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)

Monday, October 17, 2022

8:12 a.m. to 3:24 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

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Department of Gynecology and Obstetrics

Emory University School of Medicine

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Mary B. Munn, MD

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Susan S. Ellenberg, PhD

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Sarah G. Običan, MD

Associate Professor

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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

(8:12 a.m.)

Call to Order

DR. WITTEN: I'd like to welcome everybody to this hearing involving the Obstetrics, Reproductive and Urologic Drugs Advisory Committee. Before we get started, I just want to mention for the media and press that the FDA press contact is April Grant, and her email is currently displayed.

Now we're going to call to order and introduce the members of consultants. As was said, my name is Celia Witten. I'll be the presiding officer for this hearing. I'm now calling to order day 1 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 introductions

I'll turn it over to you, Dr. Choi.

Introduction of Committee

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?

(No response.)

MR. KAWCZYNSKI: Sir, you have your own phone muted.

DR. ALUKAL: Sorry about that.

My name is Dr. Joseph Alukal. I'm a urologist on faculty at Columbia University.

DR. CHOI: Dr. Eisenberg?

DR. EISENBERG: Hi. I'm Esther Eisenberg. I am the program director of Reproductive Medicine and Infertility at the National Institute of Child Health and Human Development.

DR. CHOI: Dr. Fox?

DR. FOX: Hi. I'm Michelle Fox. I'm the non-voting industry representative. I currently work at Merck Pharmaceuticals, and I'm an OB/GYN by training.

DR. CHOI: Dr. Gass?

DR. GASS: Hello? Can you hear me?

DR. CHOI: Yes. Dr. Gass, can you please introduce yourself by stating your name and your affiliation?

DR. GASS: Yes. Dr. Margery Gass, clinical professor emeritus, University of Cincinnati College of Medicine.

DR. CHOI: Thank you.

Dr. Lindsay?

MR. KAWCZYNSKI: I don't think Dr. Lindsay's on right now. We'll have to come back.

DR. CHOI: Thank you.

Dr. Munn?

DR. MUNN: Hey. I'm Mary Munn. I'm a perinatologist and chairman of the Department of OB/GYN at the University of South Alabama.

DR. CHOI: Thank you.

Dr. Shields?

DR. SHIELDS: Hi. I'm Kristine Shields. I'm the community representative.

DR. CHOI: Thank you.

Dr. Caughey?

DR. CAUGHEY: Hi. Good morning. I'm Aaron

Caughey. I'm an OB/GYN at Oregon Health and Science University.

DR. CHOI: Thank you.

Dr. Ellenberg?

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

DR. CHOI: Ms. Ellis?

MS. ELLIS: Hi. I'm Annie Ellis, and I'm serving as a patient representative.

DR. CHOI: Dr. Harper?

DR. HARPER: Good morning. I'm Lorie Harper. I'm in maternal-fetal medicine at the University of Texas at Austin, Dell Medical School.

DR. CHOI: Dr. Henderson?

MR. KAWCZYNSKI: We're still waiting for Dr. Henderson.

DR. CHOI: Dr. Hudak?

DR. HUDAK: Good morning. I'm Mark Hudak. I'm a neonatologist and chair of pediatrics, and chief of neonatology at 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 at the University of South Florida.

DR. CHOI: Dr. McAdams-DeMarco?

DR. McADAMS-DeMARCO: Good morning. I'm Dr. Mara McAdams-DeMarco. I'm an epidemiologist at the New York University Grossman School of Medicine, Department of Surgery and Population Health. I'm also the associate chair of research in surgery. Thank you.

DR. CHOI: Thank you.

Dr. Obican?

DR. OBICAN: Good morning. Sarah Obican at University of South Florida, Maternal-Fetal Medicine.

DR. CHOI: Thank you.

(Pause.)

DR. CHOI: Michael, have the other two

members dialed in?

MR. KAWCZYNSKI: No. Unfortunately, they have not yet arrived.

DR. CHOI: Thank you.

DR. WITTEN: Okay. I think we're ready to start the hearing. Let us know when they arrive. We can have them introduce themselves after the statement.

First, I'm going to read this statement at the beginning of this hearing.

In the spirit of Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the hearing.

We are aware that members of the media are eager to speak with the FDA about these proceedings, however, FDA is observing separation of functions for this matter, so members of my team in the Office of the Commissioner and I may not discuss matters related to the substance of this hearing off the public record until the

commissioner and FDA's chief scientist have issued the final decision for the agency. CDER will also refrain from discussing the details of this hearing with the media until conclusion of the hearing. Also, the committee is reminded to please refrain from discussing the hearing topic during breaks or lunch. Thank you.

Dr. Moon Hee Choi will read the Conflict of Interest Statement.

Dr. Choi?

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration, FDA, Office of the Commissioner is conducting this hearing under 21 CFR 314.530 and 21 CFR Part 15 on the Center of Drug Evaluation and Research's proposal to withdraw accelerated approval of Makena, hydroxyprogesterone caproate injection, 250 milligrams per milliliter. COVIS Pharma Group -- COVIS Pharma Gmbh, COVIS -- is the sponsor of Makena.

As part of the hearing process, the Obstetrics, Reproductive and Urologic Drugs

Advisory Committee will be discussing the available evidence. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws, covered by, but not limited to, those found at 18 U.S.C. Section 208, is being provided to participants in this hearing and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs

his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of this hearing, members and temporary voting members of this committee have been screened for potential financial conflicts or interests of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

The Notice of Hearing for this matter, published in the Federal Register on August 17, 2022, sets forth the issues to be discussed at this hearing, and as speaking, those issues involve whether a confirmatory trial verified the clinical benefit of Makena and whether available evidence

demonstrates that Makena is effective for its approved indication, which is to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The committee will also discuss whether FDA should allow Makena to remain on the market while an appropriate confirmatory study is designed and conducted.

This is a particular matter hearing during which specific matters related to Covis' Makena will be discussed. Based on the agenda for this hearing and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this hearing. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning Makena, the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Michelle Fox is participating in this hearing

as a non-voting industry representative acting on behalf of regulated industry. Dr. Fox's role at this hearing is to represent industry in general and not any particular company. Dr. Fox is employed by Merck Research Laboratories.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise of any financial relationships that they may have with Covis, sponsor of Makena. Thank you.

DR. WITTEN: Thank you.

Before I proceed with my opening statement, my opening remarks, I would like to know whether our other two members have dialed in, and otherwise maybe take a pause for a minute to try to help them get online.

MR. KAWCZYNSKI: We're working at it.

They'll be in, in a few minutes.

DR. WITTEN: Okay. We're just going to take a pause so that they can be here at the outset of the proceedings, so let us know, Mike, when they're both in. Okay?

MR. KAWCZYNSKI: Okay. Thank you.

Dr. Witten, this may take a little time because some of them are having their own individual computer issues or something, so I don't know if you want to just pause the whole hearing.

DR. WITTEN: I think we should pause the hearing until we work it out, unless it seems like it's going to take a very long time.

MR. KAWCZYNSKI: I think this could. What we're going to do is we're going to give them a direct-dial number so they can come in that way right now. Okay?

DR. WITTEN: Okay. Thank you.

MR. KAWCZYNSKI: Dr. Witten, then what we'll do is we'll take an unscheduled 5-minute break. Let's do that so that you want to make sure that they're in here.

At this time, we're going to take a 5-minute break, but we want to make sure our other two members get into the meeting. They're having their own technical issues at home, it does happen, so bear with us.

(Whereupon, at 8:25 a.m., a brief recess was taken.)

FDA Opening Remarks – Celia Witten

DR. WITTEN: Good morning and welcome to this hearing. I'm Dr. Celia Witten, deputy director for the Center for Biologics Evaluation and Research. For this hearing, however, I'm acting in the capacity of the presiding officer.

The agency has decided that the commissioner, Robert Califf, and FDA's chief scientist, Namandje Bumpus, will collaborate on the final decision and render the decision together as co-signatories. As part of the process leading up to that decision, following this meeting, I will issue a written report summarizing the advisory committee's recommendations and advice, and providing my own views on the scientific issues.

The hearing, which will take place over the next three days, has a specific focus and structure. This hearing is about the question of whether Makena should be withdrawn from the market.

Makena was approved to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton preterm births. The approval was granted under accelerated approval. The federal Food, Drug, and Cosmetic Act provides that a drug sponsor may request to expedite the review and approval of a drug intended to treat an unmet need related to a serious or life-threatening disease or condition.

Under the accelerated approval pathway, FDA may grant accelerated approval based on the drug's effect on a surrogate or an intermediate clinical endpoint. FDA's regulations require that accelerated approval be subject to a sponsor's engaging in further study to verify and describe the drug's clinical benefit where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit or of the observed

clinical benefit to the ultimate outcome.

FDA may withdraw approval of the drug approved under this pathway if, among other reasons, the required study fails to verify the predicted effect on irreversible morbidity or mortality, or other clinical benefit; a postmarketing clinical study fails to verify clinical benefit; or other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

Makena's sponsor completed an additional trial, the PROLONG study. On October 5, 2020, CDER proposed withdrawing accelerated approval of Makena and provided Covis with an opportunity to request a hearing on the proposal. In the proposal, CDER cited two grounds for withdrawing approval: the confirmatory study failed to verify clinical benefit of the drug and the evidence does not establish that the drug is effective under its conditions of use. The sponsor requested a hearing on CDER's proposal to withdraw the approval, following the FDA procedures to make this type of

request, and that request for a hearing is why we're here today.

The advisory committee that is present at this hearing is the Obstetrics, Reproductive and Urologic Drugs Advisory Committee, which I sometimes may refer to as the advisory committee or AC. Under FDA regulations, the advisory committee is asked to review the issues involved and provide advice and recommendations to the commissioner of Food and Drugs. On the last day of the hearing, I will ask the advisory committee to discuss and vote on certain questions, which were set out in the Notice of Hearing, announcing this meeting. The questions are as follows. You have it on the slide, and it also was provided to you for this meeting.

Question 1 is for discussion and vote:

Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

Question 2 is also for discussion and vote.

Does the available evidence demonstrate 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?

And the last question, question 3, is a two-part question. The first part is for discussion, and the second part for vote. The discussion question is:

Should FDA allow Makena to remain on the market?

As part of that, you may discuss whether the benefit-risk profile supports retaining the product on the market; and what types of studies could provide confirmatory evidence to verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

Then the voting question is:

Considering your responses to the previous questions, both in the discussions and votes, should FDA allow Makena to remain on the market while an appropriate confirmatory study is designed and conducted?

Covis and CDER are parties to the hearing that is taking place over the next few days. In addition to the presentations and participation by these two parties, there will also be presentations from members of the public who requested time to speak. The Commissioner's and Chief Scientist's decision will be based on the record compiled during the hearing, including the information and evidence presented here; the advice and recommendations of the advisory committee; my report; and the information submitted to the docket.

Today we'll proceed as follows. First, presenters from CDER will explain the reasons for the proposed withdrawal and provide their perspective on the specific questions for the advisory committee that are being asked at this hearing. Following CDER's presentation, representatives from Covis will have an opportunity to ask questions. After that, there will be an opportunity for members of the advisory committee and me to ask questions of CDER, then CDER

representatives will have the opportunity to ask CDER presenters clarifying questions.

Roughly 23 members of the public who requested an opportunity to speak will be provided with an opportunity to make presentations. There will be two groups of speakers today and one group of public speakers tomorrow morning. Following each group of speakers, the members of the AC, representatives of the two parties, and I will have the opportunity to ask questions of those speakers.

On Tuesday, we'll start the day with the third session for public speakers, followed by an opportunity for the AC, Covis, FDA, and me to ask questions of the speakers. After that, there will be a presentation from Covis of why it does not believe the agency should withdraw approval of Makena, and they will provide their perspective on the other questions that are being asked at this hearing.

Following their presentations, representatives from CDER will have an opportunity to ask questions, and after that, an opportunity

for members of the AC and me to ask questions of Covis. Last, Covis' representatives will have the opportunity to ask the Covis presenters clarifying questions.

On Wednesday, both CDER and Covis will have the opportunity to make closing statements. Following that, there will be an opportunity for members of the advisory committee to discuss the issues presented. This will be a public discussion, but only advisory committee members and I will participate in that discussion. The discussion will be followed by a vote by the advisory committee members on the recommendations with respect to the questions I read earlier. All the members of the committee, except the member whose role is to represent the views of industry, may vote.

Following the meeting, as noted previously, I will issue a written report summarizing the advisory committee's recommendations and advice and provide my own views on the scientific issues. Both parties will then have an opportunity to

comment on that report, along with the discussions and presentations today. The docket will remain open to the public until November 3rd if anyone else would like to submit comments on today's presentation or discussion.

The commissioner and chief scientist will consider the advisory committee's recommendations along with the rest of the record and issue a final decision. All the discussions at this hearing are being transcribed, and that transcript will be included as part of the official record of this proceeding. Therefore, comments by the advisory committee members before and after the vote will be reviewed by the FDA decision makers before issuing a final decision on this matter.

Please note that this type of administrative hearing is informal in nature, and the rules of evidence do not apply. That means that the parties may raise issues and make arguments as they see fit without my first determining whether they're relevant. It's the advisory committee's job as experts in their field to listen to the

information, ideas, and arguments presented, and consider what way they should proceed in the context of the overall hearing and the specific discussion and voting questions.

I'd like to thank in advance the advisory committee, members of the public, and representatives of the two parties in this matter for their participation in this hearing.

We're now going to proceed with the affirmative presentation from the Center for Drug Evaluation and Research, and I'll ask that each speaker please introduce yourself before you speak. Thank you, and I'm going to turn it over now to CDER.

CDER Presentation – Patrizia Cavazzoni

DR. CAVAZZONI: Hello. I'm Dr. Patrizia Cavazzoni [inaudible] --

(Pause.)

DR. CAVAZZONI: First, let me share with you how we'll proceed for the next couple of hours. I will give you an overview of my center's case for withdrawing Makena -- given the sound

[connectivity] issues, I'll start again.

Hello. My name is Dr. Patrizia Cavazzoni, and I am the director of FDA's Center for Drug Evaluation and Research. I first want to thank everyone, especially patients, patient groups, clinicians, and the members of the advisory committee, for being here to provide input to the agency to consider regarding whether Makena should be withdrawn.

First, let me share with you how we'll proceed for the next couple of hours. I will give you an overview of my center's case for withdrawing Makena. Next, Ms. Sara Rothman, my colleague in FDA's Office of the Chief Counsel, will provide an overview of the applicable legal framework. After that, Dr. Christina Chang, Laura Lee Johnson, and Christine Nguyen, all of whom have worked on this drug for years, will lay out our case for withdrawal more fully. Finally, Dr. Peter Stein, the director of our Office of New Drugs, will provide some closing remarks. I and the rest of the team will then be happy to address what I'm

sure will be many interesting questions about our presentation.

Preterm birth is a significant public health problem with devastating consequences for children born prematurely, their mothers, and families. Infants born prematurely are at increased risk of neonatal mortality and significant morbidity, as well as long-term physical and developmental impacts.

Preterm birth is a serious problem across the world, but especially in the United States where the rates are unacceptably high, particularly for certain high-risk groups. We once thought Makena was likely to be part of the answer to that problem; unfortunately, we no longer do. Specifically, based on the evidence available today, Makena is not shown to be effective. Its benefit-risk profile is unfavorable, and it should be withdrawn from the market.

In 2011, we approved Makena primarily on the basis of a single trial, the Meis trial, also referred to as Trial 002, conducted a decade

earlier. This trial showed that Makena reduced the risk of preterm birth at less than 37 weeks. It did not, however, directly address the ultimate clinical benefit of interest: whether Makena improves neonatal health outcomes.

We expected that Makena would provide this benefit based on its effect on gestational age at delivery, seen in Trial 002, but we weren't sure. In part, because of the severity of the problem, and the lack of proven alternative treatments, we approved Makena under the accelerated approval pathway, which can allow earlier access to certain treatments for serious or life-threatening conditions.

Consistent with our practice for drugs approved under this pathway, Makena's approval required the sponsor to complete a second trial, the PROLONG trial, also referred to as Trial 003. This trial, which was underway at the time of Makena's approval, would assess whether there is evidence, or not, of Makena's effect on neonatal mortality and morbidity. This trial would also

provide a second assessment of Makena's effect on gestational age at delivery.

Unfortunately, Trial 003, a trial nearly 4 times larger than Trial 002, failed to show any drug effect whatsoever, either on gestational age at delivery or neonatal outcomes, for Makena's indicated population, pregnant women with a prior singleton spontaneous preterm birth. Trial 003 also did not show that Makena was effective for women at higher risk of preterm birth; that is, women with one or more factors associated with an increased risk of preterm birth.

When we took these results to the advisory committee in 2019, back when we were considering next steps after Trial 003 results came in, they agreed with us, by unanimous vote of 16 to 0, that Trial 003 did not verify Makena's expected clinical benefit to neonates. Accordingly, the answer to the first question for this hearing is no; Trial 003 did not verify the clinical benefit we predicted when we approved Makena in 2011.

Regarding Makena's effect on reducing the

risk of recurrent preterm birth, we also carefully examined other available evidence of Makena's potential efficacy that has emerged since Makena's approval, including other randomized-controlled trials in other settings of risk for spontaneous preterm birth, as well as real-world evidence from observational studies, other than Trial 002. None of the other studies showed Makena's efficacy at reducing the risk of preterm birth.

To approve a drug under either the accelerated or traditional pathway, FDA must conclude that substantial evidence supports that the drug is effective for its proposed condition of use. In the case of Makena, at the time of approval, we determined that Trial 002 provided substantial evidence of effectiveness for reducing preterm birth less than 37 weeks, but now Trial 002 appears to be an outlier with both Trial 003 and other relevant studies failing to show that Makena is effective.

If all of the evidence available to us today was available when we were originally considering

the Makena application, we would not have concluded that there was substantial evidence of effectiveness, and we would not have approved the application. Again, the 2019 advisory committee agreed with our assessment, voting 13 to 3 that there is not substantial evidence of effectiveness for Makena's approved use in reducing the risk of recurrent preterm birth.

While this outcome is very disappointing and unexpected, it sometimes happens for drugs under accelerated approval. In fact, this is why our practice is to require another high-quality study to be completed post-approval for drugs approved under this pathway.

There is a risk that any drug FDA approves could later not be shown to be safe and effective, but that risk is higher for drugs under accelerated approval. It is a risk worth taking for certain treatments for serious or life-threatening conditions, especially when there is a lack of available alternative treatments. But where the treatment is no longer shown to be both safe and

effective, and the benefit-risk profile is unfavorable, the approval should be withdrawn.

This is the story of Makena in a nutshell. While there was only one study showing an effect on preterm birth at the time of approval, it appeared at the time that the results of the study, showing a reduction in preterm birth, were reasonably likely to predict clinical benefit to neonates.

Preterm birth was and remains a significant problem for which effective treatments are urgently needed. Unfortunately, in light of the other evidence today, Makena is no longer shown to be effective for its approved indication. In fact, Trial 002 may well have been a false positive; that is, the answer to the second question for the advisory committee is also no. Makena is not shown to be effective for its approved indication.

Here at FDA, it is our responsibility to assure that approved drugs are both safe and effective. Patients, their families, and prescribers expect that the drugs that they take and prescribe have their intended benefits and for

any ill effects associated with those drugs to be worth those expected benefits. In other words, it is important for FDA-approved drugs to have a positive benefit-risk profile.

Allowing Makena to remain on the market would expose pregnant women to serious risks, including blood clots and depression, without any assurance that they and their future children are receiving any benefit at all, much less benefit that outweighs those risks; that is, the answer to the third question for this hearing is also no. Makena's benefit-risk profile is unfavorable and does not support retaining Makena on the market.

That leaves the final question. Should Makena remain on the market while another study is conducted? The answer is no. First, based on the evidence available today, Makena is not shown to be effective for its approved condition of use. While Makena once appeared to be a promising treatment for preterm birth, at this point, Trial 002, the primary basis for Makena's approval, is the outlier among all the relevant studies.

Next, the only way to obtain evidence that could potentially be adequate to demonstrate Makena's effectiveness would be to conduct another randomized, double-blind, placebo-controlled trial. But our experience with Trial 003 shows us that this would be extremely difficult to do in the United States, and certainly could not be done expeditiously while Makena remains on the market.

Trial 003 took almost a decade to complete, and there is no reason to expect that if Makena remains on the market, a shorter time period would elapse before another trial could be completed. This is because it would be extremely challenging to recruit women at risk of preterm birth, particularly women at higher risk to enroll in a trial and risk receiving a placebo when they can guarantee they will receive Makena by not enrolling in such a trial. In contrast, if Makena is withdrawn, a new randomized, placebo-controlled trial could be conducted more quickly.

This is equally true of potentially more promising treatments for preterm birth. As long as

Makena remains on the market, starting any other treatment for this condition in the United States will be more difficult.

You will hear arguments that removing Makena from the market would exacerbate health inequities by depriving women at greatest risk of preterm birth, a group which includes Black women, of the only approved option for reducing that risk; but leaving Makena on the market while waiting for the result of another study would mean that 20 or more years likely would have gone by until another study could potentially show that Makena is effective. And based on the evidence that has emerged since Makena was approved, there is good reason to expect that the next study would likely be negative, just like the first confirmatory study was.

For this entire time, patients would presumably continue to receive Makena. A full course of Makena can entail up to 20 weeks intramuscular injections, subjecting women to serious risks and significant burdens. We believe this is simply not justifiable when it has not been

shown that babies whose mothers received Makena will benefit from Makena. In fact, maintaining Makena's approval potentially worsens the picture for those most at risk because it likely hinders the development of other potentially more promising treatments for preterm birth by making the expeditious gathering of high-quality evidence for those treatments in the United States less feasible. Accordingly, Makena should be withdrawn.

I look forward to a robust discussion of this extremely important issue today and for the remainder of the hearing. Thank you.

CDER Presentation – Sara Rothman

MS. ROTHMAN: Good morning. My name is Sara Rothman, and I'm an attorney in FDA's Office of the Chief Counsel, representing CDER in this proceeding. The purpose of my presentation is to outline the legal framework for CDER's proposal to withdraw approval of Makena. The legal framework here consists of parts of the Federal Food, Drug, and Cosmetic Act, and certain FDA regulations.

Two pathways the FDA uses to approve new

drugs are the traditional approval pathway and the accelerated approval pathway. To be approved by FDA, drugs must be shown to be both safe and effective. Under traditional approval, effectiveness is generally based on an endpoint that is a direct measurement of clinical benefit or on a surrogate endpoint that is validated to predict clinical benefit. Under the accelerated approval pathway, effectiveness can be based on a drug's effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict the drug's clinical benefit.

FDA has required sponsors of an accelerated approval product to conduct a postmarketing study to verify clinical benefit. Both traditional and accelerated approval require substantial evidence of effectiveness for the proposed conditions of use at the time of approval.

The accelerated approval pathway was established approximately 30 years ago, and it has enabled CDER to provide earlier approval of new treatment options for patients with serious or

life-threatening conditions. Accelerated approval can be based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit, rather than a direct measurement of irreversible morbidity, or mortality, or other clinical benefit.

It is important to recognize that because it is based on a prediction rather than on a direct measurement of clinical benefit, accelerated approval is associated with a degree of uncertainty about the predictive value of the endpoint. And as I noted previously, sponsors of drugs approved under the accelerated approval pathway have been required to conduct a postmarketing study to verify clinical benefit. Those studies must be adequate and well controlled.

When considering an application under the accelerated approval pathway, FDA takes into account the severity, rarity, or prevalence of the condition, including whether the proposed indication is for a serious or life-threatening illness, as well as the availability or lack of

alternative treatments, including any evidence of meaningful therapeutic benefit to patients over existing treatments.

Recurrent singleton preterm birth is one such serious condition for which there is an unmet need for a treatment for which clinical benefit has been verified. CDER approved Makena under the accelerated approval pathway based on an effect on an intermediate clinical endpoint -- gestational age of less than 37 weeks -- that was considered reasonably likely to predict clinical benefit to neonates. The approval required the sponsor to conduct an adequate and well-controlled trial designed to verify Makena's predicted clinical benefit to neonates.

The accelerated approval framework is a balance and a trade-off. It provides FDA with a degree of flexibility to give patients with serious or life-threatening diseases access to new therapies sooner, which can be an important public health benefit, but the trade-off for earlier access to drugs is uncertainty about whether the

drug's clinical benefit will be verified in the post-approval or confirmatory studies.

If a drug's confirmatory trial fails to verify its predicted clinical benefit and reveals that a drug's benefit-risk profile is unfavorable, it is important for approval to be withdrawn. Retaining approval of such a drug, even after the legal standard for withdrawal is met and CDER has determined that approval should be withdrawn, would upset the balance of accelerated approval. It would unnecessarily expose patients to the risks associated with drugs that are not shown to be both safe and effective without counterbalancing evidence of benefit. This would undermine the integrity of the accelerated approval framework and the important public health benefits that are associated with this pathway.

In sum, the accelerated approval pathway is a two-way street. The balance of approval and withdrawal are needed to make the program work, and thereby protect patients and the public health.

The law provides authority for FDA to

withdraw and approve drug from the market. The Federal Food, Drug, and Cosmetic Act and FDA regulations authorize the agency to expedite withdrawal of a drug under the accelerated approval framework if at least one of six criteria is met. Two of those criteria are relevant here. One criterion is that a postmarketing clinical study fails to verify clinical benefit. A second criterion is that other evidence demonstrates that the drug is not shown to be safe or effective under its conditions of use. Either one of those is grounds for withdrawal.

As CDER scientists will explain in more detail, both of those independent grounds for withdrawal are present here. Specifically, Makena's confirmatory trial failed to verify the predicted clinical benefit of reducing neonatal morbidity and mortality from complications of preterm birth. In addition, a second independent reason for withdrawal is that based on the available evidence, Makena is no longer shown to be effective at reducing the risk of recurrent

singleton preterm birth.

Importantly, Makena's confirmatory trial both failed to verify the predicted clinical benefit to the neonates and to even show an effect on the intermediate clinical endpoint of gestational age that was the basis of the accelerated approval.

I will close by returning to my slide about the balance of public health interests in the accelerated approval framework. Makena is no longer shown to be effective for its approved indication, and its benefit-risk profile is unfavorable. Retaining approval of such a drug would expose patients to all of the risks associated with Makena but without counterbalancing evidence of benefit, and it would undermine the integrity of an important pathway for FDA to provide patients with earlier access to potentially life-saving treatments. FDA's decision in this matter thus has important public health implications.

The next speaker will be Dr. Christina

Chang. Thank you.

CDER Presentation – Christina Chang

DR. CHANG: Thank you, Ms. Rothman.

Good morning. I am Christina Chang, acting director of CDER's Division of Urology, Obstetrics and Gynecology. I am a board-certified OB/GYN, and my division regulates drugs and biologic products used for obstetric conditions, including preterm birth.

In this presentation, I will cover the background of preterm birth, the basic results of Trials 002 and 003, and I will also discuss the clinical endpoints used to assess efficacy in the Makena clinical program, as well as their clinical relevance.

My presentation will address the first question posed by Dr. Witten. Do the findings from Trial 003 verify the clinical benefit of Makena? And as the evidence will show, CDER's response is no.

As background, preterm birth is defined as birth prior to term or 37 weeks of pregnancy, and

as an OB/GYN, I've witnessed the devastating effects of preterm birth. We recognize that preterm birth is a significant problem for women, their children, their families, their communities, and society at large. Among the approximately 4 million births each year in the United States, about 8 percent of singleton pregnancies end in babies being born early. Preterm birth is the leading cause of neonatal death, and it's a major cause of early childhood mortality and morbidity in the United States.

Babies born preterm are also at immediate risk for concerns such as respiratory problems due to underdeveloped lungs, hemorrhage into the brain, and inflammation of the intestines that require surgery. Being born premature can also result in long-term physical and developmental challenges such as cerebral palsy, debilitating hearing or vision problems, and learning disabilities. As a mother of a child who was born premature and now as an adult has developmental challenges, I am acutely aware that no drug therapies are approved to treat

the adverse outcomes of prematurity.

Why does preterm birth occur? The mechanism and causes underlying preterm birth are poorly. understood and multifactorial. These include factors related to maternal health such as maternal infection or chronic diseases, factors related to overdistension of the uterus, or anatomical weakness in the cervix from trauma or surgery. And because no single entity accounts for the occurrence of preterm birth, developing a treatment for it, has been a challenge. Furthermore, it is sometimes the case that onset of preterm labor is triggered by an unrecognized toxic uterine environment, and we have no robust evidence suggesting that slowing pregnancy with pharmacotherapy improves neonatal outcomes.

Now, I will elaborate on why gestational age at delivery is not necessarily predictive of neonatal outcomes.

In assessing therapies intended to treat the adverse consequences of preterm birth, it's key to recognize that health outcomes in the neonate is

the most relevant measure. When the therapy is supposed to improve health of the neonates, the neonate is who should derive and have directly measurable clinical benefits. Therefore, demonstrating actual improvement in neonatal health is necessary to establish the benefit of a proposed treatment for preterm birth.

With spontaneous preterm birth, the risk of neonatal adverse outcomes generally decreases with increasing gestational age at delivery, but the relationship between the likelihood and the severity of at-birth neonatal outcomes and gestational age at delivery is not linear. The later the gestational age at delivery, the less certain we are that delaying pregnancy improves neonatal outcomes.

While longer natural pregnancies generally correlate with better neonatal outcomes, it's not clear whether this relationship holds true for drug-induced prolongation of pregnancy; that is at a given gestational age, it is not clear that we would have improved neonatal outcomes when using

drug treatment to artificially prolonged pregnancy than allowing spontaneous preterm birth to occur.

With this background, let me turn to the drug product that is the topic of our hearing. Makena, or hydroxyprogesterone caproate, is a progestin. The active ingredient, HPC, was first approved in 1956 for various gynecological indications. In 2011, Makena received approval under the accelerated approval pathway to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

In 2018, we approved a subcutaneous form of Makena as well. The approved dosing regimen calls for Makena injections to be given weekly, starting as early as 16 weeks until the mother reaches either term or delivery; so a woman may receive up to 20 injections during her pregnancy.

Despite the name progestin, the exact mechanism by which Makena reduces the risk of preterm birth is unknown. With Makena, we're using the same dose as that approved for gynecological

conditions in 1956, and this lack of dose finding partly explains why Makena's indicated population is limited to only a very small segment of all women at risk for preterm birth.

Because there are no controlled clinical trials demonstrating a direct clinical benefit, Makena is not approved to specifically improve neonatal mortality and morbidity, even though this is the ultimate goal of therapy. In addition, Makena is not approved to reduce preterm birth in women carrying twins or triplets.

Delving into the data that supported Makena's approval now, the 2011 approval was based primarily on data from one randomized, double-blind, placebo-controlled trial comparing HPC to placebo. This trial was funded by the NIH and conducted by the Maternal-Fetal Medicine Unit, a network of academic hospitals. The primary endpoint evaluated was the proportion of women delivering prior to 37 weeks gestation.

Results of this proof-of-concept trial were published in 2003 in the New England Journal of

Medicine. A treatment effect was shown for a late preterm birth between 35 to 37 weeks gestation. Among women given Makena, 37 percent delivered prior to 37 weeks, while 55 percent of the women given placebo did so. In other words, treatment with Makena reduced the incidence of preterm birth by 18 percent.

At our request, the applicant also provided analyses that assessed as secondary endpoints the proportion of women delivering prior to 35 weeks and prior to 32 weeks. Although these analyses also showed reduction in preterm birth at less than 35 or less than 32 weeks than women treated with Makena, please note that the upper bound of the 95 percent confidence interval for the relative risk is very close to zero -- I'm sorry, very close to 1. In addition, the treatment difference confidence interval is close to zero. These numbers appear in Makena's label in Section 14 and will also be important later in the presentation.

Even though the trial collected information on pregnancy outcomes and clinical events in the

neonates, the trial did not prespecify in the analysis plan the assessment of neonatal outcomes. During the review, CDER requested these analyses be conducted, and therefore the neonatal health endpoints are considered post hoc analyses only.

As shown here, treatment with Makena did not confer any survival benefit by reducing fetal or neonatal deaths. Additionally, treatment with Makena failed to reduce neonatal morbidity, as shown here by the results for the composite neonatal morbidity index.

Although the data from Trial 002 were persuasive, we identified two key issues before granting accelerated approval, and these issues are again very germane today. The first issue pertains to the clinical endpoints assessed in the trial, namely the gestational age at delivery and their clinical relevance. The second issue arises from the fact that the applicant provided data only from one adequate and well-controlled clinical trial to demonstrate substantial evidence of effectiveness. I will address each in turn in more detail.

Issue number 1 is related to the uncertainty we have regarding the clinical relevance of gestational age at delivery. As I've already shown, Makena did not reduce fetal or neonatal loss. Makena also did not improve neonatal outcomes based on the composite neonatal morbidity index. Even though all gestational age-related endpoints were statistically significant, because the results from these endpoints did not correlate with clinical benefit in 002, these gestational age-based endpoints cannot be considered validated endpoints to predict neonatal outcomes.

Turning to issue number 2, which touches on what constitutes substantial evidence of effectiveness, when approving a drug product, we require substantial evidence of effectiveness, showing that the drug is effective for its proposed condition of use. We have generally interpreted substantial evidence of effectiveness as clinically and statistically significant findings from at least two adequate and well-controlled trials. Having at least two adequate and well-controlled

trials ensures independent substantiation of experimental findings and strengthens a conclusion of effectiveness. Conclusions based on two high-quality trials will generally be more reliable than those based on a single trial with persuasive findings.

In the case of Makena, efficacy results came from one adequate and well-controlled trial, and at the time of our review, there were no other sources providing confirmatory evidence that could also substantiate Makena's efficacy, however, there are circumstances in which findings from a well-controlled trial may be sufficient to provide substantial evidence of effectiveness.

We concluded that Trial 002 results did provide substantial evidence of effectiveness based on the primary endpoint of delivery prior to 37 weeks gestation, but it's also important to note that this endpoint of less than 37 weeks was only considered reasonably likely to predict clinical benefit for the neonate, and it's not a validated clinical endpoint. Therefore, as a condition of

accelerated approval, consistent with our practice, we required a confirmatory trial.

We worked with the applicant to develop the study protocol for the confirmatory trial, and discussion for Trial 003 occurred during their second and third review cycles. As in Trial 002, 003 would be a randomized, double-blind, placebo-controlled trial. The protocol ensured that the study population in 003 would meet the same eligibility criteria as in 002 so that both study populations received Makena as currently labeled for its approved use.

Because the approval was based on an endpoint that was only reasonably likely to predict benefit, Trial 003 was designed specifically to verify Makena's clinical benefit. To this end, the trial evaluated two co-primary endpoints, a gestational age-related endpoint and the neonatal outcome endpoint. Both co-primary endpoints would need to be met to reach a conclusion of effectiveness.

In Trial 003, we asked for preterm birth

less than 35 weeks because it is considered more likely to predict clinical benefit than preterm birth less than 37 weeks. We anticipated that recruitment would be difficult and made sure that at least 10 percent of the planned study population had been recruited from U.S. and Canada before granting approval.

As Makena became the standard of care in the U.S., recruitment outside the U.S. became necessary. We did not object to opening up sites outside the U.S. because global clinical programs are the norm in drug development, and also there's no biologically plausible reason to expect women at risk for recurrent preterm birth outside the U.S. would respond to a progestin differently than U.S. women.

Trial 003 took 10 years to complete, in part because enrollment in the U.S. became a challenge after Makena's approval. Before the 2011 approval, the trial was enrolling, on average, 11 participants per month. After approval, enrollment dropped to, on average, 3 participants

per month in the U.S. In all, more than 1700 women from 9 countries participated in the trial, with Russia, Ukraine, and the U.S. as the three highest enrolling countries.

Despite these challenges in enrollment, the U.S. sites still enrolled 391 women, a number that comes close to the 463 women in Trial 002, and although the number of Black women in 003 was not as large as the number of Black women in 002, we had 113 Black women who participated, and that is by no means a small number. Ultimately, 29 percent of the U.S. subgroup in Trial 003 were Black women, therefore it would be inaccurate to say that Black women were not well represented in Trial 003.

Results from Trial 003 became available in 2019 and were extremely disappointing. Not only did treatment with Makena fail to reduce neonatal mortality and morbidity, it also failed to reduce preterm delivery prior to 35 weeks gestational age. Furthermore, there was no difference between Makena and placebo in the secondary endpoints of delivery less than 32 or 37 weeks.

After receiving these results, CDER convened an advisory committee meeting in 2019 to seek input on the path forward. All 16 of the advisory committee panel members concluded that findings from Trial 003 failed to verify the anticipated clinical benefit of Makena on neonatal outcomes from complications of preterm birth. Most of the panel members also concluded that there was no substantial evidence of effectiveness, based on 002 and 003 results.

After a careful review, we agreed with the AC that Trial 003 failed to verify the anticipated clinical benefit, and it also failed to demonstrate the treatment effect on the endpoint that has supported the 2011 approval. The applicant acknowledges these negative results in 2019, and in their briefing materials for this meeting, they stipulated to this fact.

Now, Covis argues that Trial 002 alone could have supported traditional approval, based on the reduction in preterm birth less than 32 or 35 weeks. According to Covis, these are

intermediate clinical endpoints that have been empirically correlated with a reduction in neonatal morbidity and mortality. We disagree, because Covis' argument is incorrect.

First, whether an endpoint is a surrogate or an intermediate clinical endpoint does not determine the approval pathway. The question is whether that endpoint is a direct measure or is known to predict the clinical benefit of the ultimate interest. If it is known to predict the clinical benefit, traditional approval is appropriate. If the endpoint is only reasonably likely to predict clinical benefit, accelerated approval may be available.

In Makena's case, it has not been shown that the drug's effect in reducing the risk of preterm birth less than 35 weeks, or even less than 32 weeks, correlates with improved neonatal outcomes. While longer natural pregnancies generally correlate with better neonatal outcomes, let me say again that it's not clear whether this is true for drug-induced prolongation of pregnancy.

Second, even if these endpoints were known to predict clinical benefit to neonates, the reduction in preterm birth at less than 35 weeks or less than 32 weeks, as shown in 002, was not statistically persuasive enough to provide substantial evidence of effectiveness based on a single trial. Therefore, Trial 002 alone could not have supported traditional approval. In any event, Covis' argument misses the larger picture because the data from Makena's effectiveness are no longer limited to Trial 002 alone.

Today, in light of the negative results from 003 on all endpoints, including gestational age-related endpoints and neonatal outcomes, there are also other negative studies of Makena that will be discussed in the next CDER presentation. It is very clear now that there is no longer substantial evidence of effectiveness for Makena.

Returning to the first question from Dr. Witten, do the findings from Trial 003 verify the clinical benefit? The evidence shows that, no, Trial 002 failed to verify Makena's predicted

clinical benefit.

I will now turn over to my colleague, Dr. Laura Lee Johnson, who will begin by addressing question 2, posed by Dr. Whitten. Thank you.

CDER Presentation – Laura Lee Johnson

DR. JOHNSON: Thank you.

Hello. I'm Dr. Laura Lee Johnson, director of CDER's Division of Biometrics III, and a fellow of the American Statistical Association. I'll provide an overview of the statistical analyses that support CDER's proposal to withdraw approval for Makena. Put more simply, we try to understand is it the drug or Trial 003?

Moving on to question 2 posed to the advisory committee, does the available evidence demonstrate that Makena is effective for its approved indication? Considering the available evidence, Makena is not shown to be effective in reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

This figure shows the published studies and

trials conducted in Makena's labeled population that had a no treatment or placebo control for HPC. Two observational studies that we'll discuss are not in the figure. They did not report relative risk and their results were not statistically significant. We're also not showing the results of an RCT that had product quality issues.

We searched PubMed and clinicaltrials.gov for Makena or HPC studies related to preterm birth or neonatal outcomes, and we looked at all of the studies and trials Covis described in their documents. The details of those searches are in our brief. There are a few other studies in the literature that are not in this figure that we discuss in our brief, but those are usually confounded by their design; for example, there's no control for HPC and, hence, we did not consider that these were able to provide meaningful insight into HPC's effectiveness. We discussed our evaluation of them again in our brief. We did not cherry-pick; we went looking, even for studies that were of questionable design, and we wanted to find

all relevant evidence.

In this figure, you'll see the available randomized, placebo-controlled trials, 002 in red and 003 in black, and in blue, three observational studies. The vertical dashed line is at the null value for a relative risk of preterm delivery. If a confidence interval overlaps this line, then the results are not statistically significant.

As you can see, 002 stands apart from the other available evidence for the indication. When you look at the relative risk reduction of preterm delivery at several gestational age cutoffs, the data do not support that Makena reduces the risk of preterm birth.

These observational studies are done with data from the Medicaid population in Pennsylvania; academic medical centers; people with high recurrent preterm birth rates; people in zip codes with high infant mortality rates; and studies with high proportions of Black women included. Their results align with Trial 003, not 002. This other evidence demonstrates that the product is not

effective under the conditions of use.

We'll discuss a series of subgroup analyses to piece apart the questions about Makena's effect in higher risk pregnancies, then discuss power, regional differences, and the evidence of other studies. Keep in mind that post hoc exploratory subgroup analyses, especially those after the primary and overall results are negative, may be biased, and are therefore for hypothesis-generating purposes.

We have evaluated the hypotheses and assertions put forth by Covis, and few are substantiated. Trial 003 was specifically designed by the sponsor to verify Makena's clinical benefit. It failed to confirm 002, and it also failed to verify clinical benefit.

Covis asserts that Trial 002 shows higher risk women have a better response to Makena, and Trial 003 failed to include this higher risk population. Covis has asserted, using time-to-event analyses, that Black women in Trial 002 experienced a benefit from Makena in

earlier gestational time frames compared to non-Black women. Covis also suggested that Makena may have a more beneficial effect in women who had a prior spontaneous preterm birth before 34 weeks.

These assertions were not supported by their or our time to delivery analyses. Although pregnant Black women are more likely to have a preterm birth, the treatment effect of Makena is not shown to be different for Black or non-Black women, and the same is true for those whose prior spontaneous preterm birth was before 34 weeks.

This figure is from Covis. Drawing inferences from visual differences can be misleading. The results of subgroup analyses are shown in the box at the bottom of this figure. Numerically, Black and non-Black women have relatively similar hazard ratios, and if they were included, similar confidence intervals.

When looking at the p-value for the interaction in Covis' figure, it's not significant, indicating that there's no compelling evidence that the treatment effect varies by race looking at this

time-to-delivery analysis. There's a lot of discussion in the 002 statistical review about the reasons that there could be visual differences, especially at earlier time points for Black women given the earlier gestational ages at randomization and the large proportion of women at one site.

These models depend on how you define time when it starts and ends, and the entire range of what that time is. If you censor or stop the time count at 35 or 28 weeks, earlier than the 37 weeks in this figure, in analysis, you could get different results, and they answer different questions. Although I'm not showing the figure, the interaction interpretation issue is the same for the prior deliveries earlier than 34 weeks, where that p-value for the interaction term was 0.67.

Moving on to 003, there should be an asterisk on prespecified here because only some of these are prespecified. The SAP pre-planned subgroup analyses by race and cervical length, CDER had requested additional analyses, including by

region, and also we would look at gestational age at randomization that was used as the stratification factor for their randomization. The sponsor added more analyses in 2019, the others on this list, to explore post hoc whether the differences in key design aspects of 002 and 003 might clarify some of the divergent efficacy results.

These exploratory subgroup analyses, as they are in most trials, were used to assess consistency of a treatment effect and to start the exploration of differences between 002 and 003. Because only one Black woman was from outside the United States, we could not use region and race in the same model. In addition to the planned Cochran-Mantel-Haenszel, or CMH, subgroup analyses, we used logistic regression and Bayesian shrinkage estimation, an innovative approach to borrow information across subgroups in an attempt to further improve precision.

One other statistical note, the neonatal outcome variable is assessed in a group to find

post-randomization in those that are live births. Because of this, in addition to the analyses presented, CDER ran supplementary analyses, counting miscarriages, stillbirths, and other fetal deaths as having an index event. These results did not lead to different conclusions.

The sponsor's assertion that race played a role in the differences in the efficacy outcomes is not supported by the subgroup analyses. This figure shows that there is no trend for a positive treatment effect. All the lines cross over zero, the null value for a treatment difference. Let me orient you to this figure a bit.

The top black line for each endpoint provides the point estimate and confidence interval for the treatment difference used in all women in Trial 003. The use of risk difference aligns with the table in Section 14 of Makena's label and is generally our preferred metric, given the prevalence of preterm birth, although you will see relative risk as a common metric across many of our slides, and CDER does look at both.

The next line in blue provides a point estimate and confidence interval of the treatment difference using the women in that particular category, using the traditional stratified Cochran-Mantel-Haenszel method. The line below that in red shows the subgroup's estimated difference and the confidence interval using Bayesian shrinkage estimation.

So moving to regions, there was no evidence of differences by region. The U.S. numbers are shown and the complementary subgroups are in your briefing document. We do not see evidence of a differential treatment effect by number of prior spontaneous preterm births.

Covis argues Makena may have an effect in women who have had an earlier spontaneous preterm birth, but as you can see, Trial 003 did not provide compelling evidence of treatment effect in this subgroup. This graph is separating out women who anywhere in their obstetrical history had what appeared to be a qualifying spontaneous preterm birth earlier than 34 weeks.

I also realize we forgot to put on this slide that this subgroup includes 1,041 women in Trial 003. We also ran similar models, categorizing women in the trial by whether they had a spontaneous preterm birth less than 34 weeks within 5 years of randomization if it was their most recent birth and where we removed women who at any time had a full-term birth prior to randomization. No compelling evidence of a treatment effect was seen.

We evaluated groupings of risk factors, so after looking at the different risk factors one by one and not seeing a difference, we conducted additional post hoc analyses to see if the number of risk factors could identify a higher responder group. The blue bars are Makena; the higher bars are worse outcomes. Makena did not perform better in the two or more multiple risk factors group, nor with increasing numbers of risk factors.

We re-ran this with a sixth risk factor, and that includes having that prior spontaneous preterm birth earlier than 34 weeks, given the recent

emphasis on that. Makena still doesn't demonstrate an effect in reducing the risk of neonatal mortality and morbidity. It also is not improving preterm birth at 35 weeks or elsewhere.

This chart has an important message. Even if you have three or more risk factors, that is still not associated with a response to Makena. I forgot to mention, in the CDER models I'm showing today, preterm birth less than 20 weeks delivery, as well, is included. We're counting all deliveries, or births, from the time of randomization in our endpoint.

Now I want to move to the new analyses. A month ago, when CDER was presented with numerous new analyses of 003 in the briefing materials, all using an un-discussed endpoint, while they don't demonstrate Makena's efficacy, they are interesting when considering fewer trials. They are not sufficiently robust, however, to support a change in labeling.

As described in Covis' brief, the new analyses start with the U.S. women in Trial 003 and

further focus on the 294 that had a gestational age at randomization less than 20 weeks. Although we disagreed with their interpretation of the statistical review, after 3 and a half years, in table 3 in Covis' brief, some p-values less than 0.05 emerged from Trial 003, but we can't really call them p-values or interpret them the way we normally would for prespecified analyses. Still, we wanted to see if there's something here.

Remember the observed overall trial effect is null, so the results in tables 3, 8, 9 and 18 in Covis' brief are not controlled for multiplicity and several other points that Covis also caveat; but they didn't mention that that continuous endpoint, analyzed using linear regression, has several concerns, including counting stillbirths and miscarriages the same as live births. Also, a neonate born at 24 weeks might score an 8, as could one born just shy of 28 weeks.

To be clear, CDER has not determined that this is a validated endpoint to predict clinical benefit to the neonate to support traditional

approval, and when considering potential trials, we need to consider that when you probe Covis' models, they also don't appear to be robust.

For example, table 9 in Covis' brief and their slide 83 both use this restricted set from 003, and then show for their newly proposed endpoint subgroups defined by the most recent prior gestational age at delivery and an increase in the number of weeks supposedly gained when using the same variable to make the subgroup, and as a covariate in the model within the subgroup.

Although we questioned the model, we used the code provided to us, and ran the same model using the same subset of the 002 data, and the results are on this slide. They go in the opposite direction. The results across the studies are not robust. While some of the findings in these new analyses may seem compelling, and even sound biologically reasonable as well, we need to be careful about drawing conclusions, and even about hypothesis generation. Some results may replicate, and some will not.

In the end, CDER finds that there's little evidence that higher risk women have a higher response to Makena in 002 or 003, including from post hoc analyses from Covis. A merit indication like Covis proposes is not supported.

Next, we discuss Covis' assertion that 003 lacks power to detect a difference because it was conducted in a lower risk population. First, I want to discuss risk.

In this list of numbers, this is a series of recurrent preterm birth rates from the United States in Trial 003. We estimate the rate of U.S. recurrent birth is between 17 to just over 21 percent, using the CDC data for singleton preterm birth rate and the risk for recurrence reported in the literature. We also include data published from the records of the state of Georgia from 1980s and '90s and the MFMU network.

Looking at the literature Covis provided, we saw a study not on this slide. That study noted a 31.6 recurrent preterm birth rate from 2002 to 2010, a consecutive pregnancy study in Utah. In

blue on this slide are the rates of the recurrent preterm birth in 003, its placebo arm. Those rates are aligned with the expected U.S. rates. The women in 003 were not low risk.

We also compared the distributions of gestational age at prior spontaneous preterm birth deliveries between 002 and 003 to see if women differed on this risk factor. As you can see, the numbers are almost identical. The median, the 50th percentile, is off by a week, 32 weeks in 002, and 33 weeks in 003; so, women in 003 are not low risk. If you think maybe the gestational ages are off for 003, remember, the prior deliveries of 002 happened in the '90s, and many in the '80s and '70s, so if there is an issue, that would impact both trials.

Additionally, the percent of women with a full-term birth, sometimes more than one, after the qualifying pregnancy, it's 22 percent in Trial 002, almost double the rate seen in 003. On this element, women in 003 have been at more, not less, risk of a recurrent preterm birth than women in

Trial 002.

Our brief contains additional facts. The rates of recurrent birth seen in 003 are not low; they are consistent with the rate in the U.S. Makena-indicated population, and the two trials had similar distributions of gestational age as prior spontaneous preterm births. 003 participants had a lower rate of full-term births between the qualifying pregnancy and the trial. There was no compelling evidence that the subgroup analyses for women who had higher numbers of risk factors in 003, that they derived a beneficial effect with Makena.

Next, let's discuss power. Even in the lower than expected -- although clearly reasonable -- event rates of 003, there was power. The number on the left, 21.9 percent, was the rate of preterm births before 37 weeks in the placebo arm of 003. This is the same endpoint used for accelerated approval. For this rate in 003, looking after the fact, there was 90 percent power to evaluate the expected 30 percent relative

reduction in the preterm birth rate.

Trial 003 would still have had sufficient power to detect a 25 percent reduction in the rate of preterm birth. The problem with Trial 003 was not power. A much more plausible explanation is a lack of an effect. 003 had a large sample size and it had precision.

The Trial 003 results rule out preterm birth rate reductions greater than 3 percentage points. What does that lower bound mean? In this population, the chance of Makena reduces preterm birth rates by more than 3 percent is very, very unlikely. I also want to be clear that even with the lower than planned background rate, if there was a treatment effect of a 30 percent relative reduction -- in this case a 6 and a half point drop in preterm birth rates from 21.9 to 15.4 percent -- 003 had plenty of power to detect it.

Next, we see that 003 also reliably rules out not only a 30 percent relative reduction, it reliably rules out half of that, 15 percent, and is

not consistent with a relative risk reduction of more than 12 percent. If there was a 30 percent, or even 25 percent, relative reduction from the observed placebo rate in 003, we should have seen it. There was high power. Also, the trial results do not preclude that Makena potentially increases preterm birth rate, and that would not be out of line with some of the other evidence.

For those of you that prefer a picture, this is a picture of that confidence interval. I'm going to pause here and say that CDER does not support the use of post hoc power estimates because these estimates can be misleading. After a trial is complete, you should look at the confidence interval, however, in an attempt to understand the difference in the findings, we have looked at both.

In conclusion, 003 was well powered and reliably excluded a 12 percent greater relative reduction in week 37 preterm birth rate. This population was not low risk. The preterm birth rate is consistent with the indicated population in Makena. Covis argues that Trial 003 was

underpowered because women in the trial were at lower risk of a preterm birth, and that's not right. It was adequately powered to see a statistically significant reduction with its high sample size and quite a bit of precision to rule out what it was supposed to see for preterm birth less than 37 weeks, by a lot, thanks to the prospective powering of that co-primary endpoint.

Now, Covis asserts that regional differences explain the failure of 003 and that women outside the United States were not properly evaluated and were at lower risk. But as you may remember, there was not an effect in U.S. women or in women outside the United States. In recent tables by Covis, they only found an effect in U.S. women randomized at earlier gestational ages using a new endpoint and model, but the results were not robust.

Now let's discuss gestational age. Covis asserts that the women outside of the United States may have been subject to different methods of determining gestational age for their qualifying pregnancies, and thus the gestational age at

delivery for those pregnancies may have been inaccurate.

Covis suggests that these measurement differences could have resulted in the inclusion of women whose qualifying pregnancies are actually farther along than recorded, but even if that's true in 003, there was no evidence in the women who had their prior spontaneous preterm birth before 34 weeks, which were surely qualifying births; and you don't see response to Makena; and you see nothing that looks like it could be a signal, even at those earlier endpoints.

CDER's assessment is that in the prespecified analyses of Trial 003, there are no observed effects of Makena seen in women in the U.S. or outside the U.S., and if you believe Covis' assertion that there were measurement issues with gestational age that would impact 003, there's no evidence that women who had earlier, prior preterm births had a response in 003.

Covis also asserts that there is other evidence that supports a response to Makena. As

you'll see over the next few slides, the observational trials of HPC indicate that Makena is not effective. While the quality of evidence from the observational studies is not at the same level as RCTs, observational studies can provide additional evidence, and in particular, consistency across studies supports stronger conclusions.

CDER conducted a literature search in PubMed and identified five observational studies. We wanted to know would they support 002 or 003. The studies have varying designs, settings, and data sources, and were consistent with the Trial 003 findings.

Now I'll briefly discuss these studies. There are three cohort studies that attempted to use a more comprehensive confounder control with either propensity scores or a multivariable analysis to evaluate Makena's effectiveness in its indicated population, and they also controlled for a number of important confounders.

These studies represent the strongest observational studies reviewed for this program,

and none demonstrated a significant effect of Makena on preterm birth. The replication of negative results, especially in higher quality recent studies, supports the Trial 003 findings regarding Makena's lack of treatment effect.

Among those studies that use a historical control and program evaluation, the Nelson study was a prospective cohort with a historical control. They also found that the overall rate of recurrent preterm birth for the entire cohort treated with HPC was comparable to the expected rate observed in the historical untreated obstetric population.

Covis emphasized the study by Bastek because it claimed an increase in gestational age at delivery from Makena, specifically among women who did not make it to term, however, many pregnancies do make it to term. Looking at all women in the study, there was no change in gestational delivery age when Makena became standard of care at the institution.

Additionally, the study was unable to capture actual exposure to Makena and other

important patient-level data. There was no accounting for changes over time that could have explained the results.

This study does not support Makena's effectiveness. Neither Nelson nor Bastek are in our forest plot because they did not report relative risk symmetric used in the figure, however, they're also not supportive of 002's findings.

Next, the demographics for these studies; this table shows major characteristics of the study populations in the observational studies. They're all conducted in the United States in different settings and geographic regions. Their data are part of the available evidence, and they do not support Makena.

Looking in studies and trials in the indicated populations, when you look at the relative risk reduction with Makena or HPC compared to placebo, or for the observational studies, no treatment for preterm delivery for the available randomized, placebo-controlled trials in Makena's

labeled population -- 002 in red and 003 in black, and in blue, the observational studies in women eligible to receive Makena -- the data do not support that Makena reduces the risk of preterm birth.

To reiterate, does the available evidence demonstrate 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? The answer to question 2 is no.

Next, I'll briefly go over the results of preterm birth from non-indicated populations. The Price trial, published after the EPPPIC meta-analysis, showed no difference in preterm birth less than 37 weeks or stillbirth. SCAN and PHENIX were both in EPPPIC, and with 002, 003, and PROGFIRST, which had product quality issues, comprises the five singleton pregnancy trials.

SCAN was a randomized, double-blind, placebo-controlled trial that was terminated early due to futility. This trial was done in the same

network as 002 and included approximately 50 percent Black women. PHENIX was an open-label trial that used double the dose of Makena compared to no treatment. The drug was started at later gestational ages compared to other trials, and over 50 percent of the pregnancies were in women who had a prior preterm birth. Price, SCAN, and PHENIX failed to show a treatment effect of HPC on preterm birth in populations distinct from Makena's indicated population.

The EPPPIC authors state the conclusion of beneficial effect in reducing preterm birth less than 34 weeks. Although not statistically significant, the upper bound of the confidence interval is very close to 1, but this result is driven by Trial 002. In short, meta-analysis of the five HPC single gestation trials within EPPPIC did not show a statistically significant finding on the main outcome of delivery prior to 37, 34, or 28 weeks gestation, perinatal death, or serious neonatal complications.

The claim of the treatment effect among

high-risk women, those with a short cervix and prior preterm birth, is not evident. There was a very small subset to draw upon, and approximately 70 percent of that population was treated with a dose twice that of Makena's labeled dose.

EPPPIC also looked at multiple gestation pregnancies. All except PHENIX twins are double-blind, placebo-controlled, randomized trials and use the same dose as Makena, even though some have modifications to the gestational age window to start. While these trials vary, and those pregnancies are not indicated for Makena, the trials individually and summarized do not support an effect of Makena on preterm birth.

In summary, well-conducted observational studies do not show a response to Makena. RCTs in singleton and multigestation pregnancies also did not show a response to HPC.

This is what the evidence looks like without Trial 002. All of the trials we discussed are here, some point estimates to the left favoring Makena, some to the right favoring placebo. All

trials and studies have confidence intervals overlapping the null or firmly favoring placebo.

Now we need to add in 002. Because the world of evidence does include Trial 002, the only trial without negative or null results. Every set of trial results includes this null-dashed line or is on the wrong side of the line, except Trial 002. As you can see, there is no evidence of a consistent effect on gestational age cutpoints.

The studies are done in the United States: patients with more than one previous spontaneous preterm birth; patients living in zip codes with a high infant mortality rate; smokers; studies with high percentages of Black patients; studies that use Medicaid claims; multiple trials in the same U.S. network as Trial 002. There are a lot of randomized, double-blind, placebo-controlled trials here, a lot of real-world data, and a lot of different populations. Trial 003 is not the outlier; the outlier is Trial 002.

In conclusion, looking at all of the available evidence, the response to question 2 is

no. Makena has not been shown to be effective in reducing the rate of recurrent preterm birth for its indicated population, nor for subsets of that population, or for related non-indicated populations. There also has not been a demonstration that Makena confers clinical benefit to the neonates in Trial 002 or 003.

As part of approving a drug, CDER's efficacy review was focused on the RCTs in the to-be-indicated population. In recommending withdrawal beyond the legal grounds, we have looked more broadly for scientific evidence to support Trial 002. We've looked in subgroups, observational studies, and related indications. This is not a tale of two trials. There is a lot of evidence. Covis has put forth a number of assertions to try to explain the difference in findings between 002 and 003. As I've explained, none are supported by the evidence.

Dr. Christine Nguyen will now discuss questions 3 and 4.

CDER Presentation – Christine Nguyen

DR. NGUYEN: Good morning. I'm Christine Nguyen, deputy director for the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine that oversees obstetrics drugs, including Makena. As an obstetrician with family experience of preterm birth, I see the lifelong harm from prematurity, and deeply appreciate the need for safe and effective therapies. In my presentation, I will first respond to questions 3 and 4, before addressing Covis' additional arguments.

Question 3 asks, should FDA allow Makena to remain on the market? Part A asks whether the benefit-risk profile supports retaining the product on the market, and our answer is no.

As you've heard from Dr. Chang's and Dr. Johnson's presentation, Makena has not been shown effective in improving neonatal outcomes and is no longer shown to be effective to reduce the risk of recurrent preterm birth. It is associated with serious adverse reactions, and there are potential safety issues, including intergenerational safety that have yet to be

characterized.

As for all drugs, Makena has risks, and these risks can harm patients. These include reports of thromboembolic events; allergic reactions that can be serious; decreased glucose tolerance that can exacerbate gestational diabetes; fluid retention, worsening maternal conditions such as preeclampsia; and severe depression requiring hospitalization.

As there are hundreds and thousands of women using Makena, these risks are not theoretical; they are real. They happened. And let's not forget the common injection site reactions, which include pain, and swelling, and nodules. This is important, given that a woman may receive up to 20 injections throughout her pregnancy.

We take a lot of care around evaluating a drug's safety before it is approved, but as the Murphy study illustrates, sometimes safety issues may emerge only after approval with longer time horizons to permit the observation at longer term or even intergenerational effects.

After a careful review that considered the study's strengths and important limitations, we concluded the study raised questions of safety meriting further surveillance. Specifically, the study highlights uncertainty regarding the intergenerational safety to children exposed to Makena in the second and third trimesters of pregnancy while fetal development is ongoing.

The study alone would not have been a notable part of the benefit-risk calculus if Makena were effective. But given that Makena's benefit has not been demonstrated, this signal of an intergenerational cancer risk associated with HPC, the active ingredient in Makena, makes the overall benefit-risk balance for Makena even more unfavorable.

So in sum, absent demonstrated effectiveness, using Makena to prevent recurrent preterm birth in pregnant women exposes them only to risks and uncertainty. Thus, the benefit-risk balance is unfavorable, supporting Makena's removal from the market.

Part B of question 3 asks, what type of studies could provide confirmatory evidence to verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth? Our response is only a randomized, double-blind, placebo-controlled trial could do so. It is not possible to conclude or determine Makena's effect without randomization, blinding, and a placebo control. The scientific community would agree that data from the RCT would be the gold standard for causal attribution of a drug's effect.

Inherent limitations of other study designs, including observational studies, preclude their use to obtain robust evidence of Makena's efficacy, which is what we need. As preterm birth is poorly understood, it is difficult, very difficult, to identify ahead of time and control for all potential confounding factors, and these factors could be known and measurable, such as maternal age; known but unmeasured, such as access to care; or completely unknown. And these potential

residual confounding factors can easily be an alternative explanation to Makena for the cause of any improved neonatal outcome seen in studies.

Because Makena is the only currently approved therapy for recurrent preterm birth, patients who are not prescribed the drug will be different from those prescribed Makena. For example, women not prescribed Makena will likely be at lower risk of recurrent preterm birth than those prescribed Makena, and these differences rather than the drug itself may drive efficacy outcomes. And lastly, we have a 1700-subject RCT, well conducted, well designed, that failed to verify Makena's benefit on the neonate that this new trial will need to address.

As you will hear tomorrow, Covis proposes an analysis of observational data to establish the relationship between gestational age and neonatal outcomes in treated versus untreated patients and to validate benefit of weeks gained. Although such data may provide some supportive information, it is unlikely to be able to provide clarity on neonatal

benefits. Both analysis of their proposed endpoint and the attempt to validate the endpoint will be subject to all the confounding factors I've just discussed. Given the failure of the randomized Trial 002 and 003 to show a drug effect on neonatal outcomes, observational studies would not provide clarity to the important clinical questions.

Question 4 asks, should FDA allow Makena to remain on the market while an appropriate confirmatory study is designed and conducted? Our response here is no.

The sponsor has proposed conducting a new RCT entirely or mostly in the United States, and we believe the only way this could be accomplished is to have Makena first be withdrawn. Otherwise, this new trial would face the same recruitment challenges as for Trial 003 after Makena was approved in 2011, and this is particularly true for the new RCT where Covis plans to enroll high-risk patients. The best predictor for timely enrollment of a new trial is a prior experience of a similar trial under similar circumstances, and we already

know what happened in Trial 003, where enrollment in the United States decreased by 70 percent after Makena was approved.

There's no reason for us to think recruitment for a new trial while Makena remains approved would be easier this time around. Both patients and providers will be extremely unlikely to risk having patients be randomized to placebo in an RCT when the patient would be guaranteed treatment with Makena by not enrolling in such a trial.

The sponsor presented survey findings from prescribers in women whom Makena may be used that, according to the sponsor, showed a willingness to recommend and enroll in an RCT as Makena remained approved as opposed to being removed from the market. There was no qualitative work done on these surveys to ensure the participants actually understood the questions asked.

One example is where the providers were asked, "How likely are you to recommend a pregnant patient enroll in a placebo-controlled study,

comparing the efficacy of a product versus placebo, when the product has been approved by FDA?" The critical difference here is, what is it approved for; what indication?

Consider two very different scenarios. In the first scenario, the drug being investigated has been approved for indication X, so there is some available safety information, but it's investigating an unapproved use, Y. In this case the provider may recommend the patient enroll in this trial because there is some safety information, but the investigated use is something that is yet to be answered.

In the second scenario, you have a drug approved for indication X that is being investigated for indication X. In this latter case, why would providers recommend and patients be willing to enroll in an RCT that investigates the same use as the indication already approved, and this will be the case for Makena. Regardless of the questionable validity of the surveys, we already have experienced Trial 003, after Makena

was approved, and no survey could refute such knowledge.

As I will discuss later, Covis proposes to narrow the indicated use or higher risk subgroup. Covis also proposes to conduct a 400-plus person RCT in the same narrow population, and anticipates it will take 4 to 6 years to complete. Aside from the significant challenges in recruitment I just discussed, we note this small sample size is the result of an underestimation of the standard deviation. Our own estimate puts it at a much larger sample size, and such a trial would take at least a decade to complete. Further, on its face, the proposed endpoint of time to delivery will be insufficient at this time to replace direct measurements on neonatal outcomes, so those outcomes will still need to be verified.

Even if such a trial could be conducted with Makena on the market presumably by enrolling largely or entirely outside the United States, it would take at least another decade before results could be available that might possibly alter the

current negative benefit-risk calculus. Given Trial 003 was not completed for almost 10 years, despite careful preemptive planning on our part to ensure that there was adequate recruitment from the U.S. before Makena was approved, and that Covis' sample sizes for other future trials mostly range from 1200 to 3200 subjects, we think the next trial could take at least as long as Trial 003, and most likely longer to complete.

Though prescribers and patients have not had verification of the drug benefit to the neonate for the past decade, and now we concluded Makena is no longer effective for its approved use, keeping Makena on the market while another trial is conducted would mean exposing patients to a drug administered in the second and third trimesters of pregnancy without demonstration of benefit, known risks, and uncertainties for at least another decade, or even longer.

We fully acknowledge the gravity of removing the only therapy approved for recurrent preterm birth, and we don't take this lightly. However, it

is important to proceed to protect patients from being exposed to drugs that are not shown to be effective

Next, I'll address Covis' additional arguments. Covis asserts gestational age of delivery is an intermediate clinical endpoint, and therefore Makena's effect on this endpoint is a direct therapeutic effect justifying traditional approval. Covis has erroneously conflated two very different concepts.

The first concept is the type of endpoints that could be considered under accelerated approval, and these include a surrogate endpoint, which is a biomarker or a marker such as the laboratory measurement, or an intermediate clinical endpoint, which is a measurement of therapeutic effect measured earlier than effect on irreversible morbidity or mortality, or some other clinical benefit of interest.

The second concept is the ability of the endpoint, be it a surrogate or an intermediate clinical endpoint, to predict the clinical benefit

of interest -- in this case, we're talking about neonatal outcomes -- and it is this ability to predict that determines the approval pathway, not the type of endpoint.

In the case of hemoglobin A1c -- that's a validated surrogate endpoint -- it's used to support full approval of anti-diabetic therapies. When an endpoint is only reasonably likely to predict, such as gestational age of delivery, then it will follow the accelerated approval pathway, where there is still a requirement to verify clinical benefit post-approval.

As you will hear tomorrow, Covis asserts that CDER agrees that gestational age at delivery is an intermediate clinical endpoint that is strongly correlated with neonatal health. We do not agree with this position, and I'll explain why next.

Covis asserts that various gestation-related endpoints, including delivery less than 35 weeks, are known to predict neonatal benefit, and by extension can replace efficacy endpoints of

neonatal incomes. I'd like to clarify we have yet to determine any gestation endpoint to be validated at this time. There is sufficient observational evidence indicating a positive correlation, although not necessarily linear, between neonatal outcomes and gestational age of spontaneous delivery, and I emphasize the word "spontaneous" here.

This is not surprising because, in general, for preterm birth, a spontaneously longer gestation generally reflects a healthier pregnancy, and therefore healthier neonates. We cannot assume the same for drug-induced prolongation of pregnancy, and certainly not in the case of Makena. Spontaneous birth is poorly understood, and we do not know what causes the body to go into labor, resulting in preterm birth. It could be due to the reasons I've listed in the slide such as subclinical infection; subclinical uteroplacental insufficiency; fetal reasons; or other reasons where the baby would be more healthy to deliver rather than to remain in utero.

Further, the mechanism of action of Makena is unknown, so it's unclear if a drug is merely keeping the uterus from going into labor despite an adverse in utero environment, or if Makena is exerting a therapeutic effect in the process, leading to preterm birth. In other words, we don't have information demonstrating neonatal outcomes from a drug-induced prolongation of gestation to 32 weeks would be the same as those from a spontaneous preterm delivery at the same gestational age.

Covis asserts Trial 003 had unreliable methods to verify the gestational age of the qualifying preterm birth, and that there was no requirement to date by first trimester ultrasound, and particularly call out Russia and Ukraine. The sponsor did not provide any data to show that there was inaccuracy or show how this systematically impacted the reliability of Trial 003.

In this trial, gestational age of qualifying birth must be documented and cross-checked by neonatal birth weight per protocol, and this

requirement applies to all countries. We note the two treatment groups were balanced in the birth weight of the qualifying preterm birth. There's also no evidence that birth weight of babies from prior preterm birth born to Russian and Ukrainian moms were higher than other countries to indicate these babies were further along in gestation.

Lastly, any reliability issues may be relevant only if they lead to information bias; that is the reliability issues somehow consistently led to an underestimation of the gestational age and, again, Covis has not provided any such information bias. Here, reliability issues, if present, could have led to an under or an overestimation of gestational age.

Importantly, the gestational age of the qualifying preterm birth was a pre-randomization variable, therefore after randomization, any differences known or unknown and any under- or overestimation of gestational age of the qualifying birth are balanced between the two treatment groups regardless of countries.

Prescribers have discretion to exercise their medical judgment to prescribe approved drugs for unapproved uses, known as off-label use, for individual patients when they deem it is medically appropriate, but the prospect that other HPC-containing products could be prescribed off label to reduce the risk of recurrent preterm birth is not the basis to conclude Makena, a drug not shown to be effective, should remain on the market.

We also note Covis' assertion about widespread, off-label use if Makena were to be withdrawn is speculative. It is unclear whether clinicians would engage in off-label prescribing of approved HPC-containing drugs if Makena is withdrawn because of lack of evidence of efficacy.

Covis argues that Makena should remain approved because of the risk associated with compounded drugs containing HPC. HPC may be eligible for compounding provided certain conditions described in the law are met. However, the potential availability or lack of availability of compounded drugs is not the basis to conclude

that Makena should remain approved. The drug should be withdrawn because it met the grounds of withdrawal, and its benefit-risk balance is unfavorable.

Covis asserts that CDER's proposal to withdraw Makena is not consistent with how we have treated other drugs under accelerated approval, and we disagree. CDER's decision about withdrawal of a drug is based on each drug's own merits, and the same holds true for Makena.

The failure of Trial 003 to either exert a clinical benefit or demonstrate a drug effect on an endpoint that was the basis of accelerated approval is decidedly unique. In particular, none of the examples cited by Covis of drug products approved under accelerated approval, for which CDER did not pursue withdrawal, involve a confirmatory trial that failed to demonstrate a drug effect on the endpoint that was the basis of the accelerated approval.

Covis' suggestion that it is rare to withdraw a drug or indications approved under

accelerated approval ignores that many drugs or indications with negative confirmatory trials are voluntarily withdrawn by the sponsor. This slide shows some of those examples.

To highlight one, Iressa was voluntarily withdrawn in 2012 after negative confirmatory trials. Afterwards, the sponsor conducted trials to demonstrate that the drugs worked in subjects who contained a certain genetic mutation in their tumor. Thus, Iressa was approved in 2015 for just this biomarker-selected population.

In the case of Avastin where the sponsor declined to withdraw the breast cancer indication after confirmatory trials failed to verify the clinical benefit and the available evidence demonstrated the drug was no longer safe or effective for the breast cancer use, CDER proposed the withdrawal of this indication, and a hearing just like this one was held. FDA ultimately withdrew the breast cancer indication.

Covis proposes that FDA consider narrowing the drug's indication to high-risk pregnancies, but

there are no bases to do so. As shown in Dr. Johnson's presentation, there is not substantial evidence of effectiveness to support a narrow indication in any identified subgroup of Makena's indicated patient population, including pregnancies associated with certain, or a combination of, risk factors. Also, high risk is ill-defined.

Covis proposes to limit the indication to women with at least one prior preterm birth less than 35 weeks and at least one additional risk factor based on findings from post hoc exploratory analysis, using a new efficacy endpoint. This does not represent persuasive evidence of efficacy for this narrow population.

The law requires substantial evidence of effectiveness for an indication to be approved in a drug label. Thus, Covis' proposal to narrow the indication to a high-risk subgroup is really not an option. If Covis seeks a narrow indication, it will need to conduct future RCTs to provide evidence that clearly demonstrates benefit in a

well-defined population.

And finally, I'd like to address Covis' argument that removing Makena from the market would deepen health disparities and dissuade drug development for preterm birth. We believe Covis has it backwards. Our recommendations to withdraw Makena would protect women at risk for recurrent preterm birth, and especially women at high risk for a drug that not shown to be effective and only has risks and uncertainties.

FDA is committed to advancing health equities, and a critical aspect of that is to ensure Makena is indeed effective for its approved use in patients, and especially in patients with health disparities. Unfortunately, the available evidence does not show Makena is effective in those at high risk for preterm birth, including Black women.

Recall there was no differential treatment effect based on race in both Trials 002 and 003. We recognize the many social determinants of health and other factors tied to health disparities that

impact the risk of preterm birth, but as we presented previously, we cannot identify any that are associated with a consistent treatment effect across 002 and 003, nor any such effect was seen in the published literature that we reviewed.

Failing to withdraw Makena from the market when it is no longer shown to be effective would disregard the burdens associated with Makena therapy. This increases, not decreases, health disparities. Without demonstrated benefits, burdens, including discomfort, uncertainty of treatment, and time, are amplified for those with the least resources. This is a disservice to those most at risk for preterm birth because they are more likely to receive Makena therapy.

Makena requires weekly injection in second and third trimester of pregnancies and also office visits as needed. Retaining Makena's approval requires expenditures or healthcare resources without corresponding benefits to offset those expenditures.

At a time where there's an urgent need to

have therapies for preterm birth, keeping Makena on the market would likely disincentivize research and development because of enrollment challenges into a placebo-controlled trial for new promising therapies. There are also uncertainties in how to approach the trial design of these new therapies for recurrent preterm birth if Makena remains FDA approved for the same indication. This would likely further delay the development of much needed safe and effective therapy for the people in our country who need it the most.

Patients clearly need treatments that work, and this is why it's critical we make decisions based on valid scientific evidence. We understand well the significance of Makena's withdrawal, and we determined this was necessary only after careful and extensive consideration of the available scientific evidence.

Retaining the approval of Makena would be harmful. The unmet need for treatment for preterm does not mean we accept a drug lacking evidence of efficacy and that only exposes patients to risks

and burdens. Doing so does not address health inequities because these risks and burdens are felt most by those with the least resources. Maintaining approval of a drug that has not been shown to be more effective than but is riskier than no treatment would be a disservice to all patients. There's no evidence to indicate the drug works better or at all in Black patients, or those at high risk for preterm birth.

We consider the development of therapies for preterm birth a public health priority, and keeping Makena on the market would likely hinder such development. We hear the voices of patients who are asking for effective therapies, voices that include some of America's most at-risk women, children, and families. Patients want, deserve, and need safe and effective treatment. The public expects FDA-approved drugs on the market to be safe and effective. Each patient is at the core of every decision we make about a drug's approval or withdrawal.

Next, I'd like to turn the presentation to

Dr. Stein for closing remarks. Thank you.

CDER Presentation – Peter Stein

DR. STEIN: Good morning. I'm Dr. Peter Stein, director of the Office of New Drugs in the Center for Drug Evaluation and Research, and my task this morning is to summarize some of the key points from the presentations you've heard from Drs. Chang, Johnson, and Nguyen, and discuss the basis for our recommendation to withdraw Makena from the market.

I want to start with some important points that Dr. Chang discussed earlier. The clinical benefit of relevance, the clinical benefit to be assessed, is improving neonatal outcome. We know that the causes of preterm birth are poorly understood and may be triggered by an unrecognized toxic uterine environment. The risk of poor neonatal outcomes generally decreases with increasing gestational age at delivery.

We don't know whether artificially prolonging pregnancy will result in improved neonatal outcomes. We do think it reasonably

likely that a drug that extends to gestation will improve outcome, but this endpoint is not validated. Validated endpoints are expected to predict the clinical benefit that can support traditional approval.

Now, let me explain a little bit further this important point on this graphic that Dr. Nguyen showed just a little while ago. As I've already noted, later spontaneous delivery has a lower risk of poor neonatal outcomes. On the other hand, when gestation is artificially prolonged with a drug to reach the same gestational age as might occur spontaneously, whether one obtains the same lower risk of poor neonatal outcomes is not known; reasonably likely but not certain.

Trials using a surrogate or other endpoint, based upon natural history or epidemiologic observations, are not always confirmed by interventional trials; that is trials where the surrogate or intermediate endpoint is altered by a drug. Why might there be a difference? This may be because of differences in mechanism in the

spontaneous longer gestation relative to the drug-induced change, or to adverse effects of the drug, or many other explanations.

I'd like to remind you about some of the key points from Trial 002. As you've already heard, this was a proof-of-concept trial in 463 women with a 2 to 1 randomization. The study was positive, it showed a reduction in preterm birth rates, and the result of the 37-week endpoint was sufficiently strong to support approval under accelerated approval. Again, we did not consider these gestational age cutpoints to be validated surrogates, but we considered the 37-week endpoint to be reasonably likely to predict clinical benefit; therefore, to be able to support accelerated approval.

Now, the approval was based upon this single study, and that was reasonable given the serious disease and the unmet need. Applying regulatory flexibility here was reasonable given the data available at that time. Since this was approved with accelerated approval, a subsequent randomized

trial was required to verify that the drug provides clinical benefit, and this of course was Trial 003.

We've heard already Trial 003 failed to confirm the findings from Trial 002. Trial 003 was a multinational trial that included over 1700 women from 9 countries. It was nearly 4 times larger than Trial 002. The highest enrolling countries included Russia, Ukraine, and the U.S., and as you know, most drug development programs are multinational, which is appropriate when there are no expected differences, based upon either clinical practice or on the underlying disease pathobiology, and that's the case here. So, we did not expect a difference by region, and we did not see one, as I'll show you in a moment.

Now, Covis has made a number of assertions. Dr. Johnson outlined these already and provided our perspective about each one of them. First, they stated that high-risk women have a better response to Makena, and Trial 003 failed to sufficiently include this high-risk population. In fact, there's no strong evidence that a subset of women

has a higher risk to Makena in either Trial 002 or 003. Dr. Johnson has already discussed the limitations of the post hoc, non-prespecified analyses from Covis.

Next, Covis asserts that Trial 003 lacked power to detect the difference because it was conducted in a lower risk population, but in fact Trial 003 was well powered, and the population studied in Trial 003 was not, in fact, a low-risk population.

Finally, Covis asserts that regional differences may explain the failure of Trial 003; that women outside of the U.S. were not properly evaluated, were at low risk; in fact, there were no regional differences in response in Trial 003. So let me remind you of a few of these subgroup results.

Here, looking at the Black versus non-Black women in Trial 002, you can see that the responses were not different with the analysis, showing very similar hazard ratios in Black versus non-Black women, and the interaction term, based upon race,

entirely non-significant; looking at region, as on this slide, again, no differences across endpoints in the U.S. relative to the entire study population, whether looking at gestational age or whether looking at neonatal outcomes.

Now, on this slide that Dr. Johnson showed earlier, looking at women with increasing number of risk factors, you can see, looking at neonatal outcome on the left or gestational age at the 35-week cutpoint on the right, there is no difference in response to Makena. No response is seen in lower or in women with more risk factors.

Now, Covis asserts that the rate of preterm birth was low in Trial 003, but in fact the rate seen is very much consistent with the range expected in the indicated population. Here is data from a study from Georgia and based upon CDC estimates, and consistent with other studies in epidemiologic observations. You can see that the rate seen in Trial 003, in bold in blue, is entirely consistent with these rates. In other words, the rate in Trial 003 was not low. This was

not a low-risk population.

Now, I want to come back to a point that Dr. Johnson made earlier; that the study was well powered. Here, looking at the relative risk in Trial 003, and the 95 percent confidence interval around that relative risk, you can see that the interval excludes a greater than 12 percent reduction in occurrence of gestational age below 37 weeks.

Dr. Johnson also discussed with you evidence from other studies outside of Trials 002 and 003. I'll start with reminding you of the information that comes from real-world evidence studies, and as Dr. Johnson mentioned, we rigorously reviewed these studies to identify those that were robust and, particularly, that had an appropriate control.

It's important to note that these real-world evidence studies do have limitations. If appropriately designed and conducted, these can provide relevant information. Indeed, these can serve as supportive evidence in our regulatory decisions and in limited circumstances, and with

very robust studies, even as the primary evidence to support an approval.

A key point to make is that consistency across real-world evidence studies using different databases, populations, and approaches strengthen the conclusions from these studies. Here are three different real-world evidence observational studies that are well designed and included different settings, and populations, and analytic approaches, and all failed to find a significant effect of Makena.

Further, real-world evidence observational studies by Nelson and by Bastek looked within institutional rates before and after the introduction of HPC Makena and found no differences. Neither study found any effect of introducing HPC. There are other real-world evidence studies of HPC, or Makena, but these have substantial limitations.

Now turning to the randomized clinical trials in singleton gestations, there are three trials that are relevant here, a study by Price in

HIV-positive women, the SCAN study, and the PHENIX study in women with short cervix, another risk factor, studying a higher dose of HPC, but none of these studies demonstrated a significant reduction in the rate of preterm birth.

Now, regarding the EPPPIC meta-analysis that Dr. Johnson also touched on, this did not find a statistically significant effect, and this includes Trial 002. If you remove Trial 002 from this analysis, the upper bound of the confidence interval notably increases. Here is data from EPPPIC on multigestational pregnancies, a series of trials that were reviewed, and again there is no effect of Makena. You can see the summary statistics of this large number of trials with relative risks of about 1.0.

Now, this slide that Dr. Johnson also showed you is a bit busy, but I think it summarizes the situation well. There are a wide range of studies in addition to Trials 002 and 003. There are the real-world evidence observational studies, randomized trials in singleton pregnancies, and in

multigestation pregnancies. Trial 002 is the outlier. There is a consistent effect seen across the other trials, some with the hazard ratios a bit to the right, some to the left, but no pattern of consistent response to HPC.

We can conclude that the available evidence does not show that Makena is effective in reducing preterm birth or improving neonatal outcomes. As I've already noted, Trial 003 was nearly 4 times larger than Trial 002. There were no differences across subgroups or risk factors that explain trial differences. For Trial 002, I do note that the rate seen in the placebo group was higher than anticipated, based upon the prior trial done by the same network and based upon other epidemiologic information.

We also have to recall that this was a relatively small trial with a 2-to-1 randomization and, hence, an even smaller placebo group. As I've shown you, other study data do not show evidence of effectiveness. The appropriate conclusion is that Makena has not been shown to be effective in

reducing the rate of preterm birth or in improving neonatal outcomes.

Now, let's turn to risks, which Dr. Nguyen has already discussed with you. The overall safety findings from Trial 002 and 003 did not show substantial imbalances in safety events, however, it's important to recognize that clinical trials, unless really huge, do not exclude rare but clinically highly impactful events such as venous thromboembolism. Even if rare, with widely use of a drug, such events will occur and can be devastating. Risks with Makena include thromboembolic events, allergic reactions, depression, all listed in the labeling, warning, and precaution section, as well as injection site reactions, which are common and can be painful.

I also want to touch on the study by Murphy and colleagues briefly, the study that suggested an increase in the risk of cancer in children of women who had received HPC. Our evaluation of this was that it had important limitations. Certainly, the risk reported by Murphy is not an established risk

of the drug, but our assessment of this study is that it raises a question of long-term safety, meriting further active surveillance, and it points out that there may be long-term risks that are not fully understood, and this has to be a concern, especially when benefit is not established. Makena has risks, and it has not been shown to be effective, and the benefit-risk balance for Makena is therefore unfavorable.

Now, I'd like to turn to the issue of obtaining further evidence for Makena. Covis asserts that another trial could be efficiently conducted with Makena remaining on the market, but the best evidence that this is not a reasonable assertion is the experience with Trial 003. This study took 10 years to complete, with many U.S. patients recruited before Makena was approved, and the rate of recruitment in the U.S. after approval dramatically lower than before approval.

The surveys done by Covis are a distraction. A US-based trial adequately powered would likely require at least a decade to complete. There is no

reason to anticipate a trial duration shorter than seen for Trial 003, and every reason to think it may be longer. If Makena stays on the market, practitioners are left using this drug, exposing patients to the risks and burdens absent evidence of benefit; absent evidence that this drug is more effective than a placebo. With Makena off the market, the study, when following up on some of the hypotheses raised by Covis, can be efficiently conducted, and critical information could be obtained for practitioners and for patients.

Now, I'd like to turn to considering the withdrawal of Makena. As we've already discussed, an accelerated approval comes with some uncertainty. That's why a post-approval study is needed to verify clinical benefit. The accelerated approval pathway includes mechanisms to remove a drug exactly because there is uncertainty at the time of the approval whether the drug provides clinical benefit.

The law provides several criteria for withdrawal of a drug under accelerated approval:

if the postmarketing study fails to verify benefit, or if there is other evidence that the drug is not shown to be effective under its condition of use. For Makena, both of these criteria are met, although either one of them alone is sufficient to support withdrawal of the drug.

I want to come back now to the questions that were posed. With regard to the first question, the answer is clearly no. Do the findings of Trial 003 verify the clinical benefit of Makena on neonatal morbidity and mortality? Clearly, they did not.

As you've heard from Dr. Johnson, and as I reviewed with you, there is not a higher risk subgroup. Trial 003 was nearly 4 times larger, and was well-conducted and fully negative, with a good precision, excluding more than a 12 percent improvement in the 37-week cutpoint for gestational age. Observational studies and other RCTs also failed to find an effect of HPC. The conclusion is that Makena is not shown to be effective. Substantial evidence of effectiveness is lacking.

So with regard to question 2, does the available evidence demonstrate that Makena is effective for its approved indication of reducing the risk of preterm birth in women with a singleton pregnancy or the history of singleton spontaneous preterm birth, the answer is no.

Now, turning to the third question, should FDA allow Makena to remain on the market, I noted already that the statutory criteria are met, but the statute says that FDA "may" withdraw, not must withdraw, the drug. So why are we recommending withdrawal of Makena?

Well, as I've already discussed, the evidence shows that Makena is not shown to be effective from the results of the larger Trial 003, multiple well-designed observational studies, and other randomized clinical trials. Makena has risks and uncertainties, and with Makena off the market, prior experience, the most relevant way of estimating duration of the next trial, tells us that it will take a decade or more to get further information about Makena.

Practitioners are left prescribing a drug not shown to be effective with attendant risks, and burdens, and uncertainties regarding the long-term risks for a decade or more. Retaining Makena on the market hinders further studies of more promising treatments for this important problem. And finally, failure to remove Makena from the market undermines the accelerated approval pathway.

So to summarize, the evidence shows Makena is no longer shown to be effective. Substantial evidence of effectiveness is lacking. Makena has risks and uncertainties regarding risks. With Makena on the market, further information will take a decade or longer, yet with Makena not on the market, further information about the effectiveness can likely be developed more rapidly. Keeping Makena on the market hinders development of other treatments. Moreover, failure to remove Makena undermines the accelerated approval pathway.

Finally, retaining Makena on the market would be a disservice to patients at risk for recurrent preterm birth. Thank you very much.

DR. WITTEN: I'd like to thank CDER for their presentation. It's about time for a break, but prior to the break, I want to turn it over to Michael K to take us off to the break. It will be a 15-minute break. So since it's 10:40 now, we'll go to 10:55.

(Whereupon, at 10:40 a.m., a recess was taken.)

DR. WITTEN: Before we get started with the question and answer sessions, I'd like to turn it over to Moon Choi to introduce the two advisory committee members who joined us shortly after we began.

Dr. Choi?

DR. CHOI: When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Lindsay?

DR. LINDSAY: Dr. Michael Lindsay, Division of Maternal-Fetal Medicine, Emory University, Atlanta, Georgia.

DR. CHOI: Thank you.

Dr. Henderson?

DR. HENDERSON: Cassandra Henderson, maternal-fetal medicine consultant --.

DR. CHOI: Dr. Henderson, you might be muted.

MR. KAWCZYNSKI: We can hear her.

(Pause.)

DR. WITTEN: We did not hear her.

MR. KAWCZYNSKI: Okay. I'll have her do it one more time. She just spoke faintly. We heard it, but I'll let her do it one more time.

DR. HENDERSON: Cassandra Henderson, maternal-fetal medicine consultant at Garden OB/GYN in New York.

DR. WITTEN: Thank you.

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

Questioners should identify themselves before asking their first question. If a

questioner from Covis wishes to ask a question of a specific presenter from CDER, they should so indicate. Once a question has been asked, one or more representatives from CDER will answer the question, and I will also ask the CDER representatives to identify themselves before they provide their answer.

The representatives answering the questions for CDER should indicate when the answer is concluded, if possible, then we'll turn things back to Covis for the next question. If the questioner or answerer wants a specific slide displayed, please let us know the slide number, if possible.

Thank you. I'll turn it over to Covis.

DR. CHARI: Thank you, Dr. Witten.

We appreciate the chance to be here today, and to be able to ask CDER some questions, and we're looking also forward to presenting our views tomorrow.

My name is Raghav Chari. I'm the chief innovation officer of Covis, and I'm here with Dr. Gene Poggio, who's president and chief

biostatistician at Biostatistical Consulting, and Ms. Rebecca Wood, former FDA chief counsel and our outside counsel. We're going to take turns asking some questions today, and Ms. Wood will begin.

Questions for CDER by Covis

MS. WOOD: Thank you, Dr. Chari.

Becky Wood. I know there are several areas of disagreement here, but I would like to begin with some areas where I believe that there is agreement between CDER and Covis. First, I understand that there is agreement that preterm birth is a serious and life-threatening condition, and a significant public health concern with unmet need, so I understand our agreement there.

MS. HUNT: Dr. Nguyen?

DR. NGUYEN: Thank you for that question. Yes, we agree, preterm birth is a serious public health issue.

MS. WOOD: Thank you, Dr. Nguyen.

And further, I understand that there also is agreement that preterm birth disproportionately affects some of our nation's most at-risk women,

children, and families.

Is that correct? We have agreement there?

MS. HUNT: Dr. Nguyen?

DR. NGUYEN: Yes, Black women are at 50 percent higher risk of preterm birth.

MS. WOOD: Thank you, Dr. Nguyen.

And I believe we also have agreement that there are no other FDA-approved therapies for Makena's indication; is that right?

MS. HUNT: Dr. Nguyen?

DR. NGUYEN: Yes, we agree.

MS. WOOD: Thank you. Dr. Nguyen.

And also would like to turn to the legal question. Ms. Rothman, this may be for you.

I understand that CDER also agrees with Covis that the withdrawal authority is discretionary, and that as CDER said in its briefing book, CDER does possess various regulatory options when a confirmatory trial fails to verify clinical benefit; is that right?

MS. HUNT: Ms. Rothman?

MS. ROTHMAN: Under the law, FDA's decision

about withdrawal of Makena is discretionary, but it's important that in this case, CDER believes that Makena should be withdrawn.

MS. WOOD: And we all agree the statute says may withdraw, not must withdraw; is that right?

MS. HUNT: Ms. Rothman?

MS. ROTHMAN: FDA may withdraw approval. That's correct.

MS. WOOD: Thank you, Ms. Rothman.

I'd like to share some slides and ask a couple of questions as well. I'd like to focus first on the Murphy article. We were able to see some internal evaluations of that from a safety perspective, and I want to ask a couple of questions about that.

I saw in CDER's presentation that there was a suggestion that the Murphy article raised questions of safety, meriting further surveillance with respect to intergenerational safety and uncertainty with respect to long-term risk.

If I may have CS-11, please? This is just a reproduction of one of the documents that we

discussed in our briefing book. If I could have slide up, please?

This is CDER's Division of Epidemiology, and it did its own evaluation with respect to Murphy, focusing on the safety question. Do I understand correctly that it concluded, and I quote, "that the Murphy study was not sufficient quality to support regulatory decision making," and further that there was, quote, "insufficient evidence to support regulatory action"?

That was the conclusion of CDER's internal analysis. Am I correct?

MS. HUNT: Captain Moeny, I'll ask you to come to the podium and introduce yourself.

CAPT MOENY: Good morning. Captain Moeny, director of the Division of Epidemiology, in the Office of Surveillance and Epidemiology.

We did conclude that the Murphy study was not strong enough to support regulatory actions such as communications or labeling changes, but that it did raise the potential for intergenerational concerns, and we concluded our

review saying that the results -- that it was an indeterminate safety concern that merited ongoing monitoring.

MS. WOOD: And if I could have CS-12 slide up?

Didn't CDER close its evaluation of the Murphy article, classifying that it's indeterminate? Is that correct? And --

CAPT MOENY: Yes, we --

MS. WOOD: Go ahead. I'm sorry.

CAPT MOENY: Yes, we closed with a recommendation for indeterminate.

MS. WOOD: And if I could have CS-13, please?

This is a copy of CDER's Manual of Policies and Procedures called MAPP, which we addressed in our briefing book. And am I correct that under the MAPP, where there is an indeterminate safety signal, that means a safety signal for which current available information is insufficient to support a causal association between a drug and/or adverse event, and it does not, based on the

current available information or warrants further evaluation?

Is that how the MAPP defines indeterminate safety signal?

MS. HUNT: Captain Moeny?

CAPT MOENY: This is how the MAPP defines the safety signal and consistent with our conclusion for indeterminate, yes.

MS. WOOD: Thank you.

I'd like to see CS-14, please.

And do I understand, then, when you reference ongoing surveillance with respect to the Murphy article, what we're talking about is a PubMed email notification? Is that correct?

MS. HUNT: Captain Moeny?

CAPT MOENY: Yes, we're using automated PubMed searchings consistent with our usual processes within DEPI, yes.

MS. WOOD: And there's no other surveillance with respect to the Murphy study; is that right?

CAPT MOENY: The Murphy study would be also under routine surveillance. The classification for

indeterminate and continued surveillance by DEPI would be this automated PubMed search, looking for epidemiologic studies, but the Division of Pharmacovigilance would still be undertaking routine pharmacovigilance for this product.

MS. WOOD: Just as we do for all potential adverse events for the marketed product, right?

CAPT MOENY: Could you repeat? I couldn't quite hear it in the room.

MS. WOOD: Certainly. Just as we do for all marketed products, we have ongoing pharmacovigilance with respect to adverse events, correct?

CAPT MOENY: Yes, we conduct routine pharmacovigilance for all products to ensure safety.

MS. WOOD: Very good. Thank you so much.

I'd like to ask a separate question.

DR. STEIN: I wonder if I might just chime in. This is Dr. Peter Stein. I'm director of the Office of New Drugs. I just want to add to a comment from Captain Moeny.

As we said in our presentations, we agreed that this is not a definitive finding from the study. The study clearly had limitations, which were nicely outlined in the reviews and I think that you've appropriately pointed to.

We didn't conclude that this was a risk that we could base regulatory actions, such as changing labeling or even removing the drug from the market if the risk was of great enough concern, but we neither dismissed this. And I think what we pointed out is that it raises an uncertainty about intergenerational risk.

The children of women who've been exposed to HPC or Makena during pregnancy, the risk that they face long term has not been well understood, and what we concluded was that this uncertainty had to be considered; not that the risk was determined, not that the risk was established, but simply that this could not be excluded.

And I would add that the benefit-risk with evidence of benefit would have remained favorable, but absent benefit, the risks and uncertainties,

such as the uncertainty raised by the Murphy article, have to be considered, and I think that's the position we're taking. I don't want to suggest that we are communicating that we think this is an established risk; we did not conclude that. We simply concluded that continued surveillance of this indeterminate risk was appropriate.

MS. WOOD: No, understood. Thank you, Dr. Stein.

I'd like to turn to compounding. As CDER notes, if Makena is withdrawn from the market, compounded 17P would still be available.

Do I understand that position correctly?

MS. HUNT: Ms. Rothman?

MS. ROTHMAN: That's not necessarily correct. The answer is that it depends.

MS. WOOD: Is it your position that compounded 17P would still be available in the event that Makena were withdrawn from the market?

MS. HUNT: Ms. Rothman?

MS. ROTHMAN: The Federal Food, Drug, and Cosmetic Act sets forth a number of conditions that

apply to human drug compounding, and whether any drug can be compounded, consistent with the Federal Food, Drug, and Cosmetic Act, specifically the sections that directly apply to human drug compounding, depends on whether the conditions described in those sections are satisfied.

MS. WOOD: So CDER is not ruling out that 17P would remain available by compounding; is that right?

MS. HUNT: Ms. Rothman?

MS. ROTHMAN: Again, it depends --

MS. WOOD: You said it depends on a number of factors. Could you explain how those would apply here?

MS. HUNT: Ms. Rothman?

MS. ROTHMAN: I'm sorry. I didn't quite hear the question.

MS. WOOD: I believe you said whether or not a drug would continue to be available for compounding depends on a number of factors. Could you help us understand how that would apply here, and whether compounded substances [indiscernible]

would in fact be available for marketing, or compounding?

MS. HUNT: Mr. Rothman?

MS. ROTHMAN: Absolutely. There are two provisions of the Act, the Federal Food, Drug, and Cosmetic Act, that specifically addressed human drug compounding, and those were Sections 503A, and the new Section 503B that was added after the enactment of the Drug Quality and Security Act in 2013.

Section 503A describes the conditions that must be met for a human drug product, a compound human drug product, to qualify for certain exemptions from the Federal Food, Drug, and Cosmetic Act, and those are our new drug approval requirements in Section 505, the requirement to label drugs without adequate directions for use in Section 502(f)(1), and current good manufacturing practice requirements in Section 501(a)(2)(B).

Similarly, Section 503B of the Act describes the conditions that must be met for drug products compounded by an outsourcing facility to qualify

for certain exemptions from the FDCA, and those include new drug approval requirements in Section 505 and labeling with adequate directions for use in Section 502(f)(1), but not current good manufacturing practice requirements. Outsourcing facilities remain subject to Section 501(a)(2)(B).

So when we look at Section 503A and 503B, we review a number of conditions to determine whether any given compounded drug is eligible for the exemptions described in those sections. And so I'm not able to speculate on whether any particular compounded drug will be able to be compounded consistent with those conditions unless I see the actual drug that's being looked at.

MS. WOOD: But am I correct that CDER is not claiming that compounding will be prevented if Makena comes off the market? You've not made that determination.

MS. HUNT: Ms. Rothman?

MS. ROTHMAN: Whether 17P or any drug could be compounded depends not only on whether the conditions described in those sections are met, but

also other applicable requirements relating to adulteration, misbranding, and other provisions of the Federal Food, Drug, and Cosmetic Act. So I can't answer that question with certainty without seeing the particular drug product to see whether it meets the conditions described in Section 503A or 503B, whichever is relevant, as well as any other applicable provisions of the Federal Food, Drug, and Cosmetic Act.

MS. WOOD: But I take it, it stands by the statement in its briefing book that 17P may be eligible for compounding, even if Makena is removed from the market; is that right?

MS. HUNT: Ms. Rothman?

MS. ROTHMAN: Currently, 17P may be eligible for compounding if the conditions described in Section 503A or 503B are met, as well as other applicable requirements of the Federal Food, Drug, and Cosmetic Act.

DR. NGUYEN: Hi. This is Dr. Nguyen. If I may have my slide 107 pulled up, please?

So I just want to remind everyone, again,

the lack of compounding or the availability of compounding is not the basis to approve or maintain approval of a drug, especially Makena, when the drug is no longer shown to be effective. So I just want us to be very clear, the issue in front of us today is discussing issues that may impact our decision to withdraw or maintain the approval of Makena, and compounding, although I realize it is of great interest to many, is not a basis in our decision to propose the withdrawal of Makena.

MS. WOOD: Thank you, Dr. Nguyen.

[Inaudible] -- here just on the continued availability, and thank you for your slide acknowledging that 17P may in fact be available for compounding. And we know in practice that it can take years, even if an active ingredient is removed, for compounding to arrive on the do not compound list.

I guess I would ask another question -- just generally, I'd like to focus -- setting aside Makena specifically, has FDA been clear that compounded products generally -- particularly

sterile injectables -- present additional risks as compared to FDA-approved products? For example, we know that 503A pharmacies are not required to follow good manufacturing practices; is that right?

MS. HUNT: Ms. Rothman?

MS. ROTHMAN: Thank you. I'll take your question point-by-point. I'll start out by clarifying that whether a drug compounded by a 503A compounder is exempt from current good manufacturing practices, it depends. So that's not a yes or no answer. And then I'll add that compounded drugs do not undergo premarket review and approval by FDA, so they do not have a finding, a premarket FDA finding, of safety, effectiveness, or manufacturing quality. So for that reason, FDA says that, in general, as a general matter, compounded drugs can present a higher risk to patients than FDA-approved drugs.

I'll note, though, that in the case of Makena, we did review the evidence, and the evidence demonstrates that the drug is no longer shown to be effective for its approved indication.

MS. WOOD: And am I right, we cannot rule out today that compounded 17 would remain available if Makena were removed from the market? Is that right?

MS. HUNT: Ms. Rothman?

MS. ROTHMAN: Again, it depends, and I'd just like to also clarify something in my previous response.

I'd like to just make it clear that outsourcing facilities under Section 503B of the federal Food, Drug, and Cosmetic Act are in fact subject to current good manufacturing practice requirements under Section 501(a)(2)(B) of the Act. But again, it depends whether the conditions set forth in 503A and 503B, as well as other applicable requirements of the Act, are met, to answer any question about whether a particular drug can be compounded.

MS. WOOD: Thank you.

I'll turn it to Dr. Chari for some questions.

DR. STEIN: If I could just, though, add a

comment, I think it is important to note that, as Ms. Rothman mentioned, the quality of drugs that go through NDA review is a point that we have noted as assured, based upon our detailed review both of quality, and safety, and effectiveness. But there is a schema for quality as well for compounding drugs. For example, 503B compounded drugs continue to have a regulatory framework around them with GMP inspections, and there are 503A regulations as well that are intended to provide quality.

So while we certainly do agree that drugs approved through the NDA process are assured quality through our detailed review, we shouldn't give the impression that we're somehow saying that drugs that are compounded under 503A or 503B have no basis for efforts to maintain quality. There are clearly efforts both at the state and through our regulations, and inspections at the 503B level.

DR. CHARI: Thank you. This is Raghav Chari again. I want to focus on a comment that was made in Dr. Stein's closing statements, but also echoed in other parts of your presentation, where you

previously asserted that there is no difference in treatment effect for Blacks versus non-Blacks.

Can we show slide QA-81, please?

So we're trying to reconcile this position, the data you presented in 2019 in your briefing book, which contains the event rates of placebo and Makena for the Meis trial.

This is table 22 from the briefing book, and I want to draw your attention to the highlighted box, which looks at the preterm birth rate in Blacks versus non-Black subjects for preterm birth less than 35 weeks. These data show a 40 percent reduction in an event rate for Blacks, and minimal treatment effect for non-Blacks.

I'd like to get your perspective, and can you help us understand why you're saying that there isn't a difference in this treatment effect?

MS. HUNT: Dr. Johnson?

(Pause.)

MS. HUNT: Mike, Dr. Johnson is our dial-in.

DR. JOHNSON: Great. Thank you.

Thank you for your question. In your

briefing book you were specifically relating the differences using the time-to-delivery analysis. That was a time-to-event analysis. I think that it's very important to consider how you want to analyze the data. And I said that in my discussion, depending on where you want to do a cut -- your slide is at 35 weeks -- you may find differences. I think this is an important aspect as we are considering how to move forward, is to consider where do you draw the line, how do we actually account for time, and that's an important factor.

As I did say before, depending on where you decide to slice it -- and if I remember right, this is probably done -- and I'm having trouble looking at your screen. I believe these are probably Cochran-Mantel-Haenszel analyses, so that again is a different way of actually looking at the data.

I would also call to the attention, thinking about your table 3 in your briefing book, and also your table 18, so table 18, but specifically in 002, and in this much smaller subset where you

would cut it actually before 20 weeks of gestational age at randomization; using your new endpoint, you weren't seeing something that looked significant in Black patients.

So I think this is an important topic for discussion as you're trying to decide how to plan future trials, as we are all trying to decide how to move forward.

DR. CHARI: Thank you.

Certainly just to follow up on that, I'd like to get CDER's clinical perspective on the differences of these reduction rates, particularly because preterm births less than 35 weeks was chosen as one of the co-primary endpoints for the PROLONG study.

MS. HUNT: Dr. Johnson?

DR. JOHNSON: Excuse me. You wanted to know about the co-primary choice of 35 weeks?

DR. CHARI: No. I'm sorry. Let me clarify. I wanted to get a clinical perspective. I understand that you provided a statistical perspective on that view, but I'd like to know what

CDER's thoughts clinically are about whether or not there's a difference in these treatment effects when you particularly look at what was accepted to be a more relevant clinical endpoint for less than 35 weeks versus 37.

MS. HUNT: Dr. Nguyen?

DR. NGUYEN: Thank you for that question. So if I may clarify what you're asking, you're asking what our thoughts are on the treatment effect of Makena on less than 35 weeks or are you asking about less than 35 weeks in general?

DR. CHARI: No. I'm asking about the difference which we see for Blacks versus non-Blacks for less than 35 weeks from a clinician's perspective.

DR. NGUYEN: Right. So let me just take a step back. We do not see a consistent treatment effect in 002 and 003 for Black women for a gestational age, including those delivering less than 35 weeks; so I think that's an important background based on which to discuss this. When we say the race does not confer differential

treatment, what it means is whether or not you're Black or you're not Black, it didn't matter in the treatment effect.

So having sort of laid that background, as I discuss in my slide 102 -- if I may have that up again, please? I'm so sorry; 103. Thank you.

So here, most clinical relevant outcome is neonatal outcomes, and even at less than 35 weeks, although we have a lot of observational data for that outcome at 35 weeks or less, we are still left with major gaps in knowledge when a drug is inducing that prolongation to 35 weeks. So that's where major uncertainty is, and that uncertainty increases as we get further along in gestation.

DR. CHARI: Thank you.

DR. NGUYEN: So when you're asking about clinical relevance, I think that the big gap for us in understanding is what does that translate to when you add drug to it, and what does it look like for the neonate?

DR. CHARI: Thank you. I appreciate that clarification.

I'd like to now spend some time on what you have in slides 84 and 85 in your presentation, where you list all of the different studies that are part of the total evidence.

(Pause.)

DR. CHARI:

Could we have slide 85, please? Slide up. I'm waiting for that slide to present.

Could we have slide up? Thank you.

I'd just like to confirm that none of the following studies, which are really from -- I apologize; it's a little hard to see, but from Price on down, Price, SCAN PHENIX-1, AMPHIA, Briery, Combs-2, Combs-3, PHENIX-2, PROGESTWIN, Caritis, and Rouse, none of these are studying the same indication that Makena's labeled for.

So would you agree that these studies are outside of Makena's labeled indication?

MS. HUNT: Dr. Johnson?

Mike, Dr. Johnson is our remote speaker.

DR. JOHNSON: Yes. As I said in my presentation, from Price down on here are

non-indicated populations.

DR. CHARI: Great. Thank you.

So I'd also like to spend a little bit of time on three observational studies that CDER cites, which we also believe have some methodological flaws and challenges. We heard you note that there were some issues with the Bastek study, and I'd like to just spend a little bit of time going through the three studies you cited, Hakim, Wang, and Massa. So let's start with Hakim.

Could I have the slide up? Could we ask for the ability to screen share? We've got a few slides that we'd like to share. Perfect. Thank you.

I just want to lay this as groundwork, that this appears to be in a very low-risk population. From what we can tell from the demographics in the publication, the percentage of non-white subjects is between 0.26 and 0.28 percent; percentage of the population without a high school degree was 0.07 percent. The unemployment rate was 0.25 percent, and the median income of the study

subjects was in excess of $70.000.

Then further, if we go to the next exhibit, could I have OB-28? Here we go.

This database is comprised of over 1.4 million records, which is sizable, and then they sub-selected about 129,000 patients with two or more pregnancies. In this population, it looks like the incidence rate of spontaneous preterm birth is about 5.7 percent. So overall, just as a general comment, to us it seems like a very low risk population.

But that's really not the main point. We know that there are some other more significant issues with the study. I think for us, at no point in either the main article or the supplemental information is any mention or analysis made of other potential interventions or treatments in these so-called untreated populations, nor do they offer any statistics that may provide a proxy to understand whether that untreated population received any alternative treatments.

From that figure, it looks like the only

exclusions for other therapies are for therapies initiated prior to 16 weeks per that screening table. So I wanted to ask, would you agree that without this information, it would be challenging to interpret the study as a 17P versus placebo comparison?

MS. HUNT: Captain Moeny?

CAPT MOENY: Captain Moeny, Division of Epidemiology. These three studies, inasmuch as they were able to, attempted to replicate the base populations of Trial 002 and 003. In that way, they were seeking to look at other approaches and other aspects, and in different populations, and trying to find whether or not there was efficacy of Makena and, again, as you point out, they did not.

The Hakim study, you correctly note, is in a commercial claims population. Typically, these people are employed, generally tend to be a little healthier than the overall population, and so it's not surprising that this is a slightly different group than a high-risk population that you might be looking for.

DR. CHARI: Thank you for that.

Just to stay on that point a little bit further, there also seems to be missing information on pharmacy claims, so in this study while we know that the 17P subjects received a keypoint [indiscernible] injection, there was no tracking of compliance during the study. And looking at the histograms in the supplement, it looks like a significant proportion of the patients received that first injection after 20 weeks and 6 days.

So again, as a general point, would you agree that compliance information would be essential to ensuring that the comparison was appropriate between the populations?

MS. HUNT: Captain Moeny?

CAPT MOENY: I'm having a bit of trouble understanding you here. The question was whether or not claims data can robustly understand compliance?

DR. CHARI: No. I would say that we see that there's missing compliance information, as well as information that suggests that many

patients receive their first injection well after the label-treatment window, which ends at 20 weeks and 6 days. So generally speaking, do you agree that this kind of compliance information would be essential to ensuring the appropriateness of the comparison?

CAPT MOENY: So in many ways, this reflects the real-world experience of Makena, right? So these are insurance claims that are being billed out in routine patient care. So inasmuch as the real world is messy, yes, there are compliance issues in general practice with people seeking health care, and that is reflected in these claims data.

MS. HUNT: Dr. Johnson, do you have anything to add?

DR. JOHNSON: Yes. Could you please pull up our slide 76? Thank you.

So I do want to re-emphasize that there is a wide set of demographics here, so I understand that you do have some concerns about when the product would have actually been delivered, but this is an

important aspect that we need to consider when we think about the actual use of the product and its indication.

So here you'll see that, in fact, there is a wide setting of information, and some of this information also comes directly from medical records, and you see a wide range of people that have quite a bit of diversity in their race and ethnicity.

So does that help address your questions, and, Dr. Moeny, do you have more to add?

CAPT MOENY: No, Dr. Johnson.

DR. JOHNSON: Thank you.

DR. CHARI: So I'd like to just spend some time next on the Wang article, if I could have that slide, please, OB-29?

Could we please share our screen, please? Great. Thank you.

Again, here we have a very similar issue, which is that the pharmacy claims data indicate that only 50 percent of the subjects in the 17P arm of the study received at least 16 doses of 17P.

And given the label timing of the initiation of therapy, any subject delivering at 37 weeks should receive between 16 and 21 doses. The mean gestational age of the 17P arm was almost 37 weeks; it was 36.9 weeks.

So didn't the authors in this case also acknowledge these individuals did not receive 17P in accordance with the clinical guideline recommendations?

MS. HUNT: Captain Moeny?

CAPT MOENY: I believe the authors did indicate that adherence to therapy was somewhere around 50 percent or so, yes.

DR. CHARI: Yes. Thank you.

Further, also on the Wang article, did it also note about 60 percent of the subjects initiated therapy between weeks -- could I have the next slide, please, OB-32? About 60 percent of the subjects initiated therapy between 16 and 26 weeks, but it's also not clear what proportion actually initiated dosing before 20 weeks and 6 days.

So this is also for us a concern with Wang

that these subjects may not have been dosed in accordance with the labeled dosing, and therefore to draw efficacy conclusions from these data, does that not pose a problem?

MS. HUNT: Captain Moeny?

CAPT MOENY: Again, just to circle back, these are five studies that were conducted in various populations, and in various ways, and using various design methods, right? And they reflect, as best they can measure, the real world evidence of Makena's efficacy or lack thereof, lack of demonstrated efficacy. Wang also has these same issues with compliance and capture what we would see in real-world data from most practice settings, yes.

DR. CHARI: Great. Thank you.

Then a general comment about the use of all of these observational studies; if I could see OB-32, please? Thank you.

I think when you look at the prior birth histories between the populations being compared, they're not very similar, and you can see that in

terms of the percentage of subjects that had a prior spontaneous preterm birth before week 32 in the comparison arm versus the 17P arm, you can also look at the birth weight of prior spontaneous preterm births that resulted in babies weighing less than 1300 grams, where there's significant difference of 27 percent versus 11 percent.

So I think we understand the methodology, and while there was propensity scoring performed to match these, we're particularly reminded about the strong views that CDER itself has expressed about the predictiveness of risk factors, particularly for this endpoint, which is preterm birth, from various discussions we had via email on observational studies about 6 months ago.

Really, a general question is why do you consider this study -- and, frankly, any of the observational studies measuring, particularly, preterm birth as an endpoint -- as appropriate to include in the benefit-risk assessment? And would you agree that, in general, findings from these observational studies are not reliable for preterm

birth as an endpoint?

And I want to be specific about that point, given CDER's previously stated concerns to us about observational studies on that endpoint.

MS. HUNT: Dr. Johnson?

DR. JOHNSON: Yes. May I please ask for CDER slide 73? Thank you.

So I think, in fact, you are making an important point. For example, what we said is that we cannot walk away from the real-world evidence studies. They have a role; that's why we pointed to them. And I really want to point out that, in fact, many of the issues that you are bringing up are some of the reasons that, in fact, we have not agreed with proposals for the observational studies that have come to us.

So I think that it's really important, as we are coming across, trying to confirm the findings of 002 and trying to verify clinical benefit to the neonate, it's really important to have those double-blind, placebo-controlled, randomized trials.

That said, there are a lot of limitations to all studies, but there is a lot of consistency in these five studies, and in fact it's very interesting that all of these observational studies are consistent. So thinking about that, even in light of all of the limitations, that is a consistent finding versus Trial 003, and compared to Trial 003, that's very important.

DR. CHARI: Thank you, Dr. Johnson.

I'd like to just spend a little bit of time on some other factors associated with the comments that were made today. In your briefing book, in your final briefing book on page 54, there's a comment made regarding risk factors for preterm births, "CDER agrees with Covis that the study populations in Trial 002 and 003 differed." And really listening to the discussion today, it appeared that you were making a different point; that you felt that the risks of the two populations were comparable.

MS. HUNT: Dr. Johnson?

DR. JOHNSON: Yes. Thank you. I think it's

important to understand and differentiate a few things here.

Many of the elements that Covis has brought up about what could be different between the two different trials are, in fact, not that different between the two different trials. Also, we have to remember that 002 was a small, proof-of-concept study, so in that sense, there can be perhaps -- because 003 is 4 times the size; there are over 1700 patients, and women in 003, you might have a lower percentage, but in fact even more women that were in all of 002 that are represented that can be looked at.

So it's very important to actually balance and think about what you're looking at and what we need to be looking at. I might turn this over to Dr. Stein as well to provide some additional comments.

DR. STEIN: Thanks, Dr. Johnson, and thank you for the question. Peter Stein, Office of New Drugs.

So again, as Dr. Johnson said, we recognize

that 002 was a positive trial, but it was a small proof-of-concept trial and, again, it was conducted at a limited number of sites. The risk profiles of patients in these studies overlap. Are there differences in the profile? Of course there are some differences, but the proportion of patients who have various risk factors is substantial in 003, and when we look by risk factor, the question is, are women who have more risk factors -- which I think is what you're getting at; were there more women with more risk factors in 002 than 003?

But really, when you look at the analysis that Dr. Johnson presented, and I've repeated showing her slide, when you look at whether those women who had more risk factors -- and there were quite a few of them in 003, with two risk factors or three or more risk factors -- you don't see any pattern to suggest that there is a difference in response to Makena. The response numerically is it goes in actually the opposite direction with increasing number of risk factors; a small numerical difference of course.

So I think while there's a different distribution of risk, there's also a lot of overlap here, and the, I think, important point is that when you look at those who have more risk factors, you're not seeing that all of a sudden there emerges some effect of Makena in 003; in fact, that is not what is observed.

MS. HUNT: Dr. Johnson, do you have anything to add?

DR. JOHNSON: Yes. Could you please bring up my slide 52? I'm sorry; 5-2. Thank you.

I think this is the slide that Dr. Stein was referring to, or one of the slides like it, that he was referring to. When you have thousands of patients, or more than a thousand patients, I should say, you are able to do some more work. So when I mentioned that 5-factor model, those factors were developed with the sponsor prior to the 2019 advisory committee meeting, and then we also looked in the literature, seeing what was different, and as we said, there is that overlap.

So whether it's the 5-factor model, and you

look at two or more risk factors, or moving to this 6-factor model, adding in the element that you all have brought up, which is the prior spontaneous preterm births less than 34 weeks, I think you still see that there is a difficulty; and that, again, as we've said, when you look at populations that are similar to 002, you still maintain seeing that you don't have this effect on the neonate, and I think that's an important part for 003 and 002. And I think there were also significant concerns with 002, and those were described in other briefs.

DR. CHARI: Thank you.

Just out of curiosity, did you ever repeat this analysis for the U.S. subset of Trial 003, or was it just only done in the overall subset?

DR. JOHNSON: We looked at --

MS. HUNT: Dr. Johnson?

DR. JOHNSON: Sorry. Yes, we looked at the overall subset, or overall group I should say.

DR. CHARI: Understood.

I'd like to clarify --

DR. STEIN: If I could just make a point on

that, I think it's really important to look at these descriptive analyses for further information, but I want to step back and just make sure that we recognize that studies are best interpreted by looking at the overall primary endpoint prespecified in the trial. I think that's point number one.

But I think the second point is, I think also the risks of these kinds of subset analyses is that you're dealing with smaller and smaller populations of patients, subpopulations of patients. So I think it's a good point to say if you look even in the overall population, each of these group sizes get smaller; still useful descriptive information. Now imagine taking one subset and then subsidizing that further; you're further attenuating any reasonable descriptive precision in these analyses, particularly when they're not prespecified.

So I think we have to really look with some caution when we're taking subsets of subsets, or even subsets of subsets of subsets. The studies

really need to be looked at based upon their primary endpoint predominantly. Then for hypothesis generating, these kind of post hoc cuts of cuts of cuts can be useful. They may really give us some ideas about further areas of research that we would certainly want to support, but I think drawing conclusions that a drug works based upon subsets of subsets is, I think, really fraught with some risks.

DR. CHARI: Thank you, Dr. Stein.

I want to just go back on a comment that I've heard mentioned several times, that you regard Study 002 -- which was a multicenter trial of academic sites with 463 pregnant women for an orphan indication as a proof-of-concept study, and I'd like to particularly understand, it seems like this is the first time we're hearing this terminology being used with respect to 002.

Have you previously ever characterized a study as a proof of concept?

MS. HUNT: Dr. Stein or Dr. Nguyen?

DR. STEIN: I think what we're talking about

is when one starts off in an endeavor to understand whether a drug might be effective in a population, typically the first study done ordinarily in drug development, we'd call that a phase 2 trial. The term "proof of concept" I think just reflects the fact that it's an initial effort to determine whether there's some evidence or some suggestion of effectiveness, and most typically that would be followed up by two further phase 3 large adequate and well-controlled trials to establish effectiveness and to better evaluate safety.

In this instance, the result of Trial 002 in this serious disease with unmet need, recognizing that it is a smaller trial, proof of concept -- you can describe it any way you want -- it's a smaller initial trial to, I think, evaluate a very worthwhile question as to whether hydroxyprogesterone caproate was effective. It had limitations, but it certainly came up with data that was certainly promising.

I might point out that even though it was approved based upon using accelerated approval and

based upon this single study, it was really reflective of I think what we, I think, term "regulatory flexibility," meaning that we accept some uncertainty because a single trial here was used to establish substantial evidence of effectiveness, whereas typically, again, the scientific method suggests the need for confirmation, which is why we require typically two adequate and well-controlled trials. But in a serious disease with unmet need, I think it was quite appropriate back then to exercise regulatory flexibility, take the single smaller trial, and use it to support accelerated approval.

But the term "proof of concept" I think just introduces the concept, this is the first trial that was done to assess whether this drug might provide benefit and, again, that's what we had back then, and now we have a much larger data set, Trial 003, and real-world evidence information, and other randomized clinical trials that have been done subsequently.

So I think the term -- I don't want to get

too lost in the term -- is an initial effort to assess an important research question. I think that's how we're characterizing it.

DR. CHARI: Thank you.

MS. HUNT: Dr. Nguyen, do you have anything to add?

DR. NGUYEN: I would. And I think just to drive home Dr. Stein's comment on regulatory flexibility, recognize this trial was started in 1999 using a primary efficacy endpoint, gestational age and delivery of less than 37 weeks, at a time where, really, there was not evidence to show that this endpoint was even perhaps adequate to reasonably likely predict neonatal outcomes, and the neonatal outcomes that were collected really were not even prespecified in the hierarchy of statistical testing.

So we approved this drug in 2011, but realized that, indeed, we had to use regulatory flexibility to address this area of unmet need. Thank you.

DR. CHARI: Thank you.

Just by way of comment, from our perspective, the reason we don't view it as a proof-of-concept study was there were prior studies that were done, which is what led to the selection of the dose 250 milligrams.

I'd like to just quickly touch on the EPPPIC study analysis that did, and really a quick question here. When you ran the analysis of the EPPPIC studies and looked at the confidence intervals, did you also run the analysis where you excluded the trials that were outside of Makena's labeled indication; that's particularly excluding SCAN PROGFIRST, and PHENIX --

(Crosstalk.)

MS. HUNT: Dr. Levenson?

DR. CHARI: -- upper bounds of the confidence intervals?

MS. HUNT: Dr. Levenson, please introduce yourself.

DR. LEVENSON: Sure. My name is Mark Levenson, Office of Biostatistics.

Could you repeat the question again, please?

DR. CHARI: Yes. When you ran the analysis of the EPPPIC study, did you run the analysis also excluding the studies that were outside of Makena's labeled indication -- I think the three of them, SCAN, PROGFIRST, PHENIX -- and if so, what did you find with respect to the upper bounds of the confidence intervals?

DR. LEVENSON: I don't have that figure on me, but as you point out, of the five trials for the singleton EPPPIC study, only Trial 002 and 003 are within Makena's indicated population, and I think we've heard a lot about the individual characteristics and strengths or weaknesses of those studies. Thank you.

MS. HUNT: Dr. Johnson, do have anything to add?

DR. JOHNSON: Actually, I am looking. Could you please -- actually, no, I don't believe we have anything else to add. Thank you.

DR. CHARI: Thank you for that.

Then coming back to the question that was highlighted a few times around the potential

unknowns associated with prolongation of gestation, does CDER have any evidence that artificially prolonging gestation in the setting of spontaneous preterm birth can result in poor neonatal outcomes?

MS. HUNT: Dr. Nguyen?

DR. NGUYEN: Thank you for asking that question. I actually would like to answer that question in two parts. There is the efficacy part and there is the validation part, and I think your question is perhaps addressing the latter.

With efficacy, what we're trying to see is, let's assume a drug prolongs the gestation from 31 to 32 weeks, and if there is positive efficacy, we expect those delivering at 32 weeks on the drug, we expect the neonates to be healthier than the neonates delivering at 31 weeks on placebo. So that's efficacy.

Regarding validation, we are looking at drug-induced prolongation at 32 weeks, giving us babies that look just as healthy babies delivering at 32 weeks from spontaneous preterm birth. And if we see that, then from a very basic principle, we

can then rely on less than 32 weeks as a validated endpoint and could replace neonatal outcomes as an efficacy measurement.

So it's not like we're looking for worse, right? We're looking for validated endpoints, and for efficacy, we want to see improvement.

DR. CHARI: Understood. Thank you for that clarification, Dr. Nguyen.

I'd like to bring up Gene Poggio, who is our consultant biostatistician, who has one or two questions in addition to add in the remaining time we have.

DR. POGGIO: Thank you, Dr. Chari.

Gene Poggio. I really just had one question. Dr. Johnson took issue with Covis' claim about 003 being conducted in a lower risk population, and for us, perhaps, maybe one of the best summary measures of risk is the preterm birth rates in the placebo population.

So if we compare the preterm birth rates in placebo arms only, between Meis and PROLONG, for preterm births less than 37 weeks, it's a

55 percent rate in Meis as compared to a 22 percent in PROLONG, and this is PROLONG overall; and for less than 35 weeks, it's 31 percent in Meis compared to 11 percent in PROLONG; and for less than 32 weeks, it's 20 percent in Meis as compared to only 5 percent in PROLONG. Thus, we have differences on the order of 2.5 to 4 times higher rates in Meis.

So based on these rates, would you agree that Meis represented a population of patients who were at much higher risk than patients in PROLONG?

MS. HUNT: Dr. Johnson?

DR. JOHNSON: Can you please pull up my slide 59? Thank you.

I think it's important for us to understand the Meis placebo rates as well. Now, this is a list looking at 37 weeks, not 35 weeks, but when you look at the literature, you also see some similarities, and this is something that we can pull up as well.

I think it's important to understand and to question that placebo rate, and it's interesting

that you bring it up because it was a point that was discussed thoroughly at the 2006 advisory committee and it's been discussed in the reviews. So yes, you might have a lot of very different information, but I do question -- especially since I think Black women in Georgia with a prior spontaneous preterm birth less than 32 weeks is probably a fairly high-risk number that we would be looking at.

So we do need to consider if the number that was seen in Meis, how relevant it would be for today, and especially today where we've had the Affordable Care Act. We've had a lot of other things that have happened in health care to understand what may or may not be relevant to the women who would be potentially taking this product today.

DR. POGGIO: Thank you.

DR. WITTEN: I think there's time for one more question if Makena has one.

DR. CHARI: Yes.

DR. WITTEN: You're getting to your time.

DR. CHARI: Yes, just one last question here. You show the evocative visual of a balance with benefit and risk, showing that the balance for this product has moved more in the risk dimension than the benefit side. But specifically coming to a population that we're going to spend a fair bit of time tomorrow discussing, which is a high-risk population with multiple risk factors for preterm births, I'd like to understand your view on the following, which is that the additional studies that you listed in that slide 85 of yours really don't apply to the population. The observational studies, as we've discussed, have issues and also apply to lower risk populations.

Is it still your view that when you look at just the high-risk population, that any of these other studies have bearings, or can we agree that the way to judge them is to really look at the data just for PROLONG and Meis; that is Study 002 and 003?

MS. HUNT: Dr. Johnson?

DR. JOHNSON: We believe it's important to

look at all of the evidence as we have presented here today, and I'm going to turn this over also to my colleague, Dr. Stein.

DR. STEIN: Yes. I would underline what Dr. Johnson said, and I do agree with you that the most relevant information is going to be in the indicated population, so that would be the first place to go, looking at other studies.

On the other hand, I think when we're looking at other risk situations, other situations where women are at increased risk of preterm birth in singleton pregnancies, in multigestation pregnancies, what we're looking for is a signal to see if the pharmacology that was observed in 002 is supported; so it's not like the indicated population suggests that's the only possible place to look for pharmacology.

Now, would we make a strong conclusion absent 003 that those studies would preclude potential benefit in the indicated population? Well, of course not. What we're saying is here is 003 showing absolutely no lean for benefit in the

primary endpoint, and now we're looking at studies across multiple different populations of women at increased risk, and asking the question, do we see pharmacology relevant that suggests that there is effect of this drug in related risk populations, and the answer is no.

So while I perfectly agree with the underlying tenet of your question, what is the right population to extract the most robust information about the effect in the indicated population, well, of course it's in studies that are of the indicated population or subsets thereof. But I wouldn't say we would just throw out, in populations, other women at risk of preterm birth when we're asking the question does the pharmacology that we might expect to apply, apply; and the answer is clearly no.

So I think we've pointed in the real-world evidence studies these other randomized clinical trials are supportive or, I think, useful information. They certainly aren't definitive in precluding a benefit, but I think when you're

looking at a 003, a study 4 times larger than the 002, and then this whole number of randomized trials in women at risk and in real-world evidence use of the drug, when we're seeing no signal for effectiveness, we think that is useful supportive information, but I'm not disagreeing with the underlying tenet of your question.

MS. HUNT: Dr. Johnson, anything to add?

DR. JOHNSON: I do also want to remind that question 2 is about the indicated population, and we did decide, as I mentioned in my discussion, to go beyond that as well. And when you look at the underlying preterm birth rates in many of these populations that you see in the observational studies, you're going to actually see that they're -- what we would call a placebo or no treatment rates -- are in fact aligned with what you see in 003, not with 002, as well.

DR. CHARI: Thank you for that, and I'd like to really thank CDER for their time in answering our questions. We have no further questions and look forward to our discussions tomorrow as well.

Questions for CDER by the

Presiding Officer and Advisory Committee

DR. WITTEN: I'd like to thank CDER and Covis for this question and answer session, and we're now going to proceed with questions for the Center for Drug Evaluation and Research by the advisory committee members, including the temporary advisory committee members and me.

So I'd like to ask the advisory committee members to please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking it 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 can.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. And lastly, 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.

So I'd like to start by calling on Dr. Cassandra Henderson.

DR. HENDERSON: Thank you very much. I have questions, a couple of them. One, might we see a slide outlining the risks that were disclosed or discussed? Certainly we don't have the intergenerational list, but certainly blood clots, depression, injection site; is there a slide that summarizes those across the studies? Thank you very much.

DR. WITTEN: I wasn't able to hear that question.

Was CDER able to? Is there someone who can repeat the question?

MR. KAWCZYNSKI: Yes. Can you repeat it? I turned your volume up, ma'am.

DR. HENDERSON: Okay. Sorry.

Yes. I have just three questions; well, it's one question containing three things.

One, might we see a summary of the risks that have been documented? Obviously, we don't have the intergenerational risk, but perhaps a

blood clot, depression, ingestion, thromboembolism, I heard. Is there a list to actually look at the documented risks that we have seen? Thank you very much.

MS. HUNT: Could I ask you to please repeat the end of the question, which was hard to hear in the room?

DR. HENDERSON: Should I try it again? Is this louder? Yes?

MS. HUNT: Yes. Thank you.

DR. HENDERSON: Okay. Alright. Sorry.

I have a question that has three components. Is there a slide, or can we see the summary of the documented risks that have been reported with Makena? So specifically depression, we heard thromboembolism, injection site. Obviously, we don't have the intergenerational data, but is there any summary of the documented risks that have been reported? Thank you very much.

MS. HUNT: Captain Moeny?

DR. NGUYEN: I'm sorry.

Dr. Henderson, I think you are asking for a

slide showing the risks that appear in our drug label; is that correct

DR. HENDERSON: Yes.

DR. NGUYEN: Okay. May I have slide 92, please?

Is this the slide you are asking for?

DR. HENDERSON: Yes. Do we have any incidence of these occurrences. Out of the hundreds of thousands of women who've taken --

DR. NGUYEN: Sure.

(Crosstalk.)

DR. HENDERSON: -- I don't know if it's in the drug label, but I know it was presented today in the presentations.

DR. NGUYEN: Sure. Thank you for that question. I certainly can start.

The warnings that you see there are the ones that are in our drug-approved labeling, and we certainly have cases of thromboembolic events. We have some observational data to indicate that these risks were certainly seen with injectable, Depo, medroxyprogesterone acetate, which you know is

another injectable progestin.

So we do have cases of that, but do recognize that we are dealing with a relatively healthy population, so we won't really have precise incidence numbers for something that is as infrequent as a VTE event in this population. Granted, I understand pregnant women are at high risk for VTEs, but they're still healthier than the older population.

As far as the allergic reaction, we certainly have those cases, and it certainly is consistent with what we know for most drugs; somebody's going to be allergic to something, so that is a real risk. Regarding decreased glucose tolerance, we certainly have seen this in women who have used Makena. We certainly have seen this in women who have used other progestins, and the same with fluid retention, and depression and its association with progestin is a pretty well-known established association, and the injection site reactions, those numbers came from controlled clinical trials.

So a lot of the incidences that we can really spell out in our drug label come from control clinical trial databases.

DR. HENDERSON: Thank you very much.

DR. WITTEN: Thank you.

Did you have other questions, Dr. Henderson?

DR. HENDERSON: I do not. Thank you.

DR. WITTEN: Okay. We'll move on to Dr. Hudak.

DR. HUDAK: Yes. Good afternoon. I have a couple questions, but I'd like to verify my understanding thus far of the issue.

My understanding, based on the presentation, is that Trial 002 succeeded in warranting this interim approval, or accelerated approval, based on the fact that it showed a reduction in preterm births associated with the Makena therapy, although the preferred outcome of the improvement in neonatal outcomes was not met; is that that correct?

MS. HUNT: Dr. Nguyen?

DR. NGUYEN: Thank you for that question,

Dr. Hudak. Yes, that's correct. It was not designed to observe the clinical outcome of interest, which is to benefit the neonates. And from the post hoc analyses that were done, it did not have nominal statistical significance on the neonatal index either.

DR. HUDAK: Okay. Thank you for that.

So the 003 trial basically demonstrated no significant improvement in reduction of preterm birth and no improvement in neonatal outcomes at all, so that's pretty clear.

If you can put up slide number 26 of your presentation, you describe what the outcomes were in terms of composite neonatal morbidity score. The presentation presented was very interesting from a neonatology standpoint because you looked at the relative reduction in preterm births between Makena and placebo, looking at less than 37 weeks, less than 35 weeks, less than 32 weeks.

From a neonatologist point of view, we like to look at the distribution of gestational ages in a treatment group. Do you have a slide that shows

the mean and the range of gestational ages in the Makena treatment in 003 and the placebo treatment, just so I can have some handle on what the real difference in gestational age was?

MS. HUNT: Dr. Nguyen?

DR. NGUYEN: Actually, if I may ask Dr. Johnson to chime in, please? Thank you.

DR. JOHNSON: I want to make sure I'm understanding your question. So you went to actually see the distribution of the gestational ages?

DR. HUDAK: Right. So if you looked at the 295 infants who were born following Makena treatment and the 151 babies born after placebo treatment, what did their distribution of the gestational age look like, and what was the mean difference, if you will?

DR. JOHNSON: Okay. That I don't --

DR. HUDAK: I --

DR. JOHNSON: I don't know that off the top of my head, maybe; I have it for the prior deliveries, so we can try to look that up.

DR. HUDAK: Okay. Could you look that up? Because I think that's really important. I mean, if there's a one-week mean difference versus a 3-week mean difference --

(Crosstalk.)

DR. JOHNSON: So that I do know. Sorry.

DR. HUDAK: Okay.

DR. JOHNSON: I slightly misunderstood.

In 002, it was just a one-week difference in the means --

DR. HUDAK: Okay, a one-week --

DR. JOHNSON: -- and I believe in mean, that was 36 to 37 weeks. I'd have to look up the exact details.

DR. HUDAK: Okay.

DR. NGUYEN: I can address the mean as far as days/weeks for 002. For 002002002, the mean, there was about a 6-7 day difference going from 36 to 37 weeks, and when you look at the median, it was something about 35.6 going to 36.6. So it's the later preterm birth that you're seeing in fact in 002, and certainly we didn't see any real

difference in 003.

DR. WITTEN: Can you state who was that who was speaking? Sorry. Who was speaking?

DR. NGUYEN: I apologize. It's Dr. Nguyen from CDER. Thank you.

DR. WITTEN: Thank you.

Okay. Go ahead.

DR. HUDAK: Yes. So in that case, this is a relatively small difference in gestational age, it's a relatively small number of babies, and if you were to sort of say was this study really powered to define a difference in neonatal mortality, or in this composite morbidity measure, given that sort of difference in gestational age distribution, you'd have to have an awful lot of babies, which is why I think on your slide number 26, even though you do see this reduction from 17.2 to 11.9 percent, in your composite mean and morbidity score, the p-value is not significant.

But, it's worth pointing out that the other morbidities in this composite index, which are

respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 IVH, sepsis, or NEC are going to be individually very rare events once you get up above 30 weeks, except for RDS, which might be a little bit more common. But these other things here are really quite uncommon above 30 weeks.

So I question whether or not there might be other ways to look at the neonatal outcome, one of which may be just days in the NICU or days in the hospital between the two groups. That might be something that would be profoundly important I think to parents, and caregivers, and to the healthcare system as a whole.

Looking at the 003 trial, if this trial were to have found a -- this is a hypothetical question -- if it were to have found a significant reduction in preterm birth but failed to find a difference in neonatal outcomes, either by mortality or this composite index, which it obviously did not, would that have been something that would dissuade you to approve this medication?

Because again, in that trial, given the fact that the rate of preterm birth in the placebo group was much less than in the 002 trial, even with the increased number of women enrolled in that study, your likelihood of defining a change in neonatal outcome would have been probably on the order of what it was in 002.

MS. HUNT: Dr. Johnson?

DR. JOHNSON: Sure. I'm happy to start with this. When they designed 003, they actually powered it. The reason that you see 1708 patients was because they wanted to have 90 percent power to look at that neonatal index. So when they powered it, they were looking at all of the preterm birth numbers, but really what drove it was their assumption that they would have a placebo rate at around 17.2 percent for this neonatal morbidity/mortality index.

So with that, they actually powered the co-primary, so those preterm birth endpoints were powered 97, 98, 99-plus --

DR. HUDAK: Yes, yes.

DR. JOHNSON: -- percent, individually. But I do think as we're moving forward, especially given the changes -- and they were supposed to look at NICU days and things like that, but it's very hard when you are looking across a lot of different practices, and especially over a decade, to be able to understand and equate all of those numbers and translate them.

So I do think that as we're moving forward, you raise a good point, but I do know that my colleagues that are clinical would also like to address your points.

DR. HUDAK: Yes. Let me clarify my statement. So you're agreeing with what I said, I think, because even though it was powered on that 17 percent placebo rate of neonatal composite index, that posited a much higher rate of preterm births in the placebo group than they actually thought.

DR. JOHNSON: Well, actually they posited both a higher rate on the neonatal index and for each of the different preterm birth rates, however,

they did have very high power to still look at that 37-week preterm birth rate, even with the lower than anticipated.

DR. HUDAK: Yes, but the fact that it was lower than anticipated on the preterm birth meant that that 17.2 placebo rate of neonatal --

(Crosstalk.)

DR. JOHNSON: It drops about 5.4 --

DR. HUDAK: -- was never going to happen.

DR. JOHNSON: Umm-hmm; correct, sir.

DR. HUDAK: So I think that's operative in this circumstance. Thank you.

MS. HUNT: Dr. Nguyen, do have anything to add?

DR. NGUYEN: I do.

Dr. Hudak, I think you brought up actually several very excellent points that we've discussed at length. The first is 003 really not able to detect what it's supposed to detect.

I'll go back to the fact that we took regulatory flexibility with 002 because we've looked at different risk levels in that

trial -- people with one spontaneous prior preterm birth and compared that with women with more than one prior preterm birth, Black women versus non-Black women -- and there we saw a sustained treatment effect for the endpoint of less than 37 weeks. So the indicated population, the approved population, reflects those data, and 003 really was powered to look at the drug effect in that exact indicated population.

Now, as we find out, the rates are different as far as placebo rate, but please recall that the recurrent preterm birth rate in that population is not inconsistent with what we see in the U.S. population. The Meis trial was one point estimate, but there are many others, and those range from the 20's to 30's, so we're not looking at a population that had a recurrent preterm birth rate of 2 percent, so I think we need to keep that in mind.

As far as neonatal outcome, certainly at low risk, past events, yes, we could have asked for a 6,000-person trial, and maybe would have seen an effect there. I also would like to remind everyone

that the gestational age endpoints, none of it won in 003, and again, this is an indicated population.

I would say that your suggestions for considering other neonatal outcomes is an excellent idea, and certainly for a new trial, we are open to working with Covis and looking at neonatal outcomes that won't require, hopefully, trials that are 3 [000], 4,000 persons. We recognize the feasibility of those types of trial sizes.

I think your last question was, what if 003 won on the gestational age? While I prefer not to speculate, I would comment that a willingness to accept uncertainty between the relation of gestational age and neonatal outcomes certainly increases with decreasing gestational age, so I hope that addressed some of your questions. Thank you.

DR. HUDAK: Thank you for that response. I'd just like to make the point that neonatal outcomes even in very large studies sometimes is very difficult to design a difference, even though you have an intervention that makes a significant

difference on some other outcome, and that's our history of neonatal trials.

So it's not surprising in this study that there is a difficulty in defining it, and I do think that the concept of defining a significant reduction in preterm birth and, number one, not seeing an increase in morbidity, and not having an inferior outcome in that population compared to historical for your validation purposes, I think is very important.

DR. NGUYEN: This is Christine Nguyen from CDER again. Again, we've really looked for signals of efficacy in various subgroups, including those that we would consider high risk, and it really was quite negative there, so that actually surprised us. So it wasn't just the larger population that we evaluated, we really tried to subset by different risk levels, and we did not find any treatment effect there either, for neonatal outcomes or gestational age.

So it was really the failure to find positive findings in any of those endpoints that

really have led us to what we've concluded today. Thank you.

DR. HUDAK: I agree, 003 was quite surprising in terms of the neonatal outcomes; correct.

DR. WITTEN: Any more questions, Dr. Hudak?

DR. HUDAK: No, I think for the moment, I'm done.

DR. WITTEN: Okay. We'll move on to Dr. Anjali Kaimal for questions.

DR. KAIMAL: Hi. Anjali Kaimal, maternal-fetal medicine at USF. I have a couple of clarifying questions and then a follow-up question.

The first thing, this wasn't specifically stipulated, but it does seem that everyone agrees that what is needed is more study in this area, and I just wanted to make sure that CDER agrees with that; that at this point there isn't a need for additional information, and that's a part of what this process is, is to figure out how best to get that additional information.

Would you say that that would be true?

MS. HUNT: Dr. Stein?

DR. STEIN: Yes. Peter Stein, Office of New Drugs, CDER. We absolutely agree with you, and not just in terms of study for HPC. We would be very anxious, I'd say, to find other treatments to work with sponsors on studying in this population because there's clearly no question in our minds that this is an unmet need.

With regard to specifically HPC or Makena, I think the same applies. There are some interesting hypotheses that are being generated by these post hoc, non prespecified analyses, and we think that's what these kinds of analyses are for. They're exploratory, they're intended to raise interesting and important hypotheses that could generate further study, and we would be very open to discussions with any sponsor that would come in and suggest how those should be followed.

I would point out that there was relatively limited prior dose range finding. There had been some higher dose studies that had been done with different regimens perhaps, so I think there's a

lot of room for further study here to find whether or not this drug in the right population, at the right dose, the right regimen, might be effective. And I would also say, we would be very anxious to look for other potential interventions here that we would work with sponsors to develop a program around because this is really an area that has to be invested in and more research done.

DR. KAIMAL: Wonderful. That's great to hear.

My second clarifying question is just to also say, from CDER's perspective, it seems that the major issue is lack of benefit. Of course we never want to take on any harm in the absence of benefit, and I understand how that changes the calculus, but it doesn't seem that we have significant concerns, the intergenerational piece and the lack of understanding of that at this point, notwithstanding.

We do have significant concerns about the harms of this treatment. Really what we're mostly focused on is the fact that we've not been able to

demonstrate the benefit that we had hoped that it would have. Would you say that that's a proper characterization of your viewpoint?

DR. STEIN: Yes. Peter Stein, Office of New Drugs, CDER. Yes, I think that's a fair characterization. I think absent benefit, any risk imposed on patients is of concern, of course, because the benefit-risk can't be favorable with an absence of benefit.

On the other hand, if there was a hint of benefit, we would not hesitate to approve a drug that provided a meaningful benefit in a situation just because there were some risks, as long as they were not a high incident and were manageable. And certainly that was our conclusion back in 2011. We recognized that there are risks of this drug, rare, infrequent: venous thromboembolism, we've talked about them, [indiscernible], allergy, glucose intolerances seen. I won't go through all of them, but these are not risks that are not manageable, and they're not -- particularly, venous thromboembolism is not a frequent risk in this

situation.

So I think you've characterized it exactly right. In the absence of benefit, all you're left with is risk, and even infrequent risk. Even if the risk is 1 in 10,000, and you end up treating 100,000 women, you're going to get a number of really impactful events in a woman's life. So we don't discount them, but I also would say we don't overemphasize them if there's benefit.

DR. KAIMAL: I just wanted to ask that clarification because I do think -- as someone who's been a practicing MFM during this time, and then also in thinking about, we really only have two FDA-approved medications for pregnancy complications, right? Right now we have Makena and we have Diclegis.

So I think this understanding as we're thinking about what the best decision is for FDA approval, is to say that it is not that we think that this is a medication that has incurred significant harm or that we think that the harms that we anticipate have changed, but more to say

that we've gathered more information about the benefits is really important when we think about the population of pregnant people that's already been exposed to this and the many conversations that have happened between patients and providers previously, and those that might come in the future, if we're thinking about further investigation.

So I think it's important to think about those things, but really to think about the reason that we're coming to this decision is more about gathering additional information about benefit rather than uncovering additional concern about harm at this point.

DR. STEIN: Peter Stein, Office of New Drugs. I think you've characterized it very well. This is really about trying to assure that medications that women are going to get -- and this is clearly a medication that is a burden; there's many injections here.

As you said, the risks are not -- this is not a high-risk drug by any means, but it's really

about the lack of benefit here. Benefit-risk is always the balance, and with sufficient benefit, even severest can be tolerated if the benefit-risk is favorable here. As you've said I think very well, these are not by any means substantial worrisome risks, but absent benefit, that's a problem.

So you're absolutely right. The issue here is really our conclusion that there's no evidence of benefit. Effectiveness has not been shown. Substantial evidence of effectiveness is no longer present, and that's what we need to focus on. And as you said, I think further research in this broad area is really important, including potential future studies of this drug or of other drugs.

MS. HUNT: Dr. Nguyen, do you have anything to add?

DR. NGUYEN: I do.

Hi. Christine Nguyen from CDER. As an obstetrician, I would say the reason I joined the agency was my pure frustration of not having data to inform my evidence-based practice. Really, I

mean so much of what we do is off label because of exactly the lack of approved treatment that you brought up, and we can have an hour discussion why that's the case.

I would like to bring us back, that for FDA to approve a drug, it must be shown to be effective. That is criterion number one, and that has been a requirement for us since 1962 because of prior events of drugs that just had risks and ended up harming people without any demonstration of effectiveness.

So I really want us to appreciate the effectiveness part is key, and that is true in any decision we make in life. I mean, we take risks driving, but it gets us somewhere, right? If it got us nowhere, we wouldn't be driving. So I just want to make sure that's clear; for an FDA-approved drug, it really needs to be shown to be effective.

In obstetrics, we have so little control data, and here we have control data. Again, just to remind everyone, there are practices that we used to do: routine episiotomy; IV infusion of

terbutaline. We stopped doing them because we actually had decent data to show that they didn't work and could harm patients. So that's the context that we're discussing today. Thank you.

DR. KAIMAL: Absolutely. Yes, I agree with the necessity to know that we're bringing a benefit. I just wanted to clarify that aspect of it.

I just have one final question, which is just to say I started out by saying it seems that everyone agrees that there is a need for an additional study, and part of what CDER presented was the fact that there have been other drugs that have gone through a process like this, where they had an accelerated approval, and that was withdrawn.

I just wondered if any of those examples -- like are there examples within those where it was possible that other studies were done afterwards that we can say that that is feasible to do? I understand in our questions tomorrow for Covis about, wow, we think that we would do the

study if the approval remained, but is there FDA experience, I guess, with that list of drugs to say there was accelerated approval, it was withdrawn, additional information then was gained, and either a more narrow indication or different indications were able to be discovered?

That obviously only applies to the idea of 17 OHP being used for prevention of preterm birth, not the investigation of other things that might be opened up by a change in approval; but for that specifically, if we're trying to get more information about that question, is there any experience previously with this type of situation?

MS. HUNT: Dr. Stein?

DR. CAVAZZONI: This is Dr. Patrizia Cavazzoni. I'm the director for the Center for Drugs. I can think of one instance where that has happened. It may have been more, but it's certainly something that is not outside of the realm of possibility. The important thing, as you heard in the presentation, is that the study be feasible and that there are patients who are

available to enroll in the study. And as you have heard, it would be exceedingly difficult for any study of Makena to be conducted if the drug is still on the market, knowing what we know about benefit.

DR. KAIMAL: Thank you. That concludes my questions.

DR. WITTEN: Thank you.

We'll move on to Dr. Ellenberg, Dr. Susan Ellenberg.

DR. ELLENBERG: Yes. Thank you. Actually, I'd like to follow up on that because you did make a big point of saying how difficult it would be, and pointing out that it took 10 years to do the 003 study. But the situation currently is different from the situation when 003 was being carried out. At that time, you had a drug where there were no other drugs for this indication that had been approved under the accelerated approval mechanism. So now at this point, the second study was negative, and I would imagine that that would raise a lot of questions among practitioners about

whether this is a good thing to do

So I would like to understand better why you think it would be infeasible now that it's very unclear as to whether there's any benefit at all to this product, and related to that, do you have any data as to whether the use of Makena has gone down since the results of the 003 study were reported?

MS. HUNT: Dr. Stein?

DR. STEIN: Sure, and thank you for that question. Peter Stein, Office of New Drugs, CDER.

A couple of points I do want to emphasize is that our decision to withdraw the drug really focuses on the lack of evidence of effectiveness and the lack of substantial evidence of effectiveness. The drug is not shown to be effective, and that's really the focus of our decision to remove the drug rather than specifically about feasibility of the trial. But as I mentioned before, we certainly support further investigation, following up for this particular drug, hypotheses that were raised by some of the post hoc analyses, and that's where I think it's

important to focus.

You know, we're not really recommending repeating Trial 003. Trial 003 was a well-designed, well-executed study, which showed absolutely no evidence of an effect on gestational endpoints or neonatal outcomes. So replicating that study doesn't make sense, and I think it would not be very recruitable simply for exactly that reason. The trial was done, and it was negative.

On the other hand, if we're following up on reasonable post hoc analysis, exploratory hypothesis-generating analysis, that suggests maybe there are subgroups that might benefit, and perhaps exploring different doses or different regimens, I think physicians would be certainly open to considering including their patients in such a study, following up on new hypothesis, if you will, as opposed to simply trying to replicate a study that was entirely negative.

So I think it would be a recruitable, feasible study not replicating 03, but learning from it, and going on to the next set of hypotheses

that research should be done on. And we'd encourage that, and we'd work with the sponsor on developing studies following up on those hypotheses, or other hypotheses that might narrow the study to a population where a study is appropriate.

DR. ELLENBERG: Have you given thought to what a study might look like? What do you think is the most promising thing that might be studied if another study was done?

DR. STEIN: Well, we'd certainly be interested. One of the values I think of this advisory committee is we'll be hearing from all of you on what further studies, what future studies, might be useful and promising. What I'd say is we certainly would be open to hearing about any kind of data exploration that raises at least a reasonable hypothesis of areas of benefit. I think Covis has done some post hoc analysis with several subsets.

Again, unfortunately, our experience is that when you do post hoc cuts of data from negative

trials that look very promising, the next trial focusing on those hypotheses is usually negative as well. But again, given that this is an unmet need and a serious disease, we are very open for rational hypotheses to follow up on, and we'd certainly be open to ideas for how endpoints could be crafted in populations; where populations should be studied; whether further dose ranging or adding a different dose or regimen here would make sense.

I heard from the prior advisory committee member a question about using a different endpoint around neonatal outcomes. We're open to those discussions. I couldn't say we have a defined study in mind, but I could say we've certainly had internal discussions about the sort of things that might be useful to follow up on, and we're open to those discussions with the sponsor or with others who could suggest what are fertile areas for further study.

MS. HUNT: Dr. Nguyen, do you have anything to add?

DR. NGUYEN: I do. I just want to clarify

that when we were proposing to withdraw Makena for its approved use -- and again, the approved use is what's described in our drug label, a woman with a prior preterm birth and starting treatment anywhere between 16 weeks and 20 and 6-7 days. So that's where the lack of evidence of efficacy is, and it doesn't mean we're saying Makena is not shown to be effective for any use.

When we're considering trials that investigate the higher dose, early start of treatment, and perhaps a higher risk subgroup -- however that is defined -- looking at different endpoints such as some of the neonatal endpoints that were mentioned earlier; where's some clinical equipoise in those situations? So I think that's the motivation to recruit people, and encourage, and motivate people to enroll in those trials, so that's what we're talking about.

When we're talking about infeasibility, we're really talking about what if we were to do the exact trial as 003? And you're right; it would be hard to justify enrolling someone in that trial

when we have a drug that's approved for the exact indication.

DR. ELLENBERG: If serious questions have been raised about the efficacy of that drug, then I'm not so sure about that. But it sounds like, from what Dr. Stein said, the feasibility or infeasibility of doing a trial if this stayed on the market is really not a major factor in your considerations about removing this from the market.

DR. STEIN: I think that we have to focus on the benefit-risk as we see it with the data that is in front of us, the evidence of lack of effectiveness -- or the evidence, I should say, that effectiveness is not demonstrated, is not shown, and the absence of substantial evidence of effectiveness and the benefit-risk. That's really the decision. We can't say that it focuses on the feasibility of the trial; that's a consideration of course. We've noted in our slides, it's a point for discussion, but it's not the underlying basis for our decision.

DR. ELLENBERG: Thank you.

DR. WITTEN: Thank you.

I'd like to move on to questions from Annie Ellis.

MS. ELLIS: Hi. I just want to thank the FDA for having this hearing, and I want to thank the sponsor for their hard work to provide a solution for women who've experienced preterm labor and premature delivery. I had experienced that, and subsequently was on bed rest for 20 weeks on oral terbutaline before my second daughter was born at 38 weeks, who subsequently had her son at 36 weeks.

So having solutions and this very serious discussion is just so important. Seeing that 003 did not confirm the exciting results of 002 were just so disappointing, and I saw on several slides that if left on the market, it would take 10 years or more for a trial to be conducted in the U.S.

Do you have any estimate of how much quicker we could get results and approval if withdrawn?

MS. HUNT: Dr. Nguyen?

DR. NGUYEN: Thanks for that question,

Ms. Ellis, and thank you, again, for being part of our advisory committee panel.

I think if we look back at the experience in Trial 003, where 40-45 percent of the total U.S. cohort were recruited prior to Makena's approval in 2011, that gives you a little sense of the piece that may be achieved if Makena were withdrawn from the market. That compared to going from 11 subjects a month before Makena's approval, down to 3 subjects a month -- so a 70 percent decrease after Makena was approved -- I think that gives us a little bit of a semi-quantitative estimate as far as how quickly we can recruit for a new trial versus leaving the drug on the market while another trial is conducted.

It certainly would be a lot quicker with the drug off the market than it is on the market, but I think the experience from Trial 003 can give us some of that quantitative information. Thank you.

MS. ELLIS: Thanks.

DR. WITTEN: Any other questions?

MS. ELLIS: No more at this time. Thank

you.

DR. WITTEN: Thanks.

So we'll move on to Dr. Obican.

DR. OBICAN: Hello. Thank you everybody for your time this morning. Actually, most of my questions were answered by my colleague that just asked the question, but one of the questions for Dr. Nguyen is, in terms of the number of patients that would be required for a trial like this, I know you gave us some sort of range.

Can you comment a little bit about the type of women that would be involved in the trial? I know that we said that we wouldn't know that, and that a lot of that would come from us, but let's say Black women, women that are seen at a higher risk for preterm birth. What numbers are you looking at? Are you still looking at 1200, greater than 3,000, in terms of the members in that study?

MS. HUNT: Dr. Johnson?

DR. JOHNSON: Thank you. So it depends a lot on the exact design of the trial and the exact endpoint that's going to be used, but the rates

could be easily kind of close to a thousand to perhaps into the multiples of thousands, and it will depend on the endpoint and also who is ultimately going to be enrolled in the trial.

So we've done a [indiscernible], based on what Covis has proposed, so trying to actually look at much higher risk groups and try to use their rates. But again, there is such a diversity in rates, I think it's going to be difficult to pin it down right now. But part of what we want to hear is who you think and what you think should be done. I believe that's one of the questions Dr. Whitten has for the advisory committee.

DR. OBICAN: Great. Thank you.

DR. WITTEN: Other questions?

DR. OBICAN: No. Thank you so much. The rest were actually answered by my colleagues, so thank you.

DR. WITTEN: I don't see any other hands raised, but I'd just at this moment see if -- I think Dr. Lindsay may not be able to raise his hand if it's possible that he has a question, and if so,

I don't know. I know if we can get him on.

MR. KAWCZYNSKI: Dr. Lindsay?

DR. LINDSAY: Yes. Can you hear me?

MR. KAWCZYNSKI: Yes. Take it away

DR. LINDSAY: Yes. I don't have any additional questions.

DR. WITTEN: Other questions from the advisory committee?

(No response.)

DR. WITTEN: I have one question for CDER, which is we've heard a lot of discussion about 002 and 003, and how they're alike, and how they're different, and what was seen in the placebo group.

My question is, in this case, you have one smaller trial that showed something that was not replicated in the larger trial. How do you look at those two trials taken together? Do you consider the second one because it's larger, or do you look at the totality of the evidence combined, or are there some differences between the studies that you might focus on?

DR. STEIN: Thanks for that question. Peter

Stein, Office of New Drugs, CDER. Of course you're absolutely correct, there's a positive and a negative trial, and that always puts us in a challenging situation, but I think it really comes down to trying to understand the data set that we have in front of us.

As we've mentioned, the positive trial, Trial 002, was relatively smaller. We described it as a proof-of-concept trial because it was an early trial investigating this research question, and it had significant limitations, as this single site contributed more than a quarter of the patients. There was this imbalanced randomization, 2 to 1 randomization, so the size of the placebo group was relatively small, and the placebo rate was well above anticipated, and really above what's been seen in other trials and other epidemiologic observational data.

So there were limitations and there were questions, but again, at that time when the drug was approved, based upon the single trial, in the absence of other therapies for this serious disease

where there was a big unmet need, I think it was an appropriate decision really exercising regulatory flexibility.

Of course, as you know, we typically require two adequate and well-controlled trials to make up substantial evidence exactly because it's not by any means unheard that an initial experiment is not confirmed when a more definitive subsequent experiment is done. So what we're left with is an 002 trial that had limitations. It had also useful information, but it had limitations.

As we have tried to outline, we've looked at other data sources as well, not as definitive information, because 003 was certainly a much larger trial, 4 times the size of 002, well designed and well executed, and showed no evidence of efficacy whatsoever, but we then looked at other information.

We've talked about the real-world evidence studies. I think the sponsor has appropriately, as have we, pointed out the limitations of the real-world evidence data, but it's a consistent

pattern, five different real-world evidence studies that have comparison to a control group of some sort, showing no evidence of effectiveness.

We've looked at randomized clinical trials in other singleton pregnancy risk conditions, multigestational risk conditions, and again, I think the sponsor has appropriately pointed out that those were not in the indicated population, but they do look at the pharmacological effects of the drug and answer the questions of whether there are signals of pharmacodynamics, of evidence of benefit of the drug, and the answer was there's not.

So what we're left with, really, is this totality of information where we have a small prior trial that's positive but had limitations. This much larger trial that was well conducted showed definitively no evidence of an effect on gestational age or neonatal outcomes, and supported by a wide range of information from randomized trials and real-world evidence. So when we look at that body of information, I think we can say the

drug is not shown to be effective, and substantial evidence is lacking.

So I think it really comes down to the fact pattern in each individual instance when such a circumstance occurs where there's a positive and negative trial. What can we make of each trial? Where does the evidence point us? And I think here the evidence clearly points us towards a conclusion that the drug is not shown to be effective.

DR. WITTEN: Thank you.

I'd like to call on Dr. Cassandra Henderson.

DR. HENDERSON: Hi. I have a comment, not a question. Can I be heard?

DR. WITTEN: Yes.

DR. HENDERSON: Yes. Okay. Thank you.

I was part of the panel that recommended approval of the first trial, and the concerns at the time, obviously, were a very, very high incidence of preterm labor in the placebo group. I mean, almost no one's practice had anywhere near that. In the discussion, the issue and the reason it was given made sense, that those patients had

such a high incidence of severely preterm babies, babies having had that experience, that those mothers would have done anything to avoid having that again. So that actually targeted and was viewed [indiscernible] as such a very high risk, which is why the justification for that placebo group having such a high incidence of preterm delivery.

The concern -- and that's why I was asking about the risks -- back then was there appeared to be very little risk. And while we do see some of it -- I was asking about the thromboembolic disease, the diabetes, depression and other things -- those risks are certainly -- for the person who has them, that's significant. So for the large population, if there's a chance of preventing preterm delivery, those seem to be justifiable risks. Now we're looking at it may not be effective, and so that's, basically, why we're doing this.

The Meis study certainly was concerning. It was powerful and got us to think it should be

approved, but there were explanations for that high preterm delivery rate in the placebo group; so just as sort of a comment. Thank you.

DR. WITTEN: Thank you.

I am not seeing any more raised hands. Any other comments or questions for the panel?

(No response.)

DR. WITTEN: Then I think, in that case, we'll close this session at this time.

Now we will move on to the next session, which is to proceed with clarifying questions from the Center for Drug Evaluation and Research to the Center for Drug Evaluation and Research.

There will be clarifying questions by three representatives from CDER. For this portion of the hearing, we'll start with a question from a representative from CDER and an answer from a different representative from CDER, and proceed accordingly. Questioners should identify themselves before asking their first question. If the questioner or answerer wants a specific slide displayed, please identify the slide number, if

possible.

So I'm going to turn it over to CDER for this.

Clarifying Questions by CDER

MR. RAULERSON: Hi. I'm Patrick Raulerson, senior regulatory counsel from CDER. I just have a few follow-up questions, based on the last couple hours of discussion. First, I have a question for Dr. Stein, and then possibly if Dr. Cavazzoni wants to follow.

There was some discussion, especially during this last hour of questioning, about the feasibility of additional trials and how that factored into our proposal to withdraw Makena.

Could you comment further on that, Dr. Stein?

DR. STEIN: Certainly. Peter Stein, Office of New Drugs, CDER.

As I mentioned before, the decision to withdraw a drug is really based upon the evidence at the time the decision is made, and that isn't based upon the feasibility, or lack of feasibility,

of the subsequent trial that might be done. So what we're dealing with here is the smaller trial, 002, and then the larger entirely negative trial, 003, and the other supportive evidence that led us to the conclusion that the drug is not shown to be effective, and substantial evidence of effectiveness is lacking, and that the benefit-risk was unfavorable. And that's really the information that supported our determination to recommend withdrawal of the drug from the market.

Now, what we've commented on is, as sort of a byproduct of that, what is the outcome on further research in this area of studying Makena, or to that matter, hopefully other promising treatments for these patients who need treatments? And our comment was that, in fact, if anything, withdrawing it from the market would facilitate research in this area, and certainly facilitate further study of HPC, as we discussed, following up some of the hypotheses that have been raised and some of the research questions that might be answered here.

So our decision to withdraw is not

contingent upon feasibility or lack of feasibility of a trial, but what we commented on is, based upon that decision, what was the outcome with respect to further research? And I think we feel fairly confident that the withdrawal will actually, if anything, facilitate further research in this area.

DR. CAVAZZONI: Yes. I would like to echo Dr. Stein's comments. This is Dr. Cavazzoni. I'm the director for the Center for Drugs.

It is really very important to underscore that the reason for FDA asking to withdraw this drug is because there is no longer evidence of effectiveness, substantial evidence of effectiveness.

Incidentally, obviously, if we look at potential other investigations, be that with Makena or other promising therapies, that is a separate consideration, and we are always open to discussing potential additional studies with the sponsor or other sponsors. But it is really fundamental to underscore that the reason that we're here today, and the reason for FDA asking to withdraw the drug

is because the evidence no longer shows that Makena is effective.

MR. RAULERSON: Thank you, Dr. Cavazzoni.

Another question for Dr. Stein.

Can you, please clarify how CDER considered the observational studies that we discussed, and that were the subject of several questions, in reaching our determination that Makena should be withdrawn from the market?

DR. STEIN: Certainly -- and I certainly open it to my other CDER colleagues -- real-world evidence, observational studies, certainly have a role. They have a role in regulatory decision making, in fact; as well as in practice, useful information is generated to support practice decisions. But we recognize -- and I think Captain Moeny mentioned this -- that real-world evidence studies have limitations.

I think we had actually a very useful discussion between the Covis questions and Dr. Moeny's responses, and their observations, that I don't think anyone would disagree with, which is

that real-world evidence studies do have limitations. Obviously, fundamentally, they don't start with a randomized control group, and someone has to bring together a control group, and the databases are also reflecting real-world practice.

While we use these as supportive information, and sometimes if they're robust enough, even supporting regulatory decisions, we recognize that they have limitations. In this instance, as I mentioned in my presentation and I think Dr. Johnson mentioned in hers as well, what we look for is a range of different studies.

What I thought was an interesting observation, and I think the sponsor appropriately pointed out, was that one of the studies was in a lower risk population. Well, that's interesting because, really, what we were looking at is the whole range of risks. And you can see across the five studies everything from a very low risk to a much high-risk population, and that's the value of real-world evidence, is we can look at these different populations efficiently.

I think what we were pointing out is that when you look at these trials which had a control -- a manufacturer control in the sense that these aren't randomized controls but an appropriate control -- to get an estimation of whether there's an effect of the drug, there is a consistent observation that there's not.

Now again, as I pointed out, the main basis for our recommendation to withdraw the drug is the Trial 003, a large, well-conducted study that did not show any evidence of benefit on gestational age or neonatal outcomes. But we certainly looked at the fact that the real-world evidence studies gave the same message, and other randomized trials in other populations of patients with risks gave the same message. And these, therefore, just provide supportive information, to the fundamental, to the main area, to the main study, that provided the determination that the drug was not shown to be effective. And I think that's the role that real-world evidence studies can play, anything from being even a primary basis for approval, to more

commonly being supportive information.

MR. RAULERSON: Thank you, Dr. Stein.

There was also a lot of discussion, especially in the first hour and the questions from Covis, regarding the subgroup analyses. I'd like to ask Dr. Johnson to comment further on what these analyses can and cannot show us as we're considering the entire body of evidence.

MS. HUNT: And Mike, Dr. Johnson is our remote speaker.

DR. JOHNSON: Hi. Thank you.

I think it's important to understand that the subgroup analyses really are going to have to focus on hypothesis generation. So at this point, what we get concerned with is that there will be an increase in type 1 error, so you're more likely to see something that looks positive.

I think it's very important that we consider this, so we have to put them in a place to try to figure out what maybe was different, what could be plans for the future, but these actually do not support what we would need to either do changes in

labeling or, at this point, in time. They also, unfortunately, are not going to support the current evidence -- or rather, sorry, they don't support that it's an effective product. That's not shown right now with what we have.

MR. RAULERSON: Thank you.

I think there's another question from Dr. Nguyen, so I will step away from the podium, and Dr. Nguyen can ask.

DR. STEIN: Yes. Thanks. Peter Stein, Office of New Drugs, CDER. I think it's probably useful to clarify there was a lot of earlier, I think, useful discussion on off-label prescribing and how that fits in, as well, with compounding, how that fits into our consideration, and maybe I could ask Dr. Nguyen to comment on that and expand on that a little bit more.

DR. NGUYEN: Thank you so much.

May I have backup slide 241, please?

The reason I think this was an excellent point for us to address is that certainly we've considered the area of unmet need, we've considered

the advisory committee's input about patients needing an option, and certainly that would make sense if the option has been shown to be safe and effective.

I'm sorry. Is that slide 241?

MR. KAWCZYNSKI: Yes, that's slide 241. Do you want to go back one?

DR. NGUYEN: Yes. That's ok. That's alright.

I'd like to, I think, take a step back and reflect on the fact that all patient care is not static, but it does evolve with availability of data. As I mentioned earlier, we no longer do routine episiotomy, we no longer give IV infusion of alcohol to stop preterm contractions, so really, the practice of medicine will follow the science.

So to assume that, given the data that we have -- and we have a large body of evidence since 2011 -- that it should be ignored, I think we need to remind ourselves to take care of our patients, we do consider the best available evidence at the time. So by withdrawing Makena because of the

reasons of efficacy, we would send that message clearly to providers and their patients, and they would take such information into consideration. Thank you.

MR. RAULERSON: I think that concludes the questions for CDER to CDER. Thank you.

DR. WITTEN: Thank you very much, CDER.

We're now going to break for lunch. Committee members are reminded that there should be no discussion of the hearing topic with other committee members during lunch, and I think that we can still convene at around 1:55 p.m. to make sure that we're connected.

We'll ask committee members to rejoin at around 1:55 p.m. to make sure you're connected before we reconvene at 2 p.m. Eastern time. I'd like to thank you, and we'll be reconvening at 2 p.m.

(Whereupon, at 1:05 p.m., a lunch recess was taken.)

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

(2:00 p.m.)

Presentations by Public Participants

DR. WITTEN: We're now at the portion of the meeting where we're going to proceed with the first round 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, I'm going to ask each speaker to 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'll begin the public presentations. The time allotted to each speaker varies based on the amount of time requested to speak. Our first speaker is Ms. Gretchen Wartman. You have five minutes. You may begin.

MS. WARTMAN: Thank you, and good afternoon. My name is Gretchen Wartman. I am vice president for Policy and Program for the National Minority Quality Forum and director of our Institute for Equity in Health Policy and Practice. I thank the Food and Drug Administration for granting to me the five minutes I requested to present a public comment regarding the National Minority Quality Forum's perspective on whether 17P and its generics should continue to be available on the market.

For those who are unfamiliar with our

organization, the National Minority Quality Forum is a 501(c)(3) not-for-profit research and advocacy organization based in Washington, DC. NMQF's capabilities include federal and state policy analysis and advocacy; issue-specific alliance development; community-based provider quality improvement initiatives; and data collection and analytics.

The mission of NMQF is to reduce patient risk by assuring optimal care for all. NMQF's vision is an American health services research delivery and financing system whose operating principle is to reduce patient risk for amenable morbidity and mortality while improving quality of life.

Unmitigated patient risk can be measured in the incidence and prevalence of preventable morbidity and premature mortality, in avoidable hospitalizations, and in delayed access to health services. Most egregiously perhaps, patient risk can be measured by the long-standing and seemingly intractable lack of statistically significant

inclusion of marginalized population and patient cohorts, and the processes that inform the creation of new medical knowledge.

During this three-day convening, data regarding the high singleton preterm birth rates in the United States will be presented by FDA, by the sponsor, and by others presenting public comment, obviating the need for NMQF to use our short comment period to reiterate that which is well documented, and it appears not in dispute. What is also well documented is that other than 17P and its generics, there is no FDA-approved drug to prevent singleton preterm births in women with a prior spontaneous singleton preterm birth.

In response to the question before the committee -- which is, whether 17P should retain its marketing approval while additional evidence regarding efficacy is obtained? -- the National Minority Quality Forum encourages the committee to vote yes. In addition, NMQF urges FDA to work with the sponsor to identify an approach to the development of additional evidence that enables

physicians to continue to prescribe 17P, and thus mitigate the risk to patients of removing this potentially efficacious therapy from the market.

In closing, the American general public population is rapidly diversifying, and the marginalizing practices of prior centuries portend future risks for all patients. The National Minority Quality Forum strongly encourages FDA, within the boundaries of its current authorities and guidelines, to engage proactively with patients, physicians, and sponsors to develop models of research and evidence development that eliminates structural and policy inequities that confound the efforts of research sponsors to meet the stated objectives of denominator inclusivity and equity.

Thank you again for the opportunity to speak today. The National Minority Quality Forum looks forward to continuing a constructive relationship with the Food and Drug Administration, and with other agencies within the Department of Health and Human Services. Thank you.

DR. WITTEN: Thank you.

We will now move on to our next speaker, Ms. Martha Nolan.

Ms. Nolan, you have four minutes.

MS. NOLAN: Thank you.

Good afternoon. My name is Martha Nolan, and I am the senior policy advisor at Healthy Women, and I want to thank you for the opportunity to speak today to the Center for Drug Evaluation and Research advisory committee hearing with respect to its proposed market withdrawal of Makena and its five generic forms, and the only class of treatment to help prevent spontaneous recurrent preterm birth.

Healthy Women is the nation's leading non-profit women's health information source dedicated to educating and empowering women ages 35 to 64 to make informed decisions about their health care. We educate healthcare consumers and providers about advances in women's health from the latest information on diseases and conditions, to various milestones pertaining to access to care.

We ensure that women have accurate, balanced, evidence-based information on innovations in research and science, and changes in policies that affect their access to treatment and care so they are prepared to self-advocate for better health outcomes.

Healthy Women urges the FDA to maintain patient access to Makena, or 17P, an important therapy that healthcare providers say can help protect mothers and babies from preterm birth. We believe that removing access will have a detrimental impact on the health of women and burdening people [indiscernible] at risk of recurrent preterm birth, and will not impact all women equally.

Preterm birth is an urgent public health crisis in our country with approximately 1 in 10 babies born prematurely each year. According to the CDC, each year 20,000 babies die in the U.S., and that the prematurity rate has -- after declining a fraction from 2019 through 2020 -- increased by 4 percent in 2021 to

10.48 percent, a highest level since 2007.

It is well documented that complications related to premature birth are the largest contributors to infant death in the U.S. and globally, and that a history of preterm birth is a significant risk factor for recurrent preterm birth. Further, a woman's quality of life and overall well-being can be profoundly impacted by early delivery.

While prematurity can be traumatic for any woman and child, it is an issue that affects women of color and their babies much more frequently. The preterm birth rate among U.S. Black women remains nearly 50 percent higher than the rate among all other women. Currently, Makena and its five generic equivalents are the only FDA-approved treatments available for pregnant women at risk for recurrent preterm birth, and we are concerned that removing this option for healthcare providers will only worsen the crisis for those at risk for preterm birth.

The health and well-being of newborns begins

with the health of the mother, and 17P and all of its forms has played a significant role in protecting the health of mothers and their babies for nearly a decade. Proposing to withdraw 17P from the market would leave women's reproductive healthcare community without an ACOG guidance recommended standard of care and an uncertainty on treatment options.

We feel that 17P and its generic equivalents need to be continued to be available to healthcare providers to prescribe, as they need, for their patients at risk of this complex multifactorial condition while additional studies are conducted with adequate representation from the populations most affected by preterm birth.

As a woman's health advocacy organization, we believe women should have access to necessary therapies, and this is one of them. During a global pandemic, when pregnant women and the healthcare providers who serve them continue to face a unique set of challenges, Makena and all of its generic forms should not be withdrawn, and

pregnant women should continue to have access to treatment options that have potential to better their health and the health of their babies. Thank you for the opportunity to speak today.

DR. WITTEN: Thank you.

We will now move on to our next speaker, Ms. Sally Greenberg.

Ms. Greenberg, you have 10 minutes.

(Pause.)

MR. KAWCZYNSKI: We're going to have to call Sally back in, so can we go to Crystal Mullins in the meantime?

DR. WITTEN: Yes.

We'll now move on to Crystal Mullins. Ms. Mullins, you have three minutes.

MS. MULLINS: Hi. I would like to thank you guys for having me speak here. I will say that I am not being compensated for my testimony today; I just truly believe this medicine has helped me have successful pregnancies.

I will give you a little bit of backstory into my situation. I had preterm labor back in

2018. My son was born at 22 weeks. He was very unexpected. When I had that preterm labor, there was nothing they could do at that point, so after that I was very depressed and a lot of sadness in my family because of that situation. I didn't know if I was going to try again after that, but after my doctor had told me about Makena, I was like, "Okay, let's try it. I'm willing to do that."

I was very hopeful, so with that pregnancy I used the medication, got the injections every week; a great experience for me. I went all the way to 39 weeks and delivered a healthy son. He's completely healthy. I was very concerned, like, you know, what could happen with this medication, either to me or to my son, and both of us were completely fine, and we're both very healthy.

I will say I am also pregnant. Right now I'm 34 weeks with the use of Makena, so I've been using the medicine, and this is my second pregnancy, and I believe it will be successful as it was previously. I just will say that I think it would have been harmful if they would have took

this medication off of the market, just because without this medication, I would not have decided to have another pregnancy. Because of my first experience, obviously I knew there's something out there that I can take to help me get full term.

I also have a friend that is using the medication. I told her my success with it. She also has reached past -- she's at 24 weeks right now. Her previous loss was at 21 weeks, I believe. So, so far, I just want to say that this medication is great. I think women need this in their life. It gives them hope. Withdrawing it would be devastating to a lot of women. What else is out there? Nothing.

I think they need to consider keeping this medicine here for women because, I mean, it's just one of those things. If you don't have something to prevent preterm labor, it makes it really hard to want to even consider having another child because the loss, I mean, I was devastated. That's the deepest, darkest pain I've ever felt, losing a child.

So I think with the hope of Makena, I've been able to create a family. I wouldn't have kept growing my family knowing that there's nothing out there; there's nothing I can do. So I just really feel that, at this point, the research needs to be redone, or they need to look at a different population if they're saying this isn't working because it's worked for me for two pregnancies.

DR. WITTEN: Thank you.

We're going to move on to the next speaker.

Thank you, Ms. Mullins.

I understand that Ms. Greenberg is on the phone now, so, Ms. Greenberg, you have 10 minutes.

MS. GREENBERG: Thank you, and thank you, members of a panel.

My name is Sally Greenberg. I am the executive director of the National Consumers League, the oldest consumer advocacy organization. For 123 years, it's been our mission to protect and promote the social and economic justice for consumers, and to provide the consumer perspective on safe and effective medicines in patient-centered

health care.

We are deeply concerned about CDER's recommendation to withdraw all forms of 17P. We've shared our concerns with the FDA many times, dating back to our first letter in June of 2020, which urged the agency to protect patient access to this critical therapy for preterm birth. The sentiments outlined in that letter -- which was co-signed by more than a dozen maternal and infant health advocates, many of whom you're going to hear from today and tomorrow -- have been reiterated in a series of subsequent letters, statements, and requests for meetings.

Long before that, the National Consumers League spent years advocating for increased regulation and oversight of medication compounding. That's an issue that's central to the question of why pregnant women deserve to maintain access to approved 17P, the only class of FDA drugs indicated to prevent a recurrent spontaneous preterm birth.

I appreciate having the time today to share the thoughts on behalf of NCL, and wanted to start

by addressing some of the distortions and half-truths that have been floating around in the public dialogue about 17P. I'm not a scientist or a doctor, but I take our organization's mission and ethos very seriously, and it's rooted in safe products for consumers, and my responsibility as a consumer advocate I take very seriously as well. I've talked with numerous scientific medical and regulatory experts about this issue to separate fact from fiction. It's unfortunate there's misinformation about such a serious subject, but that does appear to be the case.

For example, I think you're going to hear from certain stakeholders that Makena never should have been approved, but the truth is that we aren't here today to debate the past. The class of products has been on the market for 10 years, and it's about the safety and efficacy evidence to support that. We stated very simply, we're here because of conflicting efficacy data, however, that doesn't render the original evidence null and void.

You may also hear that there's no confirmed

clinical benefit to 17P. This is not supported by the existing body of literature or the experiences of hundreds of thousands of American women, one of whom you just heard from. The primary basis for FDA approval of Makena was a randomized-controlled trial conducted through an NIH network in the highest risk preterm birth centers in the United States. The one-third reduction in recurrent preterm birth was described in the New England Journal of Medicine in 2003.

Makena's one of the most well-studied medications given in pregnancy, with data from more than 2,000 women who participated in placebo-controlled trials and more than 350,000 women treated to date. Every day, doctors prescribe 17P for their patients because they've seen evidence of its effectiveness.

You may also hear that the benefits of Makena don't outweigh the risks. This implies that there are safety issues with the therapy, but the published evidence, both from clinical trials and ongoing safety surveillance, doesn't bear this out.

We know the FDA can act when there are safety issues, and we believe that if such issues existed, the FDA, which is one of the most stringent and respected regulatory bodies in the world, would have waited until now to act.

You may hear also that there are other options that can replace 17P as a standard of care. This is simply not the case. With very few medications approved to be given in pregnancy, and no others that are beyond Makena and its generics for this specific use, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine continue to support their members' expertise in determining if Makena is appropriate for their patients, and with the ongoing regulatory situation, this fact is compelling.

Yet, the regulatory uncertainty relating to 17P has created what must be an unprecedented situation, where some providers are putting their patients on vaginal progesterone, which was previously denied approval for this indication, and

it's often prescribed in compounded form and would, therefore, not likely be covered by insurance.

I can't imagine that the FDA intended to put healthcare providers and pregnant people in this kind of position when there continues to be a safe, approved standard of care for pregnant women at risk of another preterm birth, when the issue at hand is inconclusive efficacy data from two conflicting trials, but that is indeed the situation before us.

You may also hear about the precautionary principle of public health as a reason to remove all forms of 17P from the market. Again, this is a diversion that seeks to focus this hearing on implied, non-existent safety issues, rather than on the effectiveness of this medication. I would think the precautionary principle, in fact, of public health would be much more logically applied to the use of vaginal progesterone for recurrent spontaneous preterm birth since that product was denied approval for this indication. But it is increasingly being used off label in compounded

form, and therefore not covered by insurance, and it's essentially being treated as an approved equivalent therapy.

You may also hear that the sponsor put those who speak and support continued access to 17P up to defending the product, but the truth is that the health of mothers and babies, for the National Consumers League anyway, has been one that we have had for over 100 years, and no one needs to ask us to speak up.

In fact, our first leader, Florence Kelley, she led the organization since 1899 for our first 33 years, and led the campaign to enact the first federal healthcare bill. It was known as the Sheppard-Towner Act of 1921. It allocated funds, federal funds, to combat elevated mortality rates among mothers and newborns. The money went to state programs for mothers and babies, particularly prenatal and newborn care facilities in rural states. So for decades, NCL has worked on our own and in collaboration with other advocates to ensure access to safe therapies, and that is why I'm here

today.

I'm both a mother and a leader of an organization that cares greatly about the safety and welfare of consumers and patients. This personal and shared distress over a decision that can impact the long-term health of women and babies led NCL to spearhead the Preterm Birth Alliance, a group of 15 advocacy organizations who share a common concern about the state of preterm birth in the United States and the proposed withdrawal of 17P. My colleague, Milena Berhane, who leads the Alliance, will talk on behalf of the coalition tomorrow.

I want to state plainly and for the record that the NCL believes that the FDA can create a win-win path that leads to both new data in 17P and protected access for pregnant women. I also want to conclude with a few notes about compounding and research.

Regarding compounding first, while it has a role in our healthcare system, creating a situation where more pregnant women with a history of preterm

births are given compounded drugs is an unwise course of action. Years ago, NCL led an advocacy effort to promote passage of federal legislation to strengthen laws relating to compounding a medication. We know that, if done improperly, the process of compounding can pose significant safety risks.

Yes, there has been progress since 2012, when a series of medical errors resulted in the contamination of compounded products, which in turn caused a deadly fungal meningitis to break out in the U.S. It killed more than 70 people, and it caused more than 750 cases of infection. We know that there have been at least 26 safety recalls of compounded 17P since 2012, however, since the FDA does not interact with a vast majority of compounders, it is not often aware of the problems until after the report of an adverse event or contamination, and because of this, we strongly urge that all current FDA-approved options remain available while additional studies are conducted.

Regarding the research, women who are most

affected by preterm birth are the same women who historically have been underrepresented in clinical trials. Given the conflicting efficacy data between the original approval trial and the confirmatory trial, we think it's critical that more diverse efficacy research be gathered and combined with the extensive amount of real-world evidence that exists today.

Pregnancy should be one of the most special and exciting times in a woman's life. Unfortunately, for about 1 in 10 women in America, their anticipation may be cut short because of an unexpected preterm delivery. This burden is not born equally. Black women in America have 50 percent increased rate of delivery before 37 weeks of pregnancy.

On this point, the NAACP recently spearheaded a letter to the FDA that was also signed by a number of groups, and in that letter they said, "We believe that the confirmed evidence of this treatment for Black women in this country is determinative and that any disruption of access

would be detrimental." The letter goes on to urge the agency to consider all of the available mechanisms to maintain equitable access to 17P, while additional evidence can be developed that more accurately reflects underrepresented racial and ethnic populations in the U.S. This is a compelling argument from a respected source.

So my question to the committee is why, when the sponsor has publicly said they're willing to do more research, we would leave that option off the table when there's conflicting efficacy data? To remove the only approved therapeutic option that can help reduce the likelihood of another spontaneous preterm birth, with the knowledge that the population that benefits from 17P are women of color, is not in line with consumer interest.

In wrapping up, I just want to say that the health of mothers and babies has been a focus of our organization for more than 100 years, and will continue to be so for as long as we are around. And I am here because what the NCL has always been about is protecting the rights of vulnerable

consumers and patients. So to the committee, I urge you to keep these perspectives in mind when making your recommendation to the agency. There's a win-win path here that could lead to both new data and protected access. Let's take it. Thank you so much to the committee for your time.

DR. WITTEN: Thank you.

We're going to go to the next speaker, Ms. Patricia Joseph.

Ms. Joseph, you have five minutes.

MS. JOSEPH: Thank you.

Thank you for having me today. My name is Patricia Joseph. I'm here as a mom of two, living in the Cleveland, Ohio area, and I have no financial connection to Makena. I read about this hearing in the New York Times. I just wanted to make sure you heard firsthand about my experience.

When I was pregnant with my first child, I had no indications that I would deliver early. I lived in the Bay Area at the time and was planning to deliver at Lucile Packard Hospital at Stanford just because it was convenient, and it was where my

OB delivered, but I went into spontaneous preterm labor at just under 34 weeks.

When my daughter was born, she was whisked away by a team of doctors. I didn't even hear her cry. The first time I ever held her was in the NICU. She was covered in tubes, and her arm was fastened down to a board for her IV tubes. She remained there for 21 days. Having a newborn in the NICU for that long was scary and really challenging. I am exceptionally grateful for the world-class care she received there from the nurses and doctors, but leaving that hospital every day without my child was heart-wrenching. She always had trouble putting on weight as a baby and consistently measured in the third or fourth percentile for this growth metric.

By contrast, during my second pregnancy, my OB/GYN at Stanford recommended I take Makena. I did so, dutifully going to her office every week to receive injections from the nurses, and I was thrilled to carry my second daughter just over 38 weeks. She was born past the period considered

premature, and I got to take her home with me from the hospital. I truly believe Makena gave me the best chance at carrying her to full term.

To me, any possible benefits to moms and babies clearly outweigh drawbacks. Just like most moms would, I read up on the drug and made the best decision for my family. Progesterone is not controversial or new; it is used by millions of women. I read that there is no known reports of overdose, and also that it's used to treat premenstrual syndrome, fibrocystic breast disease, adenosis, breast pain, and birth control, and has been found significantly effective for extending the life of women with endometrial cancer.

Now, I'm trained in statistics. I'm aware there are questions here of efficacy, but the thought of taking away the one safe, readily available treatment that might help prevent premature delivery seems unacceptably dangerous without a ready alternative.

I thank God I gave birth in a nationally recognized, level 4 neonatal hospital that was able

to provide the extraordinary medical attention my first daughter needed. I'm beyond grateful now that my now 7 year old is healthy, happy, keeping up in school, but she also required over half a million dollars of care in the first month of life. I also thank God I had really good insurance. By contrast, though, I took my now 4 year old home from the very same hospital just a few days after she was born. I had the completely, quote/unquote, "normal experience." She had no trouble keeping up her weight, and she hit all of her growth milestones on time.

I truly believe if there's even a slight chance that Makena made a difference in her life, we cannot deny that to others. The health effects of premature birth on children are well documented. It can be devastating for both children and families, and lasts a lifetime, especially for those mothers without access to the world-class care and financial privileges I had.

I read a quote from the AMA Journal of Ethics while preparing for today that really spoke

to me. It said, "Neonatal intensive care is one of the triumphs of modern medicine. Babies who inevitably would have died a few decades ago routinely survive today, but the success of NICU should not lead us to see them as the only solution to infant mortality or as an adequate moral response to our children's health needs. We should constantly remind ourselves that the need for so much intensive care for so many babies is a sign of the political, medical, and moral failure in developing ways to address the problems that sustain an epidemic of prematurity."

I truly believe Makena and 17P are important parts of those efforts. I urge you to keep them available to patients while additional research is completed. Thank you so much for allowing me to speak.

DR. WITTEN: Thank you.

I'd like to next call on Ms. Linda Blount.

Ms. Blount, you have three minutes. Thank you.

MR. KAWCZYNSKI: Ms. Blount didn't show up,

so we're going to move on to the next one.

DR. WITTEN: Right. So I'd like to call on Ms. Jill Escher.

Ms. Escher, you have three minutes.

MS. ESCHER: Hello. Can you hear me?

DR. WITTEN: Yes.

MS. ESCHER: Okay. Thank you.

Hi. My name is Jill Escher. I first want to say I have no conflicts to declare. I receive no Covis or pharmaceutical industry funding, either directly or indirectly. I'm a research advocate based in California, who in 2015 submitted an FDA citizens' petition to withdraw approval for Makena. The FDA at that time denied my petition in 2018, so of course I was thrilled to see new FDA efforts around this drug, and I thank you and the committee for this.

I would like to address three general matters that I believe are problematic but have not yet received sufficient attention in all of the discussions around Makena. First, let us understand that Makena is a powerful endocrine

disruptor that mimic, but does not duplicate, the molecular action of endogenous progesterone. Given that this is 2022, and we've learned a thing or two about generational impacts of hormone disrupting chemicals, it is absolutely essential that the FDA require investigation of how powerful and high dose fake hormones like 17P and Makena affect the molecular programming, not just of the fetus, but also of the fetal germ cells. And I realize that this seems like an esoteric point, but trust me, it is not.

As I explained in my written comment, during gestation, the fetal germ cells, which are the future sperm and eggs of the baby, are largely stripped of their DNA methylation, and then they are reprogrammed in a sex-specific manner, depending on if they reside in a female or male gonad. Interfering with endogenous sex hormone signaling is a very reckless undertaking during this particular phase of life. This is the most vulnerable period in the human life cycle, and despite the high likelihood of 17P exerting an

impact on the reprogramming of the fetal germline, it has been entirely ignored.

Second, if we are to expose children to acute doses of synthetic sex steroids in utero, it is morally and pragmatically imperative that we make this information available to the exposed individuals as soon as they become adults or even before. I did not know of my very heavy exposure in utero to 17P until I was 45 years old, and obtaining those records was nothing short of an absolute miracle.

Almost no people who are exposed to the synthetic sex steroids in utero have any knowledge, they have been so exposed. These exposures can have psychosocial developmental consequences, as Drs. Reinisch and Karow described in a landmark 1977 paper, in which, by the way, I was an exposed subject. We who were exposed were, in a word, more kind of Aspie. We were more independent, we were less group-oriented, we were less in need of sucker [indiscernible]. In short, the drug had impact on the sexual dimorphism and the

psychosocial outcomes of the brain.

Third, and I think this is an important point, there is an underlying assumption that in all of these debates that somehow preterm birth is the fault of the physiology of the female, of the mother, we have learned, however, especially in recent years, that the father's sperm quality plays a significant role in fetal development and outcomes. Paternal alcohol, smoking, drugs, pharmaceuticals, oxidative stress, chemical exposure, including endocrine disruptors, and even depression have been linked to adverse outcomes, including preterm births in many cases.

I think that's all I really wanted to say, and I just want to definitely, absolutely emphasize the fact that we must make medical records, to those of us who were exposed, available to all people who have been exposed, not just me. I think one of the reasons that we don't hear very much about adverse outcomes over the long term is that, virtually, none of the people who have this exposure know about it. Thank you so much for your

consideration

DR. WITTEN: Thank you.

We'll now move on to questions for this group of public presenters from the advisory committee, CDER, 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. I will start by first providing CDER, and then Covis, four minutes each to ask questions. 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 AC members, after we finish asking CDER and Covis for any initial questions, please use the raise-hand icon to indicate that you have a question, or remember to lower your hand by clicking the icon again after you've asked the question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter. Finally, it will be helpful for everyone to acknowledge the end of your question with a, "Thank

you; that's all I have for my question," so we can move on to the next questioner.

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

CDER, do you have questions you'd like to ask of the presenters?

DR. STEIN: Thank you, Dr. Witten. This is Peter Stein, director of the Office of New Drugs, CDER. We don't have questions. I just want to express our appreciation for the perspectives that speakers have shared. It was very helpful to hear, and we certainly appreciate their sharing their views. Thank you.

DR. WITTEN: Thank you.

Covis, do you have questions for the presenters?

DR. CHARI: Likewise, we have no questions for the presenters, but we would like to thank everyone for the time that they have taken to prepare their statements and be here today.

DR. WITTEN: Okay. Thank you.

Now we'll move on to questions from the

advisory committee.

Dr. Cassandra Henderson, please ask your question.

DR. HENDERSON: Thank you. Thank you very much.

I, too, would like to thank the presenters for taking the time to come in and share --

MR. KAWCZYNSKI: Excuse me. Dr. Henderson, can you please pull the mic closer to your mouth, please? Thank you.

DR. HENDERSON: Okay.

I, too, would like to thank the presenters for coming and taking the time to talk to us. I'd like to ask a question of Ms. Escher, Jill Escher. I was really taken with your presentation, and I'd like to thank you.

How did you discover you had been exposed? Was it a registry or you just got involved with the person who did the study?

MS. ESCHER: Oh, wow. This is a long story. I'll try to make it very, very short.

I have two children with idiopathic autism,

and I became very interested in the idea that something had perhaps tampered with the reprogramming of my eggs when I was in utero, resulting in abnormal dysregulation of genetic function in my children. And I looked online, and I saw that there was a study published in 1977 on children who'd been exposed in utero to either high doses of synthetic estrogens or high doses of synthetic progestin, and it occurred to me -- and I remembered back to when I was 8 years old -- that I was one of the kids who were studied.

I contacted the author of that study, Dr. June Reinisch, who was a very famous researcher on sexual development, and she had been chair of the Kinsey Institute. And my records were stored at the Kinsey Institute all those years, and that's how I got them. It was a complete fluke.

DR. HENDERSON: Okay. Well, thank you for sharing. Take care.

I'm done; no further questions. Thank you.

DR. WITTEN: Thank you.

Other questions from the advisory committee?

(No response.)

DR. WITTEN: Okay. Seeing none -- and I don't see any from CDER or Covis, I'd like to echo the thanks that CDER and Covis gave to the speakers, and we'll now continue with the presentations from the next set of public participants.

For this session, as a reminder, the time allotted to each speaker varies on the amount of time requested to speak. We'll ask you to state your name and your affiliation, if relevant to this hearing, and if you have any financial interest relevant to this hearing. FDA encourages you to state the interest as you begin.

Our first speaker is Mr. Urato, who has slides, so perhaps you can pull up the slides. You have 20 minutes. You may begin.

DR. URATO: Great. Thanks very much.

My name is Dr. Adam Urato, and I'm an obstetrician/gynecologist and the chief of Maternal-Fetal Medicine at MetroWest Medical Center in Framingham, Massachusetts. I was a

co-petitioner with Public Citizen on the 2019 citizens' petition to the FDA to withdraw approval of Makena. I appreciate the opportunity to speak at this hearing today. I'm here to strongly urge the FDA to withdraw approval of Makena. I'm a full-time clinician who takes care of thousands of pregnant women in my community in Massachusetts. I counsel patients with prior preterm birth regularly, and I've delivered lots of babies in my career, many of whom were premature. I have no financial conflicts of interest.

I continue to work to get Makena pulled off the market because I feel that it is simply outrageous that we're continuing to inject pregnant women with this ineffective synthetic hormone that carries risks for moms and babies. To understand Makena, I think it helps to start with remembering the DES tragedy.

Diethylstilbestrol, or DES, was a synthetic hormone that was used by millions of pregnant women to prevent miscarriages and premature deliveries from the late 1930s to the early 1970s. For

decades, it was promoted as effective and safe for mothers and their developing babies. It wasn't until much later that the true effects of this drug became apparent. DES resulted in severe long-term health effects for many who were exposed to it. A major part of the tragedy of DES is that despite how the drug was promoted to the public, it was not effective in preventing miscarriage and preterm births. The lesson we supposedly learned from DES was clear, and we vowed never to do this again.

I call this the DES promise. We in the obstetrical community agreed that we would never again expose pregnant women and their developing babies to a synthetic hormone that did not have good evidence of proven effectiveness, and Makena is not effective. It has not been proven to be effective at preventing preterm birth. This is clear from the scientific evidence.

The Meis trial was seriously flawed. I will not go into detail on this today, as Mike Carome from Public Citizen will be addressing this in his testimony tomorrow. Furthermore, Makena did not

show any clinical health benefit in the Meis trial. Makena then failed in the PROLONG trial. It did not prevent preterm birth, and there are now several other studies looking at real-world experience, and these do not show decreased preterm birth with Makena. We've heard about some of them from this morning. Studies from Dallas, Pennsylvania, Boston, and the United States overall show that Makena does not prevent preterm delivery, and I've listed only a few of them here. There are, as I said, more studies that the FDA discusses in their briefing materials.

Here are the results from Dallas, showing no decrease in preterm birth rates with Makena use. The results from Pennsylvania also show no benefit. Data from Boston demonstrates that even with 4-fold less Makena use, after the PROLONG trial results were known, there was no difference in preterm birth rates, and data from the U.S. overall shows the same, no decrease in preterm birth with Makena use.

Importantly, Makena has never been shown to

provide any clinical health benefit whatsoever. I just want to emphasize this. Right now, in the United States, we're injecting pregnant women with a synthetic hormone that has never been shown to improve health. So Makena has not been proven to prevent preterm birth or to have any clinical health benefit, and yet pregnant women keep getting injected with this drug. We cannot continue to allow this. In the absence of benefit, the known and potential risks of Makena are unacceptable.

It is important to remember that Makena is a synthetic hormone. It's not the same as natural progesterone. You can see that from these chemical structure images from the National Institutes of Health website. The drug freely crosses the placenta during development, so the baby is being exposed to a novel synthetic chemical compound not previously seen during human fetal development.

We must remember, chemical compounds have chemical effects on pregnant women and developing babies. This is common sense. Chemicals put into biologic systems will have chemical effects. There

are growing safety concerns. The drug label warns about injection site reactions, depression, blood clots, gestational diabetes, and stillbirth. You can see all of these risks right on the drug label.

I want to focus for a moment on stillbirth. I think Makena may be associated with stillbirth. In both the Meis trial and PROLONG, there were increased rates of stillbirth in the Makena arm. In Meis, the Makena arm had more than a 50 percent increase in stillbirths. In PROLONG, the risk of stillbirth was more than doubled in the Makena arm.

The FDA briefing document for the 2019 FDA advisory committee meeting clearly states, quote, "There appeared to be a trend toward an increase in stillbirths in both trials." Other randomized, trials, including the Rouse twin study from 2007, Grobman from 2019, and Senat from 2013 have also shown a concerning signal. Earlier this year, 2022, a systematic review and meta-analysis from Boelig, et al., comparing Makena to vaginal progesterone, showed that the Makena group had an increase in perinatal deaths, 4.4 percent versus

2.2 percent. I do not think that the science is settled on the issue of Makena and stillbirth.

Cancers in the offspring are another major concern. With DES, we've already seen that fetal exposure to a synthetic hormone can lead to cancers later in life. Caitlin Murphy and her group studied this issue with Delalutin, the same synthetic hormone as Makena, and they found increased rates of cancers in the group exposed in utero.

The effect of Makena on the developing fetal brain is another area of concern. The developing fetal brain is loaded with progesterone receptors. Makena is not the same as natural progesterone, so we can expect that Makena will affect the developing fetal brain. Several animal studies show that exposure to Makena in utero affects the brain and has neurobehavioral consequences.

Fahrenkopf recently showed that developmental exposure to Makena disrupted brain development. It disrupted the mesocortical serotonin pathway and altered impulsive decision

making. Serpa recently showed that Makena exposure during brain development led to impairment in learning. Willing recently showed that Makena exposure in utero impairs cognitive flexibility in adulthood.

Each one of these authors in their abstract note that there is little understanding -- again, that's little understanding -- of Makena's potential effects on the developing fetal brain. All of this makes sense. I call this fetal brain development common sense.

If progesterone plays a key role in the development of the fetal brain, which it does, and if Makena enters the developing fetal brain and behaves differently than natural progesterone, which it does, then we would expect to see brain alterations and neural behavioral consequences with exposure to Makena during fetal development, and there are other unknown short- and long-term potential harms.

Time and time again, we have seen that when we study chemical exposures for long enough, we

find effects and harms that we did not initially realize. In obstetrics, we've seen this with thalidomide, DES, valproic acid, and the use of antenatal corticosteroids. With Makena use in pregnancy, we are exposing developing babies to a synthetic hormone at a crucial developmental time. That raises safety concerns for me. Why do we assume it's safe to expose a developing fetus to synthetic hormones? Is there a reassuring track record of safety with doing that? Why would we make an assumption of developmental, and especially neurodevelopmental, safety?

I think it's accurate to say that when it comes to the effects of chemical exposures, the arc of history bends toward showing harmful effects over time, and this raises an important issue about outpatient counseling. I counsel pregnant women every day in my office. When I discuss a medication with my patients, I review the risks and benefits. For Makena, the risks include injection site reactions, depression, blood clots, gestational diabetes, stillbirth, and unknown

long-term adverse effects from in utero exposure. So those are the risks. And benefits? What are the benefits? There are no benefits. Makena has no proven benefits.

I would like to turn for a moment to one of the main arguments that Covis and pro-Makena sources have been making, and that is that because Black women have higher rates of preterm birth, then it is important to keep Makena on the market in the interest of racial equity. I think this argument is seriously flawed. It is true that Black women do have higher rates of preterm birth, but there's no evidence that Makena is more effective in Black women.

FDA specifically looked at this, and concluded that there is no evidence of effectiveness in Black moms. So keeping Makena on the market so that it can be injected into Black women does nothing to improve racial equity. In fact, that strategy will hurt racial equity because Black women will disproportionately be injected with an ineffective and risky drug. This approach

will put Black moms and babies at risk.

I also want to add that I think we should view this deceptive racial equity argument as an unethical corporate strategy. It just doesn't seem right to me that the groups behind this drug appear to be supporting and pushing this racial equity argument. They're essentially using high-risk Black women in order to keep Makena on the market and protect their corporate profits. This just doesn't seem appropriate or proper. How does keeping Makena on the market so pregnant Black women can disproportionately be injected with an ineffective drug, how does this improve racial equity in any way?

In summary, I'm testifying today to ask the committee to vote to pull Makena off the market. The overwhelming preponderance of scientific evidence shows that it does not prevent preterm birth. It has never been shown to have a clinical health benefit, and it carries risks for moms and babies. DES was given to pregnant women for over 30 years, and it led to tragic consequences. We're

currently at the 19-year mark with Makena. It is well past time for us to stop injecting pregnant women with this drug and for it to be pulled off the market.

In summary, the lesson we learned from the DES tragedy was clear. We would never again expose pregnant women and their developing babies to a synthetic hormone that carried risks and did not have good evidence of proven effectiveness, and yet more than 50 years later, here we are making that same mistake. History will judge us poorly if we do not pull this drug off the market, and we continue injecting this synthetic hormone into pregnant women. Thank you very much for allowing me to speak to you today.

DR. WITTEN: Thank you, Dr. Urato.

We're now going to move on to Dr. Hugh Miller.

Dr. Miller, you have five minutes.

DR. MILLER: Thank you. This is Dr. Hugh Miller. I, too, am a long practicing maternal-fetal medicine specialist who's taken care

of thousands of women, many in desperate circumstances. I really appreciate the committee allowing me to speak today. My only conflict is that I was a participating investigator in the PROLONG trial but have no ongoing relationship with Covis.

I want to start by just saying I believe in gravity, but it turns out that there are several places on earth where it doesn't operate the way we expect, including the Mystery Spot in Santa Cruz, California. However, it's because I believe in gravity that I accept the premise that a much larger study that discredits the findings of a smaller study should drive the committee's action and justify the removal of 17-OHPC from the U.S. market. But just as gravity doesn't exist in all circumstances, the conclusions of the PROLONG study should be interpreted with caution, accepting that there may be other significant elements at work.

The Meis trial, despite what my colleague suggests, was a landmark trial that changed the practice of how obstetricians manage recurrent

preterm birth prevention in the USA. The introduction of 17-OHPC in the early 2000s gave us a tool that previously hadn't existed, and it is likely that we misunderstood its value and its limitations in our enthusiasm to mitigate the scourge of spontaneous preterm births. However, that is not to say that 17-0HPC has no value, but rather it is now incumbent on us to clarify that value for whom it has ultimate value.

It is important to remember that the Meis trial was conducted under rigorous conditions, using the flagship MFMU network. The results were so compelling that the study had to be stopped by the DSMB because it was considered unethical to continue to restrict access to 17-OHPC and subject future women to the increased risk of spontaneous preterm birth. Equally relevant is the narrowness of the inclusion criteria that focused on one primary risk factor, a history of prior preterm births without accounting for the multifactorial nature of spontaneous preterm birth.

It is unfortunate that to this day, we still

don't understand the underlying mechanism that predicts spontaneous preterm birth, let alone how to defeat them. In 1998, as the Meis trial was being planned, we knew that strep, inflammation, bleeding, and placental residual interface all contributed to spontaneous preterm birth. Although we didn't call them social determinants of health at this time, we knew they also played a central role in spontaneous preterm birth by provoking many of the signs previously mentioned.

What was true then, and is largely true now, is that while these risks are real, they are hard to quantitate, and we have limited insight into how they interact with a history of spontaneous preterm birth to affect preterm birth. The PROLONG trial was helpful in clarifying that recurrent spontaneous preterm birth cannot be understood simply to the event of having previously delivered a child prematurely, but rather through the combination of their risk factors, along with genetic and environmental risks, that each woman brings to the next pregnancy.

The Knudson, or two-hit hypothesis, is well defined in other areas of medicine and may account for why the Meis and PROLONG clinical trial population, though similar, are ultimately substantially different, resulting in very different outcomes when principally only linked by one variable. Much has been written since 2019, exposing the substantive differences between these two study populations. Those differences span the spectrum of a nearly 3-fold increase in the number of prior spontaneous preterm births in the Meis trial versus the PROLONG trial, to the socioeconomic differences that exist between an indigent U.S. population and a largely Eastern European population.

The committee is well aware of these differences, and I urge the committee, at a minimum, to consider that these differences could account for the divergent outcomes of these two trials. Therefore, I think it is mistake to use the PROLONG trial to invalidate the results of the Meis trial. While it is possible that the results

of the Meis trial may represent a false positive result, it is unlikely given the quality and the size of the study, not to mention the reasons I've already given.

If you can find merit in the Meis trial, then at least consider the harm that could be created by prematurely removing a treatment that might have the merit for a smaller subset like at-risk women with a history of spontaneous preterm birth. While the efficacy of 17-OHPC has come into question, the PROLONG trial provided a lot of additional information about the drug's relative safety with respect to GBM, thromboembolism, hypertensive disease of pregnancy, and cholestasis of pregnancy. I realize that safety is not the paramount concern of this committee, but it is relevant as this committee considers the risk versus the benefit associated with this drug while it considers keeping it on the market.

We can all agree that recurrent spontaneous preterm birth is a serious problem.

DR. WITTEN: Dr. Miller, can you wrap up

your presentation?

DR. MILLER: Yes.

I guess how I would end is don't let typical perceptions of gravity or inertia drive this process. This is the time to think outside of the box, and go the extra mile by supporting further study to answer the remaining questions that clearly exists. I strongly support the retention of Makena 17-OHPC in the market so that selected women can benefit from this therapy. Thank you for allowing me to present at this meeting.

DR. WITTEN: Thank you, Dr. Miller.

Next, we're going to hear from Ms. Marianela Camarillo. You have three minutes.

MS. CAMARILLO: Hello, and thank you for the opportunity to speak today. My name is Marianela Camarillo, and I am the executive director of Miracle Babies. Miracle Babies is a 501(c)(3) nonprofit, dedicated to helping perinatal mothers and their families during their time of need by providing home-to-hospital transportation, mental health assistance via telemedicine, and supportive

services. Our tagline is "Together for a Better Beginning," reflecting the importance of the family connection in the critical early weeks and months of an infant's life, and the mental well-being of mother. We're based in San Diego, California, and we offer our services in San Diego, Orange County, and Los Angeles.

Through our programs, we seek to improve health and mental well-being and address inequities for parents through free access to all our programming initiatives. We are able --

DR. WITTEN: Excuse me. I'm having trouble hearing. Can you speak into the mic, into your microphone, Ms. Camarillo?

MS. CAMARILLO: Can you hear me now?

DR. WITTEN: That's much better.

MS. CAMARILLO: Okay. I'm sorry.

We are able to provide our free services from grants, individual philanthropy, and corporate support. For full transparency, the panel should be aware that Miracle Babies nor myself have been compensated for today or our participation in the

Preterm Birth Health Prevention Alliance, but we have received past sponsorship from COVIS Pharma.

We at Miracle Babies see firsthand the stress, financial strain, and difficult decisions that are made by NICU families. This unexpected journey is one that no parent hopes to experience. We join the Alliance, as we are one of the only agencies in the region providing direct services to parents with hospitalized infants. We again see firsthand the disproportionate disparities to women of color. For example, our transportation passengers are 15 percent African American and over 60 percent Hispanic.

A few years ago, we at Miracle Babies surveyed our past program beneficiaries, and we asked parents of preterm babies, "Would you have wanted to know if you were at risk of delivering early?" Of our program beneficiaries that responded to our surveys, two-thirds said they didn't know they were at risk of preterm labor; 95 percent said they would have wanted to know if they were at risk of preterm labor; and 98 percent

responded they would have wanted to know even if their doctor couldn't change their outcome.

The words our respondents best use to describe how they felt when their baby was born prematurely, "scared, stressed, anxious, and sad." Words best used to describe how they might feel if they knew they were at risk of a preterm baby, "able to plan, knowledgeable, prepared, and proactive."

As a member of the Alliance, we collectively seek to improve preterm birth outcomes in the U.S. by maintaining access to safe FDA-approved treatments and advocating for more diverse medical research that adequately represents the experiences of women of color. For more than a decade, maternal-fetal medicine specialists, including our founder who's a director of Scripps' perinatology, have safely used 17P and its generics to help women with recurrent preterm birth carry their babies closer to term.

We believe maternal mental healthcare providers and their patients should have the

opportunity to decide whether 17P would be beneficial to them in their pregnancy. We appreciate your time. We are together for a better beginning. Thank you.

DR. WITTEN: Thank you.

Now we're going to move on to call on Ms. Suzanne Robotti.

Ms. Robotti, you have five minutes.

MS. ROBOTTI: Thank you. As executive director of DES Action USA, and the founder of MedShadow Foundation, and as a DES daughter myself, I am here to warn you that Makena is clearly today's DES. Neither of the two nonprofits that I run accept money or support from pharmaceutical companies. I have no conflicts of interest.

Like DES, Makena is a preterm birth drug not proven to prevent preterm birth. Makena has growing signals that it may be causing harm just like DES. Despite the FDA's call for Makena to be pulled from the market in October 2020, this synthetic hormone is still being marketed, sold, and injected into pregnant women.

The full name for DES is diethylstilbestrol. It is a synthetic hormone that was prescribed to millions of pregnant women who were told it would prevent miscarriages and premature deliveries. It was prescribed from the 1940s until the 1970s when, by sheer luck, a linked tumor and deadly vaginal and cervical cancer called clear cell adenocarcinoma, or CCA, in young women was linked to their exposure to DES in the womb. The cancer most often occurred in women in their early 20s and late teenage years. This is 20 years after their mothers were given DES.

Over the years of follow-up and research, DES has been shown to also increase breast cancers in the mothers who were given DES. The daughters exposed in the womb were found to have an increased risk of breast and CCA cancers, along with structural anomalies in the reproductive tract, leading to infertility, stillbirths, and miscarriages. The daughters also suffered a high rate of endometriosis; uterine fibroids; early menopause; and the constellation of other

conditions.

DES sons exposed in utero showed genital organ complications with problems such as small testes and/or undescended testes; epididymal cysts; hypospadias; among other issues. Another third generation, the grandchildren of those DES mothers, are seeing indications of preterm birth delivery; delaying menstruation regularity; skipping periods; hypospadias; and genital defects.

Preterm birth is a serious medical risk that deserves a medicine that is proven to work and proven not to harm the fetus. Unfortunately, Makena is not that drug. Makena is an old drug, which is previously known as Delalutin, and then Gesteva. Both were removed from the market years ago. Makena's prescribing information already lists possible adverse effects, including depression, blood clots, gestational diabetes, injection site reactions, and even notes a possible link to stillbirth. Finally, a recent study showed increased risk for cancer in children who are exposed to this synthetic hormone in utero, echoing

what was seen in the use of DES.

The FDA's lead statistician voiced her opposition to Makena's approval and was ignored. Makena was not only approved, it became the standard of care. As a condition of the accelerated approval, the FDA required Makena's maker to conduct a second appropriately designed trial. The results of the second trial, PROLONG, were announced in March 2019. Makena did not prevent preterm birth. An FDA advisory committee met in October 2019 to review the research. That committee recommended removing FDA approval and withdrawing the drug from the market.

Even if Makena was effective, the long-term risk to the children are unknown and are not being researched. Since the children are not being tracked, how can we ever know the long-term harms of Makena? Makena crosses the placenta and enters the fetal brain, reproductive organs, and permeates the body. Both animal and human studies suggest that synthetic progestins can affect the developing fetal brain, leading to learning and behavior

differences in childhood.

I am a DES daughter. I could never have children. I started the non-profit MedShadow because of my exposure, because all drugs have side effects, and people have the right to know the risks, along with the possible benefits, of any drug a doctor recommends. My hope is that the world will never see another DES tragedy. I've spent the last 10 years doing my best to keep that from happening.

Makena has the ability to harm the mother, the child, and even the child's child. When you make your recommendations about Makena, remember, you are making decisions for three generations. Safety first, especially when the company cannot even prove that it works. Thank you for your time, and thank you for your service to the FDA.

DR. WITTEN: Thank you.

Now we're going to move on to our next speaker, Ealena Callendar.

Ms. Callendar, you have five minutes.

DR. CALLENDAR: Hello. Thank you for the

opportunity to speak today on behalf of the National Center for Health Research. I'm Dr. Ealena Callendar, an OB/GYN with a master's in public health and a senior fellow at the National Center for Health Research. Our Center is a non-profit think tank that conducts, analyzes, and scrutinizes research on a range of health issues, with a particular focus on which prevention strategies and treatments are most effective for which patients and consumers. We do not accept funding from the companies that make products that are the subject of our work, so we have no conflicts of interest.

In OB/GYN, preterm delivery is one of the most difficult challenges that we face. The causes are complicated and not well understood, but the associated harms are clear and devastating. We all want an effective intervention that will reduce the number of babies delivered too early and lead to better maternal and fetal outcomes.

Unfortunately, current data do not indicate that Makena is the solution we have been seeking.

We strongly encourage this advisory committee to recommend withdrawing approval of Makena and removing the drug from the market. The reason is simple. The confirmatory trial failed to verify clinical benefit, and there is not substantial scientific evidence to establish the drug's effectiveness for its approved use.

Patients must have confidence that FDA-approved drugs are safe and effective. Allowing this drug to remain on the market would undermine the legitimacy of FDA approval and harm the patients that rely on the drug. If the FDA does not withdraw approval of a drug after research shows that it is not effective, what does FDA approval mean? Who can patients and doctors trust?

Makena was approved by the accelerated pathway in 2011 with the condition that the company complete research to confirm clinical benefit. The subsequent trial failed to show that the drug either decreased the frequency of preterm birth or decreased neonatal complications associated with preterm birth. In the simplest terms, the company

has not met the conditions of approval, and therefore approval should be withdrawn.

Preterm birth is a serious problem in the United States and throughout the world. Some have cited the fact that Makena is currently the only FDA-approved drug to help reduce preterm birth as justification for keeping it on the market, but that only makes sense if it has benefits that outweigh the risks. Makena's label warns of multiple adverse reactions that we have discussed here, so based on the current evidence, treatments with Makena exposes women to many risks, but no proven benefit.

The rate of preterm birth in the United States is 10.1 percent today. Among Black women in the U.S., the rate is 51 percent higher than for all other women, but we reject the argument that Makena should remain on the market for this high-risk population given that there is no scientific evidence that Makena is more effective in Black women. Both trials showed similar results for Black and non-Black women. Although the

confirmatory trial had a lower percentage of Black participants compared to the initial trial, even the initial study population was not representative of Makena's intended treatment population.

In 2006, the FDA expressed concern that the number of extremely high-risk patients in the initial trial may have overestimated Makena's efficacy. The original trial paper states, "Our results may not be generalizable to women whose risk factors for preterm delivery are different from the women in this trial." We can't conclude that Makena is more effective for Black women because the initial study was not designed to show that.

Preterm birth is a complex condition for which there is no consensus about the exact cause or about the contribution of individual risk factors. Twenty percent of preterm births are induced for complications in the mother or fetus. Another 25 to 30 percent are spontaneous and unexplained. Makena is indicated only for women who have had a prior preterm birth, but most

preterm deliveries occur in women with no history of a prior preterm delivery.

While Makena is the only FDA-approved drug indicated to prevent preterm birth, it is by no means the only plausible method to address this condition. An interdisciplinary approach is required to further understand the factors that lead to preterm birth and to develop new approaches for prevention. Improvements in the management of hypertensive disorders and diabetes will help decrease the need for medically indicated preterm deliveries.

Recent advances in the field with immunobiology and genomics may need lead to novel therapies, and many experts believe that improving strategies to reduce the health impact of systemic racism would lead to better outcomes for Black women in the U.S. Meanwhile, clinicians may use mechanical therapies, including cerclage and cervical cautery, or vaginal progesterone, where studies have found clear evidence of benefit.

For the last 11 years, it has been the

responsibility of the sponsor to prove that Makena is safe and effective, and the company has failed to accomplish this. If the drug has a different level of efficacy for Black women, high-risk women, or any other subset of women, the company must have better data to support this claim. It would be very difficult at this point to enroll patients in a new randomized-controlled trial while the drug remains approved and on the market.

We strongly encourage the committee to recommend withdrawal of Makena's accelerated approval and require that Makena is removed from the market. Thank you.

DR. WITTEN: Thank you.

And now we're going to move on to our last speaker of this session, Ms. Alanna Temme.

Ms. Temme, you have three minutes.

MS. TEMME: Hi. Yes. My name is Alanna Temme, and I am just calling to speak. I am a mom of three, and my first daughter was born at 34 weeks, which was -- I think someone mentioned it earlier on the phone. It was terrifying, it was

overwhelming, it was scary, and she was in the NICU, and luckily she ended up being perfectly fine and healthy in the long run. But I did use Makena for my subsequent two pregnancies, and my second daughter was in until 38 weeks, which is a totally different experience with a newborn at 38 weeks from 34 weeks. And then my son essentially had to be evicted because he decided to stay in after 40 weeks.

I'm not a scientist or anything, other than I just know anecdotally for me, it worked, and I didn't really do anything differently between my three pregnancies, except for I used Makena for my last two. I will say I hope that there's some consideration of the anxiety and worry that bringing home a preterm baby causes mothers. Being fortunate to have full-term children is certainly a blessing, especially when it's your first. Coming early I think makes it even worse. So I hope the committee considers my story when thinking about what to do moving forward, and that's all I have.

DR. WITTEN: Thank you for your

presentation.

We're now going to proceed with questions for this group of public presenters from the advisory committee, CDER, Covis, and me, and we'll proceed as in the last session. Anyone wishing to ask a question of a public presenter must identify the specific presenter to which the question is being posed. I'm going to start by first providing CDER and Covis four minutes each to ask questions, and 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 you have a question, and remember to lower your hand when you have asked your question. When acknowledged, remember to state your name for the record before you speak and direct your question to a specific speaker. Finally, it would be helpful to acknowledge the end of your question with a, "Thank you; that's all I have for my questions," so we can move on to the next question.

I'm now going to turn things over to CDER for their four minutes to ask questions, and after that's concluded, we'll turn things over to Covis for their four minutes.

So I'm turning it over to CDER.

DR. STEIN: Thank you, Dr. Whitten.

This is Peter Stein, OND, CDER. We don't have any specific questions. Once again, we really do appreciate the really various and very helpful perspectives that were shared by the public speakers, but we don't have any specific questions. Thank you.

DR. WITTEN: Thank you.

And Covis?

DR. CHARI: Thank you, and as well, we from Covis don't have any questions. Again, we want to thank all of the speakers and presenters for taking the time to share their views, and we hope everybody has a great afternoon.

DR. WITTEN: Thank you.

I don't see any hands raised from the advisory committee. Yes, there is one now.

Annie Ellis?

MS. ELLIS: Hi. I just want to thank all the public speakers who are representing mothers, or who have cared for mothers, or who have been mothers or had a mother, for all the work that you do and for coming and sharing with us. I wish that this was a very easy and clear decision, but I want to let you know that I see you, and I hear you all. You're all in my heart, as my head needs to think about the data. Thank you.

DR. WITTEN: Thank you for your comment.

Other comments or questions from the advisory committee members?

Sorry. Did you have a question?

(No audible response.)

DR. WITTEN: No.

Other comments from the advisory committee?

(No response.)

Adjournment

DR. WITTEN: Okay.

I would like to also thank these speakers in this past session for their thoughtful remarks, and

now it's time to adjourn hearing day 1. I'd like to thank the committee for their attention, to thank the public, CDER, and Covis for their participation today. We are looking forward to continuing this hearing tomorrow, starting with a continuation of presentations by public participants.

Day 1 of the hearing is now adjourned. We will reconvene tomorrow, October 18th, at 8:20 a.m. 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 all, everyone.

(Whereupon, at 3:24 p.m., the hearing was adjourned.)