterm births above about 32 weeks. This slide might suggest that you might get a week of benefit, but really the benefit's being

accumulated by those less than 30 or less than even 28 weeks. Then what you're showing is the average benefit, but it's really mostly the weight is the earlier.

Did y'all stratify by clustering, like looking at, say, 32 to 34, or 34 to 36 weeks, with the prior --

DR. CHARI: Absolutely, and you're correct that when you start to look at it in that fashion, you do see diminishing benefits. But also I think the error bars on those groups obviously get pretty big because the sample sizes are pretty small.

I think what we did as part of these analyses was to really coalesce around a clinical hypothesis of what high risk is, and eventually the basis of this was to try to define something around a prior birth gestational age cutoff plus additional risk factors, because we know that if you simply cut based on these analyses at 34 or 35, it's not clinically that meaningful necessarily.

So we were looking to see what kind of group is going to give you at least a 2-week-ish change

or a delta so that that's going to be meaningful. So we realized that we have to have something around prior birth history, but also have other additional risk factors folded in, and that was a combination of this type of analysis that guided our thinking on the cutoffs, plus holding in kind of clinically well-recognized risk factors to propose the type of practical population subsets that we wanted to suggest for restricting the label.

DR. CAUGHEY: Yes, that makes sense to me, and I guess what I'm trying to think about is one of the ways to decrease the width of your error bars would have been to include some of the patients from Europe.

Did you look at those patients in the same way or they just showed no difference no matter what?

DR. CHARI: It's interesting. They showed absolutely no effect, and it's not surprising. I'll just quote a simple-minded statistic, which can kind of tell you why you're not seeing an

effect. Even in patients with high-risk factors in Europe, you're only seeing, for the less than 35-week endpoint, about 12-13 percent preterm birth rate.

So if you think about what that means, when we censor this analysis at 35 weeks, 90 percent of that population that you're looking at is getting past the censoring point, which means they cannot contribute to the numerator, but they're contributing to the denominator. So not surprisingly, you're seeing absolutely no result for ex-US, and it coincides with this notion that we seem to be seeing greater, a more measurable therapeutic effect, a clinically relevant therapeutic effect, in higher risk. And when you're talking about even that kind of 12-13 percent preterm birth rate in the placebo arm in what is, quote/unquote, "a high-risk population in Europe," that is simply not going to show up in this week's gain because nearly everybody is already going past 35.

DR. CAUGHEY: It just seems to me that when

you design the future trial, if you use gestational age, you'll probably have to cut off at 30, not 35 weeks, although, as you pointed out, you may get there with a combination of other risk factors, and I think those need to be sorted out.

Anyway, thanks for this work, and the next trial is going to be really important, obviously.

DR. CHARI: Thank you.

DR. CAUGHEY: That's all my questions.

DR. WITTEN: Thank you.

I'd like call on Lorie Harper.

DR. HARPER: Thank you so much for your presentation. Dr. Caughey actually had just hit on one of my questions, but if you could go back to slide 83 or 84, showing the difference in gestational age in the weeks gained.

One of my questions is about if there's a difference in the weeks gained for Makena patients versus placebo patients, does that translate into the difference in gestational age at delivery?

DR. CHARI: Right. This is an analysis, and I'll ask Gene Poggio, our biostatistician, to come

up and explain the nuances of this analysis. But very simply put, while it's weeks from time of randomization to birth capped at 35 weeks, it's adjusted. There's an adjustment made for gestational age. But why don't I have Dr. Poggio explain the nuances of that, if you wish.

Dr. Poggio?

DR. POGGIO: Hi. Gene Poggio.

Let me try and answer your question, but I'm not sure if I have it right. So just to be sure, in these analyses, these are based on linear regression models for weeks gained with the treatment, but they're adjusted for the gestational age at randomization. The one I'm looking at is -- and obviously treatment is in the model and the mean gestational age as predictor variables, so all three of those are in the model.

DR. HARPER: Yes. I guess my question is, in the group left [inaudible] -- less than 28 weeks, who in this model gains an additional 3 weeks because of Makena, is what the argument is. If you look at just those of the prior preterm

births less than 28 weeks, does that actually translate into a difference in gestational age at delivery, or is it that there was a difference in the randomization of gestational age?

DR. POGGIO: Are you talking about those at exactly 28 weeks or the whole category less than 28?

DR. HARPER: In those 37 women whose prior spontaneous preterm birth was less than 28 weeks, did you do a subgroup analysis that just compared their gestational age at delivery between groups?

DR. POGGIO: You mean separate from the model or in terms of the model?

DR. HARPER: Separate from the model.

DR. POGGIO: I don't -- we didn't do an analysis -- really, all of them are based on the model because we want to adjust for gestational age at randomization, but gestational age at randomization is balanced between the groups.

DR. CHARI: Yes. I think just to make sure we're answering your question correctly, the gestational age of randomization is not impacting

the analysis, so what you are seeing is a true clinical gain. It's just that it's being done from time from randomization, but it adjusts for it so that you're actually looking at a clinical gain.

DR. HARPER: Okay. Thank you.

DR. CHARI: So if somebody was randomized during their gestational period, that's taken into account in this analysis.

DR. HARPER: Thank you.

DR. POGGIO: You'd get the same result if on the left, in the model the dependent variable was gestational age -- anyway, nevermind. I think that's going to confuse the matter. I think you got the answer, so sorry.

DR. WITTEN: Do you have any other questions?

DR. HARPER: That was my question. Thank you.

DR. WITTEN: Thank you.

Next, I'm going to call on Michael Lindsay.

DR. LINDSAY: Yes. Thank you for an excellent presentation, and if you're allowed to do

a third trial, my question is, how confident are you in your 4-to-6 year time frame to conduct the trial?

The reason I asked that question is I thought I heard from CDER yesterday -- and I may be paraphrasing it, but one of the reasons not to consider a trial was that it would take more than a decade or more to do a trial. So how confident are you that you could do the trial in 4 to 6 years?

DR. CHARI: Thank you for that question, Dr. Lindsay. I think we are very confident that it can be done based on the survey results that we've done, both with non-academic sites as well as with the survey that you heard Dr. Blackwell conduct and present earlier today.

I think the big difference between 2011 and today is that there are now a large number of physicians who are no longer as convinced about the efficacy of Makena, and that there's considerable doubt that has been cast with respect to its role in the prevention of recurrent preterm birth, that we believe that there is a return to equipoise, and

our surveys seem to back this up.

But I want to also remark that to the extent that there are any limitations in these feasibility analyses, we are willing to sign up for those study conduct milestones, which would, I think, have some real teeth to them in terms of holding our feet to the fire with respect to that timeline.

DR. LINDSAY: Thank you.

DR. CHARI: I would suggest that the other piece that I want to remark is that, based on our methodology, we're suggesting the study can be done with just 400 subjects, which is a lot different than the 1700 that was recruited for PROLONG.

DR. WITTEN: Thank you.

We're going to go to the session on clarifying questions from Covis to Covis, but before that, I'll just take the chair's prerogative to just ask one final question, which is, we heard some discussion yesterday from CDER, and also from members of the public, about longer term safety concerns, potential safety concerns. I'm just wondering if Covis is thinking of doing anything to

look at these or has any plans in that regard.

DR. CHARI: Yes.

If I could have the backup slide on the proposed observation study. I think it's BU-2.

I'm sorry. This is not CDER's slides. I'm asking our Covis team, and then, Mike, may I have slide share, please?

MR. KAWCZYNSKI: They do have slide share. Your team will work on it. Here it comes.

DR. CHARI: So, Dr. Witten, we really want to have this discussion in much more depth with CDER because I think there are a number of different ways in which one can plan this, and in particular, one can extend the observation time period to include longer term outcomes as well.

As you know, the prior studies have looked at major and minor morbidities and deaths in a 28 or 30-day time frame. The rough concept here is that there are two treatment groups that are being proposed in this. You have 17P-treated mothers that's indicated for the Makena label, and then you've got untreated mothers. I apologize; there's

a typo on that, it should say untreated mothers.

These would be women who are more akin to the observational surveys that have been done by Manuck, et al., who looked at these larger obstetric cohorts and arrived at a clear understanding of what they believe is the week-on-week change in terms of the major and minor morbidities and deaths, as it shows from 28 weeks all the way through full-term.

So the idea here is that for each of these little bins that you see less than 28 weeks -- 28 to 29, 29 to 30 -- we would collect observational data on whatever we believe are the outcomes of interest for babies that are born in that particular window, and those could be short term, and those could potentially also include long-term data. And by establishing that comparison, what we want to show is that there is an equivalence, if you will, between pharmacological prolongation using 17P compared to the spontaneous birth population of untreated mothers. Of course, you have to select out

patients who received other forms of progesterone, et cetera. Then once you show that, or if you don't, and you see any meaningful deviation between those trend lines and the changes of rates, I think that will be a sign that there's something else going on.

One of the reasons we felt comfortable proposing the concept of an observational study to do this is given our ability to perhaps access far more significant sample sizes to be able to probe this answer, but also that this is unlike preterm birth. The association in the healthy population between morbidity and mortality and gestational age at birth is a much more clear, established trend line, both for individual events, as well as in terms of aggregated event rates.

So given all of that body of knowledge, the comparison on a week-on-week basis between these outcomes, and between treated mothers, it seems to us to be a reasonable comparison, and certainly, Dr. Witten, we can design it to include both short-term as well as long-term event rates.

DR. WITTEN: Thank you.

We'll now proceed with clarifying questions by three representatives from Covis. For this portion of the hearing, we'll start with a question from a representative from Covis, and then answer from a different representative from Covis, and proceed accordingly.

Questioners should identify themselves before asking their first question, and if the questioner or answerer wants a specific slide displayed, please identify the slide by slide number.

DR. CHARI: Thank you, Dr. Witten. Becky Wood will moderate this session for us.

Clarifying Questions by Covis

MS. WOOD: Thank you, Dr. Chari.

Becky Wood for Covis. I'd like to ask Dr. Sibai to come up, and the question I'd like to pose to Dr. Sibai is, if Makena were withdrawn from the market, what would you do for your patients? What would be left?

DR. SIBAI: Baha Sibai. Thank you for the

question.

I think there will be three options; doing nothing. And for us as physicians and for the patients, it will be very difficult to sit across from our patient to tell her, "I don't have anything to offer you," yet she's at risk for having a preterm birth at 24 weeks or 26 weeks.

The second option is to put the patient on bed rest, but that has never been shown to be effective. It really takes away the life, the real normal life of a woman. She cannot go to work. She cannot do any house activity, and in essence, really, we made her disabled. The other option is really cerclage.

In my opinion, these are the only three options we'll be left with if Makena is not on the market.

MS. WOOD: Thank you, Dr. Sibai.

I'd like to ask Dr. Sibai a second -- sorry, Becky Wood for Covis. I'd like to ask Dr. Sibai a different question.

Dr. Sibai, could you please comment on the

relationship between gestational age and neonatal outcome? Specifically, does prolonging gestational age result in improved neonatal outcomes. And in answering that, would you kindly comment on CDER's suggestion that pharmacologically prolonging gestational age induces harm, including a toxic uterine environment?

DR. SIBAI: Baha Sibai again.

Dr. Hudak is really the expert in gestational age and neonatal outcome; however, for me as an obstetrician, gestational age matters for the following reason. Gestational age at delivery is an indication whether the baby is going to be admitted to a neonatal intensive care unit. At our institution, and I will say most institutions in the United States, being born at less than 35 weeks gestation means you are going to be admitted to a neonatal intensive care unit by policy and protocol.

The second important thing, the neonatal morbidity, whether it's going to be minimal, moderate, or severe, is dependent on gestational

age at time of delivery. If you are born in a late preterm birth, you will be admitted to the neonatal intensive care unit. The number of days might be limited. However, if you are born at less than 34 weeks, the number of days spent in the neonatal intensive care unit will be markedly increased.

When we push it down to less than 28 and less than 24 weeks, which is really the fetal viability area, then every day matters because babies born at less than 28 weeks have a significantly increased risk for intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, and cerebral palsy. Really bleeding in the brain has serious complications, not to mention necrotizing enterocolitis.

All of these are serious. I have seen babies I delivered myself, where they spend their first year in the neonatal intensive care unit. So should we take this really as something that's minor? For those who are at risk, 24 weeks, I do rounds every day, and when I go back, I have several of them waiting for me on the floor. The

first thing I tell the patient is, "Congratulations. You have gained one more day." For me, getting one day in utero translates to probably a reduction, somewhere about 2 to 3 days, in the neonatal intensive care unit at this early gestational age.

So any gestational age should be considered one of the most important factors in our consideration of whether the baby is going to be born or not.

The next question?

(No response.)

DR. SIBAI: The next question I'm really going to address is, really, prolonging gestation by pharmacologic agent in an environment that's considered hostile and toxic and bad. I'm going to use, really, two examples, which I deal with on a daily basis for sure.

One of them is women who develop severe preeclampsia, now called preeclampsia severe features at gestation less than 32 weeks. I actually conducted a trial. This baby patient had

a very hostile environment. Particularly, in addition to having preeclampsia, they have fetal growth restriction.

May I have slide SI-2, please?

This is a randomized trial I conducted in women who had severe preeclampsia between gestational age 28 and 32 weeks. I want to show you that gaining an average of 2 weeks in utero -- and these patients' pregnancy was prolonged using antihypertensive medications to control blood pressure and continue pregnancy compared to another group, where we gave them steroids and were delivered afterwards.

You can see the rate of respiratory distress syndrome was reduced by more than 50 percent; necrotizing enterocolitis went from 11 to 0; bronchopulmonary dysplasia, from 9 to 12 percent; and intraventricular hemorrhage went from 7 to 2 percent.

Another example that we deal with are women who come with premature rupture of membranes.

Can I have the next slide, please?

Premature rupture of membrane is another one which is considered a hostile environment for the fetus. This is a multicenter randomized trial that was conducted, again, by the Maternal-Fetal Medicine Network. I was part of the group who actually designed this trial, and the lead author was one of my ex-fellows.

In this trial, we randomized patients to give them antibiotics for 7 days versus placebo. You can see that the median time to delivery in the antibiotic group was 6 days versus 2.9 in the placebo. If you look at the composite neonatal outcome, it was significantly reduced in those receiving antibiotics. The rate of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage are also reduced even though they are not statistically significant, but this is very important clinically meaningful information.

This really argues against the notion that pharmacologic prolongation of pregnancy does not lead to improved outcome compared to a group of

women who deliver at similar gestational age. Thank you for your question.

MS. WOOD: Thank you, Dr. Sibai.

I have no further questions. I'd like to turn the podium back over to Dr. Chari.

DR. CHARI: Thank you, Ms. Wood, and thank you, Dr. Sibai.

I'd like to take this opportunity, finally, to thank the presiding officer, thank the advisory committee, as well as CDER, for all of their questions and input today, and look forward to hearing their feedback on the path forward. Thank you again.

Adjournment

DR. WITTEN: Thank you.

Thank you to Covis and to the advisory committee, and members of the public who participated. Day 2 of the hearing is now concluded, and we'll adjourn. We'll reconvene tomorrow, October 19th, at 8:00 a.m. Eastern time.

I don't know, Mike, if you have any special instructions. I ask that the members please take

the time beforehand to log in to make sure we're ready to begin on time. Thank you.

(Whereupon, at 4:02 p.m., the hearing was adjourned.)