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)

Wednesday, October 19, 2022

8:31 a.m. to 11:21 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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

Joseph P. Alukal, MD

Associate Professor

Department of Urology

Columbia University Irving Medical Center

New York, New York

Esther Eisenberg, MD, MPH

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

Margery Gass, MD

(Chairperson)
Professor of Clinical Emerita
University of Cincinnati College of Medicine
Fred Hutchinson Cancer Research Center
Seattle, Washington

Michael K. Lindsay, MD, MPH

Luella Klein Professor

Division of Maternal-Fetal Medicine

Department of Gynecology and Obstetrics

Emory University School of Medicine

Atlanta, Georgia

Mary B. Munn, MD

Professor and Chairman

Division of Maternal Fetal Medicine

Department of Obstetrics and Gynecology

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

Mobile, Alabama

Kristine E. Shields, MSN, DrPH

(Consumer Representative)

Shields' Medical Writing & Consulting, LLC

Pipersville, Pennsylvania

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

Michelle C. Fox, MD, MPH, FACOG

(Industry Representative)

Distinguished Investigator, Global Clinical Development

Global Clinical Development

Merck Research Laboratories

126 East Lincoln Avenue

Rahway, New Jersey

TEMPORARY MEMBERS (Voting)

Aaron B. Caughey, MD, MPP, MPH, PhD

Professor and Chair

Department of Obstetrics & Gynecology

Associate Dean for Women's Health Research & Policy

Oregon Health & Science University

Portland, Oregon

Susan S. Ellenberg, PhD

Professor Emerita, Biostatistics

Medical Ethics and Health Policy

Perelman School of Medicine

University of Pennsylvania

Philadelphia, Pennsylvania

Annie Ellis

(Patient Representative)

White Plains, New York

Lorie M. Harper, MD, MSCI

Associate Professor

Department of Women's Health

Division Chief, Maternal-Fetal Medicine

University of Texas at Austin, Dell Medical School

Austin, Texas

Cassandra E. Henderson MD, CDCES

Maternal Fetal Medicine Consultant

Garden OB GYN

Physician Advisor, Rockwood Partners DPP

New York, New York

Mark L. Hudak, MD

Professor and Chair of Pediatrics

Chief, Division on Neonatology

University of Florida College of Medicine - Jacksonville

Jacksonville, Florida

Anjali Kaimal, MD, MAS

Professor and Vice Chair of Clinical Operations

Department of Obstetrics and Gynecology

Morsani College of Medicine

University of South Florida

Tampa, Florida

Mara McAdams-DeMarco, PhD

Associate Professor of Surgery and

Population Health

Associate Vice Chair for Research, Department of

Surgery

New York University

New York, New York

Sarah G. Običan, MD

Associate Professor

Division Director, Maternal Fetal Medicine

University of South Florida

Tampa, Florida

C O N T E N T S

P R O C E E D I N G S

(8:31 a.m.)

Call to Order

Reconvening Statement

DR. WITTEN: Good morning. My name is Celia Witten, and I'm the presiding officer for this hearing. Today we'll have presentations, closing statements, by CDER and Covis, followed by the advisory committee discussion and voting on the questions.

I now call to order day 3 of the October 17 through 19, 2022 hearing, conducted with the Obstetrics, Reproductive and Urologic Drugs Advisory Committee. Dr. Moon Hee Choi is the designated federal officer for this hearing and will begin with the roll call.

Roll Call

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

your affiliation.

Dr. Alukal?

(No response.)

MR. KAWCZYNSKI: Dr. Alukal is going to be a little late.

DR. CHOI: Thank you.

Dr. Eisenberg?

DR. EISENBERG: Good morning. Esther Eisenberg. I'm an OB/GYN Medical Officer at the National Institute of Child Health and Human Development, NICHD.

DR. CHOI: Thank you.

Dr. Fox?

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

DR. CHOI: Thank you.

Dr. Gass?

DR. GASS: Hello. I'm Margery Gass, OB/GYN, Clinical Professor Emeritus, University of Cincinnati, and past Executive Director of the

North American Menopause Society.

DR. CHOI: Thank you.

Dr. Lindsay?

DR. LINDSAY: Good morning. I'm Michael Lindsay. I'm an OB/GYN, Director of Maternal-Fetal Medicine, Emory University.

DR. CHOI: Thank you.

Dr. Munn?

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

DR. CHOI: Thank you.

Dr. Shields?

DR. SHIELDS: Hi. I'm Kristine Shields. I'm a retired OB/GYN nurse practitioner. I have a doctorate in public health, UNC. Thank you.

DR. CHOI: Thank you.

Dr. Caughey?

DR. CAUGHEY: Hi. Aaron Caughey, Department Chair, Professor, OB/GYN at Oregon Health and Science University.

DR. CHOI: Thank you.

Dr. Ellenberg?

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

DR. CHOI: Thank you.

Ms. Ellis?

MS. ELLIS: Hi. I'm Annie Ellis. I am serving as patient representative. I have a personal history of preterm labor, and it is also in my family.

DR. CHOI: Dr. Harper?

DR. HARPER: Hi. I am Lorie Harper. I'm a maternal-fetal medicine specialist at the University of Texas at Austin, Dell Medical School.

DR. CHOI: Thank you.

Dr. Henderson?

DR. HENDERSON: Hi [inaudible] -- maternal-fetal medicine at Garden OB GYN in New York.

MR. KAWCZYNSKI: Ma'am, can you reintroduce yourself?

DR. HENDERSON: Hi. Cassandra Henderson.

I'm maternal-fetal medicine at Garden OB GYN, a consultant in New York.

DR. CHOI: Thank you.

Dr. Hudak?

DR. HUDAK: Good morning. I'm Mark Hudak. I'm a neonatologist and Chair and Professor of Pediatrics, University of Florida College of Medicine in Jacksonville.

DR. CHOI: Thank you.

Dr. Kaimal?

DR. KAIMAL: Hi. Anjali Kaimal, and I'm a maternal-fetal medicine specialist, and I'm Professor and Vice Chair of Clinical Operations at the University of South Florida in the Department of OB/GYN.

DR. CHOI: Thank you.

Dr. McAdams-DeMarco?

DR. McADAMS-DeMARCO: Good morning. I'm Dr. Mara McAdams-DeMarco. I'm an Associate Professor and epidemiologist at the NYU Grossman School of Medicine, with appointments in the Department of Surgery and Population Health. I

also serve as the Associate Vice Chair for Research in the Department of Surgery. Thank you.

DR. CHOI: Thank you.

Dr. Obican?

DR. OBICAN: Good morning. Sarah Obican from the University of South Florida, Maternal-Fetal Medicine Division Director.

DR. CHOI: Thank you very much.

DR. WITTEN: Thank you.

We'll now proceed with the closing statement by the Center for Drug Evaluation and Research. I ask that the speaker please introduce yourself before you speak.

Closing Statement by CDER - Peter Stein

DR. STEIN: Good morning. I'm Dr. Peter Stein, director of the Office of New drugs, CDER. My role today is to summarize our assessment and provide the committee our basis for recommendation to withdraw Makena from the market. I know you are now fully familiar with the facts, so I will review the situation only briefly.

Trial 002, the Meis trial, was completed in

the early 2000s. It had been initiated to follow up on a meta-analysis of several very small trials from the 1970s and '80s in a range of populations and at a range of doses. Trial 002 had limitations. The randomization was 2 to 1, which meant that the placebo group was relatively small, and a single site contributed more than a quarter of the participants. I'll come back to some of these limitations in a few minutes.

The results of Trial 002 were unquestionably promising, with a strong p-value for the reduction in advance of preterm birth of gestational age under 37 weeks. I would add that this study did not show evidence of benefit on the most important endpoint, improved neonatal outcome. It's important to remind you that only the week 37 gestational age endpoint had a persuasive p-value. The p-values of gestational ages less than 32 and less than 35 weeks were not strong or persuasive, and would not have supported approval based upon a single trial.

I want to discuss this point a bit further.

For a single adequate and well-controlled trial to support approval, we usually consider that it has to be statistically very persuasive, generally as persuasive as having two independent positive adequate and well-controlled trials. This is not, however, by any means a rigid threshold. It can be modified based upon the seriousness of the disease and the unmet need. That's one of the ways we can apply regulatory flexibility, accepting more uncertainty regarding the statistical robustness of the findings.

Accelerated approval is another form of regulatory flexibility, and it is one that FDA applied to Makena. Accelerated approval involves accepting the uncertainty of the ability of the surrogate or intermediate clinical endpoint to predict the desired clinical benefit; here, the ability of the drug's effect on gestational age less than 37 weeks to predict improved neonatal outcomes.

I mentioned regulatory flexibility here, in part, because of Covis' focus on the concept and to

highlight that FDA is willing to, and has, employed this flexibility, including with respect to Makena itself. So as you are aware, on the basis of improved preterm birth rate less than 37 weeks, an endpoint we concluded was reasonably likely to predict neonatal benefit, Makena received accelerated approval. With accelerated approval, a post-approval study to verify benefit was required.

We've already heard the outcome of that study, the PROLONG trial, or Trial 003, a study that was nearly 4 times the size of Trial 002 and was a well-designed and executed trial. I want to underline, most importantly, that this study found no evidence of effectiveness on the prespecified co-primary endpoints of neonatal composite index or events of preterm birth under 35 weeks in the overall study population, and no effect on the gestational age less than 37-week endpoint either, so not confirming the gestational age endpoint upon which the drug was given accelerated approval.

A trial must be first and foremost evaluated based upon its primary study hypothesis or

hypotheses. Trial 003 was, and that means it was a fully negative trial, full stop. After that, all one is left with is speculation and post hoc data dredging and exploration. At this point, we are searching for hypothesis to inform further studies, clearly a valuable exercise, but we are no longer seeking evidence of effectiveness from that trial, and we cannot rely on post hoc analysis to turn a decisively negative study into a positive one.

With a negative result of Trial 003, you've heard that the sponsor has raised concerns about the study, and we agree that understanding why a trial has failed is important. It helps in the design of the next study, but it cannot be the basis for concluding that a drug is effective.

Trial 003 was a multinational trial, as are many if not most large clinical trials. The trial included women outside of the U.S., especially from sites in Ukraine and Russia. Covis has suggested that perhaps women from these countries were not properly assessed with regard to their qualifying pregnancy. We've already addressed this point.

Birth weights of the qualifying preterm birth in babies born to mothers in Russia and Ukraine were not greater than birth weights of the qualifying pregnancy in the U.S. In other words, there is no reason to believe that these women did not, in fact, have a prior preterm birth.

We've heard concerns about differences in clinical care in these countries, yet no such differences were suggested that would alter the response to the drug, and we've certainly not heard any reason that preterm birth in Ukraine and Russia is somehow a different disorder than in the US, and therefore might be less susceptible to response to drug. In fact, preterm birth is a global problem, and there is no evidence that the pathogenesis of this disorder differs across regions. That's why including patients from these countries was reasonable and planned for by the sponsor from the start of the trial.

The women in Ukraine and Russia did have a relatively low rate of preterm birth than did the U.S. patients, but the rates were clearly elevated

from women in these countries. Around 20 percent had a preterm birth. This is relative to a background rate of about 8 to 9 percent and similar to the reported U.S. rate with a prior preterm birth of about 21 to 22 percent.

I remind you that we did not find any risk factors, including race, that meaningfully modified the response to Makena in Trial 002 on its primary endpoint. In other words, there were no effect modifiers, factors that raise or lower the extent of a drug's response. So merely because these women in Ukraine and Russia from Trial 003 may have had fewer risk factors is not a basis to dismiss the results from these women.

They really can't have it both ways, concluding that the drug worked in Trial 002 regardless of the presence or absence of a risk factor, as Covis showed in their slide, and then concluding that because women did not have a particular risk factor, they were not able to respond to the drug in Trial 003. These women had a preterm birth rate that was elevated, and could

certainly have had an improvement in their rate of preterm birth with the study drug, but they did not.

We noted that the U.S. subgroup in Trial 003 was approximately equal in size to the size of Trial 002 and showed no effect of Makena, but again the sponsor points to differences in risk factors among these women versus in Trial 002, despite the fact that they did not find that risk factors were effect modifiers.

As I've already noted, Trial 003, a trial nearly 4 times the size of Trial 002, was a fully negative study. That's the most robust important result. Its conclusion was based upon what was prespecified and has appropriate statistical control, but I'd like to discuss with you the subgroup observations.

As we noted in our presentation, we did look at the prespecified subgroups and saw no differences in response. There was no effective drug seen in any subgroup. We then did some further analysis looking at additional risk factors

and combinations of risk factors, and whether you look at individuals who have one or more, or two or more, or three or more of the known risk factors, no response differences were seen. No effectiveness was seen in any such subgroup across levels of risk factors.

The sponsor's also done some initial additional post hoc exploratory analysis from Trial 003, omitting most of the patients and doing a variety of cuts, starting with a subset of U.S. patients, and as I noted on Monday, then finding subsets of subsets, and found some nominally significant findings. Yet, these same findings were generally not seen in Trial 002, nor were these findings observed when you expand the population to include women outside of the U.S. In other words, these are not robust reliable observations, perhaps interesting hypothesis generating, but not reliable evidence.

To remind you, these were not prespecified, not controlled for multiplicity, not consistent between trials, and not consistent in U.S. versus

ex-US women; in other words, not evidence upon which to base regulatory decisions such as changing the indication nor, I would suggest, guide clinical practice decisions.

Just as an example, Covis showed some analyses suggesting that in their subset of subsets in Trial 002 and 003, they could show that patients may have gained about a week in the duration of gestation. The Trial 002 analysis excluded about two-thirds of the patients from that trial, and the Trial 003 analyses excluded 95 percent of the patients from that study; hardly robust.

If we were looking at this data in a new drug application and discussing whether or not there was substantial evidence of effectiveness, I can say that CDER's answer would be no, but I will leave you to consider your answer to this. And based on our discussion yesterday, it would seem that Covis and CDER agree on the limited hypothesis-generating nature of this evidence, and you heard from Covis yesterday some very detailed explanations of why the analysis might have been

inconsistent across trials, or inconsistent in U.S. versus ex-US women. Again, such a post hoc speculation is helpful in raising hypothesis to test, but should worry us if we are using such speculation as the basis for a regulatory decision.

So we're left with the positive Trial 002 and the much larger Trial 003, which was fully and completely negative on the prespecified endpoints. In asking why this might be, I'd like to have us consider some of the limitations of Trial 002. In this regard, the much higher than anticipated preterm birth rate in the placebo group is worth some discussion.

Now, certainly we have to take the results from Trial 002 at face value, and generally should avoid cross-study comparisons. Indeed, that's what CDER did in the first place in our assessments that led to the approval of Makena, but in the context of the fully negative larger Trial 003, this finding does need to be reconsidered.

This rate seen in the placebo group of 55 percent for preterm birth events less than

37 weeks was discussed at prior ACs. This rate is higher than seen in other trials or reported in epidemiologic observations. Indeed, this rate was raised in the publication of the Meis trial.

In our presentation we noted results from a report from Georgia at a time unlikely to be impacted by HPC, showing a 37 percent rate of recurrent preterm birth less than 37 weeks, which is exactly the rate seen in the Makena treatment group. I note that the sponsor also reported no epidemiologic evidence or any other evidence showing a similar placebo group rate from any trial.

Then we looked at other data bearing on the question of Makena effectiveness. Clearly, there was a robust discussion over the past two days of the use and limitations of results from real-world evidence, observational analyses, and other randomized clinical trials. We noted in our presentations that real world observational studies have limitations. They can be confounded and they reflect the limitations of how a drug is actually

used in practice, yet we found five studies that did have a reasonable design and found no evidence of HPCs or Makena's effectiveness.

From one of the studies we discussed, the Bastek study, we provided you the primary prespecified study objective, which was to compare the preterm birth rate prior to and after the introduction of Makena, and it showed no difference, and Covis discussed a subset analysis. But once again, we need to focus on the prespecified analyses. Post hoc analyses support hypothesis and do not strongly contribute to evidence of effectiveness.

Then we looked at a wide range of other randomized clinical trials, and as we and Covis agree, these are largely not in the indicated population, so don't directly bear on the efficacy in this population, but they can provide information about the pharmacologic action of the drug in related conditions of increased risk of preterm birth. The absence of response outside the indicated population is not alone strong evidence

that Makena is not effective in the indicator population, but certainly with multiple trials seeing some suggestion of an effect, would have been reassuring, yet none was seen.

Now turning to EPPPIC, as we pointed out, in the set of studies with singleton pregnancies, including studies outside the indicated population and a study with a higher dose, there was no statistically significant effect, even as the upper bound was just above 1, however, after omitting Trial 002 from the analysis, the upper bound is well above 1.

Now, I want to turn to discussing the safety of the drug and how that factors into our recommendation. We agreed that the safety profile of Makena has not substantially changed. There are serious risks that are described in the labeling. Now, Covis presented information on reports of spontaneous events from Makena, and I noted that there were 36 spontaneous reported events of venous thromboembolism.

Putting aside that we'd expect

underreporting, especially of events that are labeled, I remind you that such events, even if very infrequent are not minor and can be life-threatening or even fatal. I don't say this to raise red flags regarding the safety of Makena, but only to say that for a woman to be exposed to any risk in connection with the labeled use of an approved product, and especially a serious risk, there must be evidence of benefit that outweighs those risks.

So Makena has established risks and uncertainties for other risks. We discussed the Murphy study that reported increased cancer risk in children exposed in utero to HPC. This study had limitations. We and Covis agree on this, but neither did we dismiss this risk, and it does raise the concern that long-term safety in the children of women treated with Makena is not fully understood. We cannot merely dismiss this, especially since evidence of benefit is lacking.

As I concluded on Monday, absent the evidence of effectiveness, we are only left with

risk. The benefit-risk balance from Makena is not favorable and does not support leaving the drug on the market. Now Covis has argued that we should nonetheless leave the drug on the market, and they assert that they can rapidly complete another study. I remind you that it took 10 years to complete Trial 003 that recruited 391 women in the U.S. with Makena on the market, and they want to do another study with more U.S. patients than in Trial 003, and claim it could be done in 4 to 6 years. I doubt it.

I ran studies when I was in the pharmaceutical industry for 20 years, and the best predictor of future recruitment is past performance. I recognize that Covis has cited surveys that were conducted with questions that I do not think provide substantive insight into likely study feasibility. Again, I think to expect rapid recruitment now, when that was not in evidence before, seems fanciful.

And let's be clear. The size of the study is by no means resolved. To demonstrate that there

is evidence sufficient to support the likelihood of neonatal benefit, a much larger trial may well be needed. Ten-plus years is likely; assuming it will be faster is not a good bet. And of course the outcome is uncertain. Our experience with testing post hoc hypotheses from negative trials is that more often than not, the subsequent trial is also negative.

But I also want to be very clear. Our recommendation to withdraw the drug from the market is not based upon how long it will take to complete another trial. It is about the evidence in front of us today: a smaller trial that was promising and a fully negative, much larger, well-designed and conducted study, and results from real-world evidence, observational studies of HPC or Makena, and other randomized clinical trials, also supporting the conclusion from Trial 003 that Makena has not been shown to be effective.

We are recommending withdrawal because two legal grounds for withdrawal are clearly met. The confirmatory trial failed to verify clinical

benefit and other evidence demonstrates that the drug is not shown to be effective for its approved indication. At determining that two independent legal grounds for withdrawal are satisfied, we concluded that the drug should be withdrawn because the benefit-risk balance is unfavorable. Not to do so here would up-end the intention behind the accelerated approval pathway, one that pairs earlier access for promising treatments with withdrawal if the drug does not pan out.

We heard from many clinicians and patients over the past days, and we heard them very clearly. They want an effective drug on the market and can accept some uncertainty. So do we, and so can we if the data and the science support it. But the current data in front of us does not leave us with some uncertainty; it leaves us with a lot of uncertainty. When we approved Makena, we accepted some uncertainty, applying regulatory flexibility. As I've noted, that's not where we are now.

We do not have evidence that Makena is effective. The regulatory flexibility that Covis

suggests we employ here is not appropriate. Setting the precedent that merely having a reasonable hypothesis of benefit absent evidence is sufficient to maintain a drug's approval would be very troubling. Based on what we know today, we cannot support leaving the drug not shown to be effective and with known risks on the market.

I wanted to clear up a few points raised regarding precedents. Covis mentioned midodrine, noting that it was approved under accelerated approval and despite negative confirmatory trials was not pulled from the market. What Covis did not tell you is that the confirmatory trials did see improvement in standing blood pressure, the endpoint that supported accelerated approval. In other words, the surrogate endpoint that supported the accelerated approval was still observed in the confirmatory trials; certainly not the case for Makena.

They also pointed to the cancer drug Iressa, and noted that labeling was modified with a narrowed indication. If the indication was

narrowed to patients already on the drug who had an objective response to this drug -- and let me remind you that shrinkage of a tumor or survival long beyond expected survival for cancer are reasonably robust indicators or response to that drug. That same information is by no means available to support a labeling change for Makena.

Finally, Iressa was subsequently withdrawn from the market, and when a new trial, following up on reasonable hypothesis of a subset of high responders, identified and demonstrated effectiveness in this responder population, the drug was then approved and returned to the market with an indication focused on this population, and now with a favorable benefit-risk balance.

So I would ask that you focus on the information in front of you in your discussion and vote, and be careful about basing your recommendations for our regulatory action on post hoc, non-prespecified and non-robust analyses.

You heard from some practitioners that no treatment is the worst outcome. We disagree. It

is clearly worse to provide a drug requiring weekly injections, exposing patients to serious risks, both established and uncertainties, without evidence of benefit. Hope is a reason to keep looking for options that are effective, whether we find them here or elsewhere. Hope is not a reason to take a drug that is not shown to be effective or keep it on the market.

I'd add that as we at FDA make decisions based on data and science, so do many practitioners. Several speakers pointed to the marked decline in the use of Makena over the past several years, and suggested that this reflected our assessments and the AC discussion back in 2019. Well, I'd like to raise another possibility that clinicians have actually looked at the evidence and are not convinced that Makena is effective and that using this drug is not in their patients' best interest. It is time that we withdraw Makena from the market.

To be clear, this is not an easy decision for anyone, including those on the CDER team.

We've heard Covis' arguments. We've heard from the 2019 advisory committee meeting, from healthcare providers, the input from patient organizations, and from patients themselves. But taking all of the information into account, the evidence that we have today, the science supports withdrawing the drug. That's what we believe is in the best interest of patients, and we stand ready to work with drug developers to find therapies for this serious condition. So we did think this was a promising treatment but, unfortunately, we no longer do.

I want to thank the advisory committee members for their time and efforts, and also the sponsor for engaging in a very important discussion, and of course the many patients and practitioners who are looking for answers. I hope that further studies of Makena and other potential treatments will be successful. Thank you.

DR. WITTEN: Thank you, Dr. Stein.

We'll now proceed with the closing statement by Covis, and following that, we'll take a

15-minute break. I ask that the speaker please introduce yourself before you speak.

Closing Statement by Covis - Raghav Chari

DR. CHARI: Good morning. I'm Raghav Chari, chief innovation officer at Covis Pharma. I will conclude by summarizing our proposed path forward and by sharing a position on the questions posed to this committee.

Covis is committed to executing a robust plan to confirm the clinical benefit of Makena and to address the outstanding questions raised by CDER, while at the same time continuing to meet the critical needs of a higher risk group of patients. This includes our willingness to focus labeling on the high-risk target patient population; a randomized-controlled trial to confirm Makena's effect on an intermediate clinical endpoint; and an observational study to validate the benefit of prolonging gestational age on neonatal morbidity and mortality with 17P treatment.

This is a practical approach that will preserve access by enabling the treating physician

to make an individualized benefit-risk determination in consultation with their patient.

Our post hoc analyses have identified a higher risk patient population. When looking at the results in women with multiple risk factors, including a spontaneous preterm birth before week 35 and one or more additional risk factors, we see a consistent benefit with Makena in both the Meis and PROLONG trials.

I note that CDER has just acknowledged that Meis is a positive clinical trial and not as suggested yesterday, a proof of concept. As we discussed yesterday, PROLONG is a failed study conducted in a population in which it was not possible to confirm the Meis results. Therefore, PROLONG is not a definitive negative study and does not negate Meis.

I'd like to acknowledge the comments we heard yesterday and reiterate that we're not proposing that race biologically differentiates patients, and at the same time it is well documented that preterm birth disproportionately

impacts women who are Black and other minorities in the United States. These and other social determinants of risk are factors in defining the higher risk population where Makena is most likely to be effective.

We're proposing to conduct a third randomized-controlled trial in this higher risk population. As we talked about yesterday, our analyses indicate that a sample size of 400 patients randomized in a 2 to 1 ratio between Makena and placebo would be sufficient to confirm benefit. The primary endpoint would evaluate the mean increase in time from randomization to birth capped at 35 weeks for Makena-treated patients compared with placebo. We estimate that the proposed trial can be completed in 4 to 6 years.

Yesterday, we heard the questions from the panel about the time it would take to complete a third randomized-controlled trial. We are prepared to work collaboratively with CDER to finalize and launch the study as expeditiously as possible.

Based on our feasibility assessments, we are

confident that we can meet our enrollment targets for this trial. We've conducted multiple surveys with physicians, patients, and investigators to evaluate the willingness to participate in another trial. These surveys support that providers will be more likely to refer patients to a trial with an approved product compared to a trial of a withdrawn product.

Specifically for the prevention of recurrent preterm birth, 80 percent of providers reported that they would consider recommending a pregnant patient enroll in a placebo-controlled study when the product is FDA approved. In contrast, only 15 percent would consider referring patients if the product had its marketing authorization for this indication withdrawn. This research suggested enrolling a clinical trial following withdrawal is likely to face more significant challenges than if the product would remain on the market.

Since PROLONG was published three years ago, we estimate that the use of Makena and its generics has dropped approximately 45 percent in the United

States, reflecting a greater clinical equipoise than at the time when PROLONG was being enrolled. It is for these reasons that we're confident a third randomized clinical trial can be enrolled in the United States with the product still on the market. However, given the concerns regarding the feasibility of conducting such a trial, we would also commit to study conduct criteria and to voluntarily withdrawing Makena if these criteria are not achieved.

These checkpoints would come during an interim efficacy analysis for futility, and a 24-month check on enrollment projections, and based on the final outcome of the study. In all cases, if any of these indicate that prespecified criteria cannot be achieved, or have not been achieved, we will work with the FDA to withdraw the product on the market.

As a final step in our path forward, we are open to conducting an observational study. The goal of this study will be to establish the relationship between gestational age and neonatal

outcomes in treated versus untreated patients to validate the benefit of weeks gained on 17P. The results of such a study would confirm or refute that the benefits of pharmacological prolongation of gestation can be inferred from the known associations of gestational age with neonatal health outcomes.

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

We have stipulated that the findings from PROLONG do not verify the clinical benefit of Makena on neonatal morbidity and mortality in the study population. However, when a confirmatory trial fails to provide additional confirmation of clinical benefit, that is the beginning and not the end of the analysis.

Next, you will be asked to discuss and vote on whether the available evidence demonstrates that

Makena is effective for its approved indication of reducing the risk of preterm birth in women with a singleton pregnancy who have had a history of singleton spontaneous preterm birth.

We stand by the significant outcomes observed in the Meis trial. The Meis trial demonstrated statistically significant reductions in preterm birth with Makena across all prespecified endpoints and all key subgroups, but we recognize the questions and concerns that were raised by the PROLONG trial.

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

Based on extensive post hoc exploratory analysis, we've identified a higher risk target population of women who achieved a consistent benefit with Makena in both the Meis and PROLONG trials. Therefore, we are asking to work with the

agency to align the labeling for Makena with this higher risk subset of patients. This could include narrowing the indication, expanding the limitations of use, modifying the clinical study section of the labeling, or other solutions such as a Dear Health Care Provider Letter. We will also continue to not promote Makena. Our commercial efforts will focus exclusively on maintaining patient access.

While CDER has challenged the results of the PROLONG trial, specifically with respect to the benefits in the subgroup of patients, in a target population of higher risk patients, we do see a consistent benefit with Makena.

Here we see the overall results for the continuous endpoint of time from randomization to delivery capped at 35 weeks for the proposed high risk target population for both PROLONG-US and Meis. For PROLONG-US, the estimate is 1.86 weeks, or about 13 days, and for Meis, the estimate is 1.33 weeks, or about 9 days.

I'd like to take a moment to reconcile these data with the conclusions presented by CDER. We

acknowledge that the PROLONG trial did not show a benefit on the categorical endpoints of preterm birth less than 35 weeks or less than 37 weeks, which were the endpoints presented by CDER in their subgroup analysis. The challenge with these categorical endpoints is that women who received 17P and achieved a meaningful increase in gestational age relative to placebo -- for example, from 30 to 32 weeks -- would not be captured.

Our analysis avoids that problem by using a more sensitive outcome measure that should detect clinically meaningful increases in gestational age in all periods of pregnancy through 35 weeks of gestation.

I'd like to acknowledge the question yesterday about the interpretation of the gestational age data. The weeks gained seen in this analysis correspond to the true increase in gestational age at delivery. This is because our analysis controlled with gestational age at randomization. We also see a consistent effect in the target patient population for the dichotomous

endpoints of preterm birth less than 37, less than 35, and less than 32 weeks.

I also note the confidence intervals for the less than 35 and less than 32 weeks for the Meis subgroup, which speak to the strength of the efficacy signal seen in this population. The available evidence demonstrates that Makena remains effective for a higher risk subset of patients.

Finally, CDER has presented a forest plot of studies and suggested that these are representative of Makena's efficacy. I'd like to reinforce that aside from Meis and PROLONG, the studies shown in this figure are not relevant to our discussion. For reasons Dr. Greene and I covered during this hearing, the three observational studies have significant flaws and limitations. Similarly, the list of RCTs in women outside of Makena's labeled indication such as those with twin or triplets are not relevant to this proceeding.

To summarize our position on the second question, the Meis trial remains substantial evidence of Makena's efficacy. Additionally,

post hoc analyses of PROLONG-US support that Makena is effective in a higher risk subset of patients at greatest risk of preterm birth. Therefore, we're proposing to limit the use of Makena to patients who are at higher risk and need access to the therapy while we execute on our path to address the outstanding questions.

Next, the committee will be asked whether Makena should remain on the market and, importantly, whether or not FDA should allow Makena to remain on the market while an appropriate confirmatory study is designed and conducted. While PROLONG was unable to confirm the benefits observed in Meis, it did not reveal any unexpected or new safety concerns. It did reaffirm Makena's overall favorable safety profile.

These are the integrated safety data from the Meis and PROLONG trials, which reflect a favorable safety profile comparable to placebo for maternal and fetal risks. Additionally, CDER has brought up VTEs. The same integrated safety data show an incidence of 0.07 percent in Makena versus

0.1 percent in placebo. These data were provided on page 70 in our briefing book.

So the question remains, what now? CDER agrees that the standard for withdrawal of accelerated approval is permissive. They acknowledge, quote, "CDER possesses various regulatory options when a confirmatory trial fails to verify clinical benefit." Accordingly, FDA has the authority to allow Makena to remain on the market while another trial is conducted.

We urge this committee to recommend that Makena remain on the market for at least this subset of higher risk patients while we collect additional evidence to confirm its benefit. Our proposed path forward will confirm the benefit of Makena in the target population and address the remaining outstanding questions raised by CDER, while at the same time continuing to meet the critical needs of patients at a higher risk of preterm birth.

Covis respectfully requests that its proposal receive proper review and consideration by

the agency as we continue to welcome a collaborative path forward in the best interest of patient care. As we have heard over the last two days, and as reflected in the docket, many organizations, including those who specifically represent at-risk populations, agree that Makena remains an important treatment option for reducing the risk of preterm birth.

We remain committed to executing a robust plan to confirm the clinical benefit of Makena. We look forward to hearing the perspectives of the committee members and would like to thank CDER, the advisory committee, and all of the public participants for their important and valuable perspectives. Thank you.

DR. WITTEN: Thank you. We'll now take a 15-minute break, so we'll resume at 9:30.

(Whereupon, at 9:13 a.m., a recess was taken.)

Advice and Recommendations by the Advisory Committee

DR. WITTEN: We'll now proceed with

questions to the committee that I presented earlier, although I'm not going to read them aloud again. For each question, we'll have a discussion and then a vote. While this hearing is open for public observation, public attendees may not participate except at the specific request of the committee.

I'll start by presenting each of the three questions, which we will discuss in turn. Following the discussion for each question, there will be a vote on that question. Following the vote, I will ask each individual to state how they voted and why. After we have completed that process for question 1, we'll go on to the next question and repeat the process for questions 2 and 3.

So we'll now proceed with the discussion for question 1.

Can you put question 1 up, please?

Question 1 for discussion: Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal morbidity and mortality from

complications of preterm birth?

Dr. Ellenberg, I'll call on you first.

DR. ELLENBERG: Well, I think there isn't much to say [inaudible] -- my understanding is that [inaudible] -- agrees with CDER that the findings of 003 --

DR. WITTEN: Sorry. I'm having trouble -- you're cutting out, Dr. Ellenberg. Can you repeat that?

DR. ELLENBERG: I was saying, I think [inaudible] -- my understanding is that Makena agrees with CDER that the Trial 003 does not verify the benefit seen on the earlier trial.

DR. WITTEN: Okay. Thank you.

Dr. Hudak?

DR. HUDAK: I find the question a little bit odd because Trial 002 did not demonstrate benefit on neonatal morbidity or mortality under the statistical analysis. Trial 003 certainly didn't verify and didn't suggest a signal.

DR. WITTEN: I'm sorry. Say that again.

DR. HUDAK: Trial 003 did not suggest any

signal of a reduction on neonatal morbidity or mortality per the definition used in that trial.

DR. WITTEN: Yes. Thank you.

Any other comments?

(No response.)

DR. WITTEN: Okay. Seeing none, I think we can proceed to the vote with this one, so can you put up the voting question? Thank you.

The voting question, which I will read -- so there are no further points of discussion, and I will go on to the vote.

Voting members of the advisory committee will use the Adobe Connect -- oh, I think those are instructions from Dr. Moon.

I'm going to read the voting question.

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

Dr. Moon, can you read the instructions for voting?

DR. CHOI: Voting members of the advisory committee will use the Adobe Connect platform to

submit their vote for this hearing. The industry representative is a non-voting member. After the presiding officer has read the voting question into the record and all questions and discussions have been completed, the presiding officer will announce that voting will begin.

DR. WITTEN: Okay. I'll now restate this voting question one more time.

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

The voting will now begin. You have 30 seconds before the vote closes.

(Voting.)

DR. CHOI: You have 15 seconds before the vote closes.

(Pause.)

MR. KAWCZYNSKI: Dr. Moon, can you read the results?

DR. CHOI: The voting has closed and is now complete. Once the vote results have been displayed, I will read the vote into the record.

For the record, we have 15 no.

The vote results are displayed. I will read the vote totals into the record, and then I will read off the names and the vote for each voting member.

(Pause.)

DR. WITTEN: Are you reading off the names and the votes?

DR. CHOI: Yes.

Dr. Caughey, no; Dr. Kaimal voted no; Ms. Ellis voted no; Dr. Henderson voted no; Dr. Eisenberg voted no; Dr. Alukal voted no; Dr. Shields voted no; Dr. Harper voted no; Dr. McAdams-DeMarco voted no; Dr. Gass voted no; Dr. Hudak voted no; Dr. Munn voted no; Dr. Lindsay voted no; Dr. Obican voted no; Dr. Ellenberg voted no.

DR. WITTEN: Thank you.

I will now ask everyone who voted to state their name and their vote, and an explanation for their vote or any additional comments you'd like to provide.

We'll start with Dr. Alukal.

(No response.)

DR. WITTEN: Dr. Alukal?

(No response.)

MR. KAWCZYNSKI: Your phone is muted, sir.

DR. ALUKAL: Excuse me. I don't have any additional comments beyond what Dr. Ellenberg and Dr. Hudak said.

DR. WITTEN: Okay.

Dr. Caughey?

DR. CAUGHEY: No additional comment.

DR. WITTEN: Dr. Eisenberg?

DR. EISENBERG: No additional comments.

DR. WITTEN: Dr. Ellenberg?

DR. ELLENBERG: I voted no; no additional comments beyond what I said before.

DR. WITTEN: Dr. Ellis -- Ms. Ellis?

MS. ELLIS: Hi. I voted no, and nothing to add.

DR. WITTEN: Dr. Gass?

DR. GASS: I voted no; no additional comments.

DR. WITTEN: Dr. Harper?

DR. HARPER: I voted no; no additional comments.

DR. WITTEN: Thank you.

Dr. Henderson?

DR. HENDERSON: I voted no; no additional comments.

DR. WITTEN: Dr. Hudak?

DR. HUDAK: I voted no, and no additional comments.

DR. WITTEN: Thank you.

Dr. Kaimal?

DR. KAIMAL: I voted no, and no additional comments.

DR. WITTEN: Dr. Lindsay?

DR. LINDSAY: I voted no, and no additional comment.

DR. WITTEN: Dr. McAdams-DeMarco?

DR. McADAMS-DeMARCO: Hi. I voted no, and no additional comments.

DR. WITTEN: Dr. Munn?

DR. MUNN: I voted no, and no additional

comment.

DR. WITTEN: Dr. Obican?

DR. OBICAN: Good morning. I voted no, and no additional comments as well.

DR. WITTEN: And Dr. Shields?

DR. SHIELDS: I voted no, and I have no additional comments either.

DR. WITTEN: Okay.

In summary of the answer to this question, it's a consensus from the panel that the findings from Trial 003 don't verify the clinical benefit of Makena on neonatal morbidity and mortality for complications of preterm birth.

We'll now proceed with question 2 and start with a discussion period. I'm going to put up the question, and we'll discuss this issue. Please use the raise-hand icon to indicate you have a comment or question and lower your hand by clicking the raise-hand icon after you finish speaking.

The question for discussion: 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?

I just want to comment before we move on to discussion for this question that there's been considerable discussion about subgroup analysis during the course of this meeting. Of course, all the discussions at the hearing are transcribed, and that transcript will be included as part of the official record of the proceeding, so any comments you make before and after this discussion and vote will be reviewed by FDA.

But I do want to point out that the question under examination here is related to Makena and whether it's effective for its approved indication; so I welcome comments on this question.

We'll start out with Dr. Hudak.

DR. HUDAK: Yes. Thank you.

This is a limited question, as you point out, and it pertains to the totality of the evidence for both fully enrolled populations. I think that there is agreement between CDER and

Covis on this issue that, looked at individually, the 002 study did provide a strong signal; that use of Makena in that population did reduce the risk of preterm birth in women with a singleton pregnancy with a history of a prior spontaneous preterm single birth. Study 003, looking at the entire population, provided no signal of benefit of Makena, looking at all of the women involved, irrespective of site, of geography, and so forth.

So I would say that from the point of view of having two studies that provide similar signals, they did not, so I think this limited question -- limited to the entire populations of both studies, there is no evidence to demonstrate it's effective.

DR. WITTEN: Thank you.

Other comments? Dr. Ellenberg?

DR. ELLENBERG: Yes. Dr. Hudak said the 003 study was negative, and in regard to the issue of the power of this study, which was raised a number of times by Covis, this could be of interest if the data from 003 was leaning -- that is if there was a

substantial estimate of effect size -- but because of the low event rate, it was not statistically significant. That would be one thing. That is not what we saw in 003. We saw something that overall did not have any suggestions of efficacy.

I think that the many subset analyses that were looked at, that were presented to us, may show some potential. This is always tricky ground. When I was at FDA, we certainly saw cases where a study was overall negative but looked very positive in a subgroup, and when a second study was done, there was no effect at all.

So we know these can be false positive when you have a big database and you hunt through for signals. Some of these signals may be worth following up, but overall I don't think that effectiveness has been demonstrated with the available evidence.

DR. WITTEN: Thank you.

Dr. Henderson?

DR. HENDERSON: Thank you. I'm concerned that certainly the Meis study was very problematic

with high preterm delivery rate in the placebo, but I don't think that the 003 negates Meis. There are problems with it, but it did show some interesting findings and reasonable findings for decreasing delivery at 37 weeks.

I'm concerned about the 003 study, and it was pointed out certainly by the sponsor, the low level of minority women. And I'm concerned that the target population of Black women in the U.S., if we don't focus on that target population, we may miss the opportunity to show a benefit of Makena.

I think that for certainly race, there's no biologic plausibility for it being effective differently, in different race populations, however we do know that race is sort of a surrogate for racism and all the structural inequities that we talked about during the meeting, and I think that targeting a population that is at risk, particularly Black women in the U.S., may show something that will be beneficial.

We certainly heard reports, anecdotal, from patients, and providers, and others, so I think

that certainly the data other than Meis would say, no, we don't have that evidence, but I think the 003 does not negate some of the findings that we saw in Meis. Thank you.

DR. WITTEN: Thank you.

I'm wondering if there are other comments from the advisory committee about looking at the two different studies and different outcomes, and what the interpretation would be.

Dr. McAdams?

DR. McADAMS-DeMARCO: Thank you. Dr. Mara McAdams-DeMarco.

My concern is that there is no effect measure modification by race. There was no interaction in either trial, suggesting that there will not be a differential impact of the medication on preterm birth by race. So to me, even in subgroups, there has not been shown evidence in 003 that preterm birth would be prevented with the use of this medication.

DR. WITTEN: Thank you.

Annie Ellis?

MS. ELLIS: Hi. Thank you.

I think I'm still just so disappointed that the strong signal that was seen in 002 was not confirmed. I hear all the reasons why the Trial 003 might not have been adequately designed or include the proper population, however, I really think that if 003, with all those flaws, would have shown an effect, we wouldn't be sitting here today.

And I wish that we weren't sitting here today, but when I see one trial that was very strong and one trial that showed no difference, I feel a return to equipoise; we just don't know. The way the question is written, for the approved indication, we just don't know. Thank you.

DR. WITTEN: Thank you.

I'll call on Dr. Eisenberg.

DR. EISENBERG: Yes. My comment relates to the fact that there may be geographical issues that have not necessarily been exposed in that a large number of the women in Meis were in the south of the United States, and there may be something geographically that affects the benefit that is

seen of Makena in 002.

Clearly, those differences in preterm birth outside the United States compared to inside the United States would argue that there are geographical issues at play -- at least that is a hypothesis to be explored -- and that may affect the benefit that was seen and affect the success of Makena in the United States as well.

DR. WITTEN: Thank you.

Other comments?

You need to raise your hand, or lower your hand, Dr. McAdams-DeMarco.

Other comments about the two studies and the differences of the studies?

MR. KAWCZYNSKI: I think she has another question, ma'am.

DR. WITTEN: Ah, okay. Good. I'll call on you again.

Dr. McAdams-DeMarco? Sorry.

DR. McADAMS-DeMARCO: Thank you. I do have a second comment.

With regard to ex-US patients, the rates of

preterm birth were undoubtedly known prior to the start of the trial by the sponsor. These things that are being brought up now as flaws were in fact identifiable during the design phase of the study, so I'm feeling that it's just a bit of a disingenuous argument to say that the study design now explains the null results; the low rate in the Ukraine and Russian populations now explain the results.

Furthermore, the evidence provided by CDER clearly shows that, again, there is not effect measure modification. There are no differences of the drug's treatment in U.S. and non-US patients. Thank you.

DR. WITTEN: Thank you.

Other comments on this question?

(No response.)

DR. WITTEN: Any comments on the studies or the other evidence that was provided during the discussions?

Dr. Hudak?

DR. HUDAK: Yes. I think a lot of

discussion will ensue with respect to the third question, but since Dr. Ellenberg did bring this up, I do think, and I agree with her, that there are pros and cons of looking at unstructured or unplanned subanalyses, and I would echo her comment that, yes, many studies have shown in a subanalysis that there may be an effect in a particularly limited population. Many times that effect is not confirmed.

So I think that a lot of argument has been made that this drug could benefit from further study, and I agree with that statement, but that does not mean that the weight of the evidence, the entire population can be discarded in this question. So I think we'll have some robust discussion with respect to question number 3.

DR. WITTEN: Thank you.

If there are no further comments or discussion, we'll move on to the vote on this question.

Any last comments before we do that?

(No response.)

DR. WITTEN: Okay.

We've displayed slide with voting question 2. Thank you.

I will now restate voting question 2. The instructions for the vote are the same as previously. I'm going to restate voting 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 who have a history of singleton spontaneous preterm birth?

The voting will now begin. You have 30 seconds before the vote closes.

(Voting)

DR. CHOI: You have 15 seconds before the vote closes.

(Pause.)

DR. WITTEN: I think we need one more vote.

DR. LINDSAY: I did not receive a ballot. This is Michael Lindsay.

DR. WITTEN: Oh.

MR. KAWCZYNSKI: Michael Lindsay, you're logged in. Look at the bottom of your screen for Adobe Connect.

(Pause.)

MR. KAWCZYNSKI: Dr. Moon, do I have permission to close the vote?

DR. CHOI: Yes.

MR. KAWCZYNSKI: And I will broadcast the results, and if you can go ahead and read them.

DR. CHOI: The vote results are displayed. I will read the vote totals into the record, and then I'll read off their names and the votes for each voting member.

For the record, we have 1 yes, 13 no, and 1 abstention.

Dr. Caughey voted no; Dr. Kaimal voted no; Ms. Ellis voted no; Dr. Henderson voted yes; Dr. Eisenberg voted abstained; Dr. Alukal voted no; Dr. Shields voted no; Dr. Harper voted no; Dr. McAdams-DeMarco voted no; Dr. Gass voted no; Dr. Hudak voted no; Dr. Munn voted no; Dr. Lindsay voted no; Dr. Obican voted no; and Dr. Ellenberg

voted no.

DR. WITTEN: Thank you.

I will now ask everyone who voted to state their name and their vote, and an explanation for their vote, or any additional comments you would like to provide regarding the vote.

We'll start with Dr. Alukal.

DR. ALUKAL: Yes. I'm Dr. Alukal. I voted no, based specifically on the fact that the question is asking us whether or not we believe there to be evidence of this effect. We've discussed over the past couple days that, really, we can limit our consideration to the two studies that have been discussed and that we all sort of agree on are less than ideal.

Obviously, that has to do, at a fundamental level, with questions of study design and enrollment, and we do have in those two studies divergent results. This would be a confusing problem if you had two less than ideal studies, but they did show you the same meaningful effect. So I think you can't conclusively answer this question

that, yes, there's an effect.

I'm not rambling through this just to hear myself talk. I think it's important to keep this in mind as we move on to the subsequent question of what are we to do next?

DR. WITTEN: Thank you.

Dr. Caughey?

DR. CAUGHEY: Yes. I voted no as well, and I really agree with what Dr. Alukal just said. Fundamentally, the question before us is, has it been shown to be effective for the indication of prior spontaneous preterm birth? And I think when you look at that body of evidence, the answer has to be no. The issue of subgroups might be something you might address going forward, but that's not in this question, so I voted no. That's it.

DR. WITTEN: Thank you.

Dr. Eisenberg?

DR. EISENBERG: Hello?

DR. WITTEN: Yes?

DR. EISENBERG: Did you ask for my comment?

DR. WITTEN: Yes, please.

DR. EISENBERG: Yes.

I abstained because the question, is it effective, if you turn that around and say is it not effective, one cannot say that it is not effective either. And I think that the question, although you cannot demonstrate an effect -- or you cannot say that these studies in their totality demonstrated effectiveness, you cannot say that these studies also did not demonstrate effectiveness because of all the discussion points that have been made previously.

So it really depends, and I think additional studies need to be done in order to answer the question. I don't think that question can be answered with the data that we have.

DR. WITTEN: Thank you.

Dr. Ellenberg?

(No response.)

MS. ELLIS: This is Annie Ellis. I voted no. We don't know if it's effective or not effective because the two trials had different

results. And I would just like to take one moment to just thank the women who volunteered to participate in both these studies; that even though the results were different, the information matters, and their participation matters. That's all.

DR. WITTEN: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: Yes. I voted no. I think we have one study that was positive on an intermediate clinical endpoint, and one much larger study that was not positive on any endpoint, not even leaning. So it seems clear to me that efficacy was not demonstrated. There is no way that studies can ever definitively prove that a drug had no effect. Even if we had two definitively negative studies, it would be possible. There's always uncertainty in these issues.

So that's not what we're saying. I wouldn't say that there's proof that it's ineffective, but I think we're basically back to square zero, where we

were before anything was studied. We just don't know. So I believe there's no demonstration of effect.

DR. WITTEN: Thank you.

Dr. Gass?

DR. GASS: Yes. Generally, we expect the larger studies to iron out some problems in the original smaller studies, and that didn't pan out in this case. The company has indicated that they think they can do another trial that would be more convincing, and I would encourage them to do that because certainly this is an important health issue in this country.

DR. WITTEN: Thank you.

Dr. Harper?

DR. HARPER: Hi. Lorie Harper. I voted no. I don't really have additional comments. Compared to what has been said, I think the body of evidence does not support effectiveness for the general population of women with a prior singleton preterm birth.

DR. WITTEN: Thank you.

Dr. Henderson?

DR. HENDERSON: Hi. Thank you.

I voted yes, and it really comes down to the Meis trial. I voted yes when we first did the preliminary approval, and I think because I think there's some evidence that it is beneficial. And I think if there's actually no benefit, with the risk that we've already demonstrated or discussed during the hearing, then it shouldn't be on the market. If there's no benefit, then clearly there's no reason to have any risk.

I think the Meis supports that there may be some benefit, and I think that the 003 trial obviously was not helpful. It was a negative trial with all the limitations we talked about. So I think given the Meis and given the fact that that suggests there is some benefit, that warrants taking a risk that we've been submitting women to for these years, so I voted yes. Thank you.

DR. WITTEN: Thank you.

Dr. Hudak?

DR. HUDAK: Yes. I think this is an

interesting question and interesting responses. I voted no because I think from an intellectually honest perspective answering this particular question, the weight of the evidence did not support effectiveness for the indication, the labeling indication, which is the entire population.

I think that Dr. Eisenberg's careful semantic consideration is something that I do understand, but that's not incompatible with a no vote in my mind. I do think the question asks whether or not there is sufficient evidence to say that this drug is effective. I think saying no to that does not close out the possibility that the drug may be effective in certain situations or certain populations, but as the question is written, I think the intellectually coherent answer is no.

DR. WITTEN: Thank you.

Dr. Kaimal?

DR. KAIMAL: Hi. Anjali Kaimal. I voted no. I think sort of echoing some of the prior

comments, such as to say that much of the discussion has focused on the fact that more study is needed. Given the way that the question is worded as to whether the evidence so far demonstrates effectiveness of the approved indication, which is prior preterm birth less than 37 weeks, I think it's clear that while we might want to investigate an additional population for that specific question, the evidence does not support that that medication is effective.

DR. WITTEN: Thank you.

Dr. Lindsay?

DR. LINDSAY: Yes. I voted no also. By looking at the totality of the evidence, the way the question is worded, there was no other option but to vote no, but as a clinician, I'm sort of disappointed that the drug has not been shown to be more effective.

DR. WITTEN: Thank you.

Dr. McAdams-DeMarco?

(No response.)

DR. MUNN: Hi. This is Dr. Munn. I voted

no. I guess I'd like to echo what Dr. Hudak said about intellectual honesty, that the body of evidence right now doesn't currently support its indication. Thank you.

DR. WITTEN: Thank you.

Dr. McAdams-DeMarco?

DR. McADAMS-DeMARCO: Hi. Thank you.

Under accelerated approval, the sponsor was required to conduct a high-quality trial to confirm this endpoint, and it failed to do. That, with the totality of the evidence, including high-quality real-world evidence from the pharmaco-epi studies suggest to me that the only way to answer this question was no.

DR. WITTEN: Thank you.

Dr. Obican?

DR. OBICAN: Yes. Sarah Obican. I also voted no, and similar to some of my colleagues that have presented here -- Dr. Lindsay -- I agree, and am really sad about the findings from the 003 trial. I can't say anything else other than the deep sadness, but the totality of the evidence

showed that it is not effective, and to answer this question I also voted no.

DR. WITTEN: Thank you.

And Dr. Shields?

DR. SHIELDS: Yes. This is Kris Shields. I also voted no. I hope that the sponsor will go on and do additional trials to more definitively answer this question in certain populations. Thank you.

DR. WITTEN: Thank you.

I guess I'll summarize the discussion and the vote by saying that the vote was 13 no, 1 yes, and 1 abstain. There was, I think, general agreement in the committee that there was some disappointment that Trial 003 didn't provide a better outcome, but that the weight of the evidence didn't support a yes vote on this question.

The one point that was made by the person who abstained, and there was support from this from a number of the committee members, was that the studies didn't show ineffectiveness; the evidence simply didn't show effectiveness, and further study

was encouraged; and then there was also one member who believed that the answer should be yes, based on the weight of evidence from the Meis trial.

That's the summary of the vote, and we're now going to proceed with question 3. And as before, we're going to start with the discussion period. We have the question put up.

Can we make it any larger on this? I don't know. People should have it in front of them, I hope. But I'm going to read the question, and then we'll have a discussion.

The question for discussion is: Should FDA allow Makena to remain on the market? As part of that discussion, you may discuss whether the benefit/-risk profile supports retaining the product on the market; what types of studies could provide confirmatory evidence to verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm births?

Then the voting question: 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?

As I mentioned for the previous study, this question is asking about Makena with its labeled indication of reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. However, if you have additional comments about some of the populations that were discussed during either the meeting yesterday, you can make them during the discussion period, but the vote should be on that specific question.

I also want to clarify that the bullet about studies that could provide confirmatory evidence, there was considerable discussion about a study proposed by the sponsor yesterday, which was a study aimed at looking at the intermediate clinical endpoint. They also briefly mentioned an observational study to look at confirmatory evidence. So when you're talking about studies, it would be helpful to be clear about the study and what kind of study objectives you're discussing or

recommending.

So anyway, I will open it up for discussion, so we'll start with Dr. Eisenberg.

DR. EISENBERG: I believe that the product should remain on the market in order to be able to do a study that could answer the question. I think the point that if the drug is taken off the market, then people will question whether to go on it and will make it extraordinarily difficult to recruit patients for the study.

I think you have to weigh that if it's taken off the market, then being in the study may be the only way to get the drug. On the other hand, you may have compounding pharmacies that come into the picture. I think weighing all of the pros and cons, I would say the weight is towards keeping Makena on the market in order to be able to do a confirmatory study, with the caveat that if you cannot recruit and if you don't show benefit during an interim analysis to an intermediate outcome, then you stop the study, and then take it off the market.

The types of studies I think that could provide confirmatory evidence, randomized-controlled -- a placebo-controlled trial would be one type of study, but I would suggest that there is an arm of patients that are allowed to stay in the study but select the treatment if they do not want to be randomized and followed forward. That is one type of study.

The other type might be a comparative effectiveness trial, and the comparator would be a comparator that a maternal-fetal medicine specialist could agree upon. I'm not going to get into the design of that study, but I think that might actually improve the recruitment if there was something that one could compare in terms of reducing preterm birth.

I do think that extending the amount of time before delivery does reduce neonatal morbidity because it likely reduces the neonatal intensive care stay and other contributing outcomes. I think that that is an important intermediate outcome.

DR. WITTEN: Thank you.

Dr. Kaimal?

DR. KAIMAL: Actually, it's a clarifying question. It seems to me that much of what we've spent the past two days talking about is what additional studies we'd like to do, and at least to me, it feels as though discussion, both from CDER and from Covis, with all of the carefully prepared information, does focus on the idea that we have unanswered questions that we would really like to have answered. Overwhelmingly, everyone who had testified, whether it was a patient or a provider, knows that this is an impossible clinical question that we really need a better answer to.

My question, I guess maybe is for CDER; I'm not sure exactly. What's being proposed by Covis is to say they will narrow the indication to a higher risk population and simultaneously perform a study in that higher risk population. And my question is -- really just from a regulatory perspective -- is that a possibility, which was sort of raised during the discussion but I think not really definitively answered?

I know that, obviously, the situation with PROLONG was that there was accelerated approval, and then there was an ongoing study for the same indication, but we're now in a different situation with the body of evidence that exists now.

So I guess that's my question for whoever can answer as to, if this is proposed, is that actually a feasible way forward? Because I don't think there's anybody who feels that we have definitively settled this question.

The question is, what is the best way to move forward? I'll pause there.

DR. WITTEN: Okay.

Well, I think I will give you an answer, which probably won't be entirely satisfying, but it's probably the best answer that I can give, which is we need the advisory committee to provide scientific and clinical opinions and conclusions on the specific questions we've posed to you at the hearing through voting on the questions.

So I've already explained that for question 3, for the vote, we're asking specifically

if we should allow Makena to remain on the market, meaning remain on the market with its current indication, while an appropriate confirmatory study is designed and conducted.

So that's the question we're asking you to vote on. That's also the discussion question, but nonetheless, I think you can discuss other options or other issues you might suggest, and when you vote, you can explain in your vote what other considerations you think might apply.

I can assure you that all the discussions at the hearing, which are transcribed, become part of a transcript that is the official record of this proceeding, and your comments matter. Your comments matter before and after the vote, and they'll be reviewed by FDA before the commissioner and chief scientist issue a final decision on this matter.

So I hope that answers your question, at least, to the best of my ability. That's the answer.

DR. KAIMAL: [Indiscernible] -- the answer

there is that the question before us to vote on is Makena stays on the market with the current labeled indication while additional study is done; is that correct?

DR. WITTEN: That's correct.

DR. KAIMAL: Okay. Thank you. That's all. That completes my questions.

MR. KAWCZYNSKI: Dr. Witten?

DR. WITTEN: Yes?

MR. KAWCZYNSKI: Dr. Witten, we have both CDER and Covis wanted an opportunity to answer. It's your call.

DR. WITTEN: They can make a very brief answer, each.

MR. KAWCZYNSKI: Who would you like to start with?

DR. WITTEN: We can start with Covis.

MS. WOOD: Thank you, Dr. Witten.

We would just point out that this question is not tied to the current indication. The question here is asking for judgment about whether the current benefit-risk profile supports the

product remaining on the market. We believe there is ample authority that CDER/FDA possess to make appropriate changes to labeling, as we discussed. So we would encourage the question to be answered as written, and it's not about the current indication.

DR. WITTEN: Thank you.

Now, can we hear from CDER?

DR. STEIN: Dr. Peter Stein, Office of New Drugs, CDER.

I do want to be clear that our assessment is that there is not substantial evidence that supports the effectiveness of this drug, so it does not support the current indication. And as I pointed out earlier, the evidence to provide support for any other indication is really based upon post hoc, non-prespecified analysis that were inconsistent between studies, which we don't consider constituting substantial evidence of effectiveness. And for there to be any indication, the current indication, or a narrowed indication, there still has to be substantial evidence that the

drug provides that benefit.

So once again, regardless of whether we're talking about the current indication, or we would be talking about a narrowed indication, that still must be supported by persuasive evidence, substantial evidence that the drug has that effect. And our conclusion, as I earlier noted, was that there is not substantial evidence of effectiveness.

The drug has not been shown to be effective with regard to its current indication, and with regard to any other use of the drug, the post hoc, non-prespecified analyses do not constitute substantial evidence and do not demonstrate the effectiveness of the drug for any narrowed indication.

DR. WITTEN: Thank you.

So now we'll have lots of other comments from the committee, I see.

Dr. Fox?

DR. FOX: Hi. Michelle Fox. I am the industry representative, so I'm not allowed to vote, but I did want to express my opinion for

consideration.

The in drug development there is a prespecified way of what you have to do to get a drug approved, and 99.9 percent of products that are under development fail and never make it to the market. And I'm hearing from CDER that if this drug had gone through the regular pathway, it never would have made it to the market because the data does not establish that it is effective.

I keep that in mind as I'm trying to consider whether this drug should come off the market while hopefully the sponsor finds an ability to study it more and see in which specific populations it may work, but I don't feel that it should remain on the market while that is being done.

Steps were accelerated because of the nature of the disease, and the confirmatory studies failed to show effect, so I don't feel that it's appropriate to continue to have the FDA state that they're going to leave a drug on the market that they continue to state is ineffective so that women

can take it, while the sponsor goes back to figure out if the drug actually works.

I understand it may be hard to study this if the drug is withdrawn, but I think that it needs to be proved that the drug is being withdrawn due to concerns for efficacy, and any clinical trial that anyone is enrolled in, in a drug that has not been approved, and is under development, they don't know if the drug works. That's the whole point of the clinical trial.

So if we don't know if the drug works, we need to go back to finding out if it does, so I don't really think that withdrawing it should be preventing people from enrolling in a trial. It's not a safety concern, so it should not be as detrimental as it's being made out to be. Thank you.

DR. WITTEN: Thank you.

Dr. Hudak?

DR. HUDAK: Yes. Thank you. I have a little bit of introductory comments, then I'll address the question.

I think we've all listened over the course of two, going on two-and-a-half, days now to many physicians, patients, advocacy representatives, and certainly we've heard a great deal of passion on both sides of this question. I want to acknowledge that, and I think those are legitimate feelings that people have, their experience, their background, and all of that.

I also fully empathize with the desire expressed by patients and physicians to have some therapeutic option for this really critical issue of preterm birth, which is a major, major problem in this country. But I will point out, on the other hand -- certainly in my field, and I can't speak for others, but in neonatology -- the short history is replete with many, many samples of therapies being used as a therapy -- because we need a therapy -- that had later proved to be, at best, ineffective, and in worse case, actually harmful; not saying that that's the case for this drug, but I think we need to consider that.

I'm also sensitive to the disparity issues

that have been raised. We've heard people say that it would be not a good thing to pull the drug from the market because that would reduce access by vulnerable populations to a potentially effective therapy. But I've also heard people say it would be unfair to keep the drug on the market and expose especially these vulnerable populations to an effective therapy that carries a tremendous burden of weekly injections from before 20 weeks onward, but I think people have spoken on that issue on both sides.

With respect to this particular question here, I think that Dr. Stein's answer was absolutely what I expected it to be, having spent many, many years on FDA's advisory committee. I think it is important for us to make sure that we avoid going down the pathway that will cause regulatory chaos. I think that the accelerated approval has very clear expectations, and these were not met in Study 003.

So I think rather than going down some rabbit hole and suggesting that this drug should

remain on the market, not necessarily because of the benefit-risk profile, but because of the opportunistic issue of we need further study, and only by keeping the drug on the market will be able to affect that study, is not appropriate and so forth.

With respect to the issue of benefit-risk, I think that the benefit-risk profile, as we've heard in totality, does not support retaining the product on the market for the indicated label used. I take some issue, I think, with the feasibility of doing studies with the drug on the market or off the market, so just to elaborate on that a little bit, if the drug were to remain on the market, we have some data from Covis about physician surveys that say physicians would be more likely to enroll patients in the study of efficacy in this limited group high-risk group.

However, from a patient perspective, that means that they're going to be a lot of women who are going to get the therapy for which we have no evidence of efficacy, and if I were a patient in

the high-risk group and the drug is on the market with an approved indication, I would say I'm not participating in this study because why are you saying that -- you can't say out of one side of your mouth that we don't know whether it's effective or not, and therefore we need to study it in you, who are particularly at high risk, but say it's available to anybody else on the market.

As a patient, I would say, "No. I'll take the medication." It would be the rare patient, I think, that would have the equipoise to read through all of this and understand the nuances involved in this, and agree to participate.

So I think even if you had more physicians willing to participate in trials, the greatest patient recruitment would be infinitesimal. Off the market, however, I think one could persuade physicians and patients to participate in the study because it is an area that everybody is saying we have equipoise, we really don't know, and there are some signals that it may be effective. It needs to be verified, so I'll say that.

Then finally, in terms of the types of studies that could be used, I think one has to go back to the drawing board on this because I think both the obstetrical and the neonatal outcomes, as they were recently put together for Study 002, as I said yesterday in retrospect, are not the best outcome measures. They don't provide full information, and I think they need to be carefully reconsidered.

I think particularly for the neonatal outcomes, if they are redefined intelligently, you could potentially hope to identify a clear benefit if you achieve the primary outcome -- if you achieve the surrogate outcome of significantly reducing preterm birth in a much more limited number of patients.

I particularly agree with the suggestion by one of the members yesterday that in terms of the eligibility criteria, that the study be limited to women with a past history of preterm birth at 32 weeks or some lower point, and younger than that because beyond 32 weeks, even in the subanalysis,

the evidence of efficacy is very, very mild.

Less than a week prolongation of gestation can be -- you're actually going to see in the neonatal population, because of that, above 32 weeks are really going to be very, very minimal. So I think you're really going to want to target the very high risk group of mothers and infants.

So for this question here, I would say I do not think that FDA should allow Makena to remain on the market. I think to do so would introduce complete regulatory chaos and set precedent that we don't want to have go forward for other medications, and I've already talked about the study, so my answer is no.

DR. WITTEN: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: Yes. Thank you. Susan Ellenberg. I think there are two main rationales that have been put forward for keeping this on the market now. One is the unmet need issue and what is the issue of the feasibility of doing a study that I think everybody agrees, both Covis and the

FDA, would be needed.

With regard to the unmet need, I would say that unmet need is not a sufficient basis for having a product available when you don't know it's effective. Nobody needs a drug that doesn't work. While we don't know for sure that the drug doesn't work in any population, we don't have good evidence that it does work in any population. We have hints and suggestions that cannot be taken as even close to definitive.

Remembering my days of working in AIDS research when in the early days AIDS activists were anxious to have access to anything that was in development, and quickly learned that having lots of drugs in their medicine cabinet, where they didn't know which ones work, if any of them worked, was not useful.

With regard to the study, as I said before, I think we're back to square one on this. We're back to the situation where you just don't know. At the beginning of a development program, after you do phase 2, you have promising results from

phase 2, otherwise you wouldn't go on into phase 3, and then you do a phase 3 study, and I think that's where we are with this drug.

I don't really buy that a new study couldn't be done if Makena was removed from the market. This could be presented to the community as a situation not where we don't know that the drug works, but there's not sufficient evidence to show that it works, and we need to try and find that out because there are some of these hints.

I agree with the previous statement that it's not obvious to me why it's going to be easier to do it if the drug stays on the market. People will be able to get it then, and may not choose to be in the study. Furthermore, if it's on the market, it could tamper with the development of other drugs. I don't know what else is out there in the pipeline for preventing preterm birth, but having something on the market that some people clearly believe in seems to me to make it more challenging for another manufacturer to do a placebo-controlled trial, which I think is needed

since we don't have evidence that anything really works in this study. Thank you.

DR. WITTEN: Thank you.

Next, I'll call on Dr. Alukal.

DR. ALUKAL: Thank you. Dr. Alukal.

So I'm a urologist, and therefore had no clinical experience with this drug, and I think that maybe puts me on different footing than a lot of the people who have weighed in. Sometimes an outsider's perspective can be useful, although I do find, myself, that much of what I was about to say I think has been summarized by Dr. Hudak and Dr. Ellenberg.

The general point I wanted to make was I think there are some false choices being presented here. The idea that we should be allowing the drug to remain on the market for the purposes of being able to perform a confirmatory study, as was alluded to already, the overwhelming majority of drugs that are studied are not actually available for the general population with the indication, obviously, they're being studied.

The follow-on that was made by several people yesterday is the idea that, well, people would be disinclined to participate in a study if they suspected that the drug had been on the market and then withdrawn. At the same time, we have a number of people who've pointed out there doesn't appear to be anything else clinically available to patients in this space. So I suspect that there is a clinical need that it's being maintained to exist; there should not be a problem enrolling people into this study, even if the drug were withdrawn from the market.

Relatedly, I think when we start talking about the idea that there are certain members of the population who are going to be disadvantaged by not having access to this drug, that implies something that we don't yet know. It implies that the drug is effective. We don't know that. All of us have been discussing that from various perspectives, this morning in particular, and it implies that the drug is safe. So we don't yet have a definitive answer on that as well, so I

certainly think further study is warranted.

Obviously, this is a truly meaningful clinical need, but the idea that the drug is allowed to remain on the market during that window of time, when we don't have data supporting a decision to do that, I find it hard to accept that, especially when, as has been alluded to, the idea that all medications have some risk associated with them, why are we exposing people to that risk when we can't clearly state to them this medication has benefits for you in terms of your clinical need?

DR. WITTEN: Thank you.

Dr. Lindsay?

DR. LINDSAY: I just wanted to share my perspective. I was involved in the 2019 meeting where this question was first discussed, and my perception, really, it's been modified. But at that meeting, my perception was that we had a positive trial and a negative trial and that there needed to be a tiebreaker or a third trial done.

Then in the two-year interim, we're now here discussing taking Makena off of the market, and in

terms of the discussion, I've learned something, but it's still my feeling that we still need to have a third trial, sort of as a tiebreaker, to look at the issue because it's such an important clinical question. I'm looking at the totality of the evidence, and I can't honestly say that Makena is effective, but I'm still not convinced that there isn't a subpopulation that it may be effective in.

Now, the question that you ask is whether the medication should still be on the market while that question is being addressed, and I'm learning something in the discussion in terms of whether or not it needs to be, but I really want to reiterate the importance of at least doing additional trials because I left the meeting thinking that I don't know whether there would be a sponsor who would be willing to invest money in terms of doing a trial, and after hearing this discussion, and over the course of the last couple of days, my skepticism about that, it's not as great.

So in summary, I think there needs to be

another trial. Whether the medication needs to stay on the market, if you can do the trial without the medication being FDA approved, then I'm supportive of that. So those are my comments.

DR. WITTEN: Thank you.

Ms. Ellis?

MS. ELLIS: Hi. Like Dr. Lindsay, I also participated in the 2019 advisory committee, and just to bring things back to a human level, it is brutally painful, but there's nothing available. In 2022, in the United States of America, the inequities that exist and the state of neonatal morbidity and for mothers, it's just painful on so many levels.

So I'm thankful for the research. I'm thankful for the discussion, but I know what it's like to be put on bed rest and to fight and try to bring a baby, who is smaller than the preterm baby that happened earlier, and to keep her viable and give her the best chance. I know what it's like to go on a drug that was the best available at the time, which for me was a little terbutaline, which

was later found out to have some really bad adverse effects to the mother. I also know what it's like to be on bed rest for 6 to 8 weeks, and crawl out of bed against your doctor's orders so that you can care for a 3 year old.

So I just wanted to bring that human level back to this. When I look at the benefit-risk question, the safety profile, overall it seems safe. The long term are some unknowns, but it feels mostly safe, although it is unclear. But I also know that the FDA requires that new drugs be safe and effective, not safe or effective.

I also am familiar with the accelerated approval pathway, and please forgive my not sophisticated language here, but I see it as conditional, and it's based on surrogate endpoints, or intermediate endpoints, that require a confirmatory trial. So it's kind of like driving on your donut spare until it's confirmed and then converted to full approval, and nothing at this point rises to that level of evidence.

So we continue to have an urgent unmet need

that requires more data. I think we're all on the same team here. We all want what's best for mothers and babies, and from a biostatistical viewpoint, which I have no experience -- and it really takes a lot of effort for me to even have a basic understanding, but I do know that we need the p-value so that it can reach statistical significance, and be meaningful, and be a real result.

Sometimes when I see a lot of mathematical gymnastics being used to cut things in different ways, and try to squeeze out a subset that has benefit, I have concerns, but I also know that this is retrospective, and anything retrospective requires prospective validation. So we need this information. I think everybody agrees we need this information, and is it feasible to get this information while it's still on the market?

If I was presented with participation in a clinical trial and randomization, if this was on the market, I would find a way to get it. I would want Makena, based on Meis. And I think we need a

bigger study than what's proposed, and we just need to find answers, and we need it as quickly as possible. That's all I have. Thank you.

DR. WITTEN: Thank you.

Dr. McAdams-DeMarco?

DR. McADAMS-DeMARCO: Thank you.

First and foremost, I just want to thank Ms. Ellis. Her participation has been stellar, and the sharing of her experience is incredibly moving to me, and I imagine to all the committee members, so first and foremost, thank you.

I too am a mother, and I deeply feel for those who are faced with such limited options and moving towards your second pregnancy. I am going to switch hats and put on my epidemiology and statistics hat, though, to review the evidence. I've been trained and been doing this for the last two decades, and I really want to echo a lot of the comments that Dr. Hudak and Dr. Ellenberg have stated earlier.

The only point that I wanted to drive home here is to say that when a drug is approved by the

FDA, there is an expectation that it's both safe and effective. If we are thinking about at the place that Dr. Hudak brought up, I believe that the only way we can really find that there is equipoise is once a drug is removed from the market. This to me reflects basic first principles of clinical trials and would be the most ethical way to move forward with randomizing patients to either receive the study drug or this control. Thank you.

DR. WITTEN: Thank you.

Dr. Gass?

DR. GASS: Yes. This is a difficult, challenging, and somewhat painful discussion when we look at it from all angles, but I'd like to take a step backwards and just look at the bigger picture.

First of all, the company has already had the benefit of an accelerated approval process, and when we look at the data, we see that there's no strong evidence that the drug is effective. And standing back from this more existent perspective to look at the FDA and the advisory committee

essentially disregarding a large study that said that there was no effectiveness to this product, and yet allowing it to continue on the market, I think would reflect very poorly on the FDA and our advisory committee.

So to do this would undermine the credibility of these two groups, so I think from that perspective I would recommend that the drug be withdrawn until we can get the data that really show effectiveness, which is what is required of most drugs that are approved.

DR. WITTEN: Thank you.

Dr. Obican?

DR. OBICAN: Thank you. Sarah Obican. I actually echo the humanness side of this whole discussion, and for Ms. Ellis as well, and we certainly owe a debt of gratitude to all the pregnant people who are participating in trials. It's so important, and I hope they all understand that.

From the perspective here, some of the things I'm struggling with is having another trial,

which may be warranted. My question is how to have that personal conversation with patients and we truly have equipoise? And if the drug is on the market, how do you have that conversation with them, as well as if FDA approved, but we still don't understand if it's beneficial or not in the substantive population, and would you be part of the trial? I think that would be really difficult to recruit.

I understand the survey that was done, and that is somewhat reassuring, but I am also really concerned of that really coming to fruition. It's really hard to have trials done in our field, and to have that organized, I think will take another 4 to 6 weeks. The 4 to 6 years -- forgive me -- is the time frame possibly what we would need in terms of patients, but the time frame ahead of that would be very long, and I'm concerned certainly about that. My biggest thing, I think, is discussions with the patients.

My other one is my concern for the outcome. I think what we're really worried about is the

neonatal outcomes. We're worried about how those babies are going to do in the NICU, and is there a benefit if we are delivering them at earlier gestational age? We hope that gestational age is a good surrogate. I just worry about that being helpful in this particular situation. Thank you. That's all from me.

DR. WITTEN: Thank you.

Dr. Eisenberg?

DR. EISENBERG: This discussion has been very helpful, and I really do value the comments made by Dr. Hudak and Ellenberg, and everyone else. So I am still struggling with -- it is the framework of the FDA that we have to have effectiveness. I think that it's really hard to backtrack once you've given accelerated approval. And I would say that the subsequent trial, although it's been done, has many flaws, and I think that the question that I have is, at what point does one remove the accelerated approval if you haven't had an adequately -- well, if the study that has been done was flawed and is unable to answer the

question? That's my question. I do value the points made by the other members of the committee.

DR. WITTEN: Thank you.

Are there any other comments or questions?

Dr. Henderson?

DR. HENDERSON: Thank you.

I'm concerned, when I voted on the second question. If the drug has no benefit, given that there are risks -- as we've already talked about, thromboembolic and other ones -- it clearly should not be on the market. If there's no benefit and there is risk, there's no reason for it to be on the market. But I do think there is some benefit from the Meis trial.

I think that one of the risks that we haven't talked about -- some in the trial but it's not in the insert -- is the intergenerational risk. I think that if we go for it with another study, and even this current availability on the insert, there should be a discussion to patients about the potential intergenerational risk.

We've mentioned thalidomide and DES. My

guess is that most of the young people who take this don't know anything about thalidomide or DES. I think that there should be a little brief blurb in there about that, and perhaps the sponsor might add to their observational study a registry, something on the order of a DES registry that's maintained at the University of Chicago so we can follow these offspring.

My concern about taking it off the market is the prevalence of the compounded 17 hydroxy in all the pharmacies that are around -- well, certainly in the Bronx and Manhattan -- and I worry about that. And I think if this is taken off the market, my concern is that the compounding will increase, and I think if it is taken off the market and a study moves forward, I think that many people would not participate because they would not want to get the placebo; they'll get the compounding.

So I'm concerned about if there is any possibility that there may be a benefit, that we have already put that out to the professions and also to patients that they may seek it another way,

and get something that we don't have any control over, and we don't know what the fetus may be exposed to. Those are my comments.

DR. WITTEN: Thank you.

Any other comments or questions before we go in for the vote?

(No response.)

DR. WITTEN: Okay.

If there are no other comments or questions, we're going to move on to the voting. The voting process will be the same as it was for questions 1 and 2. I'm going to restate the voting question now, voting question 3.

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? I'll just mention that, as before, you'll get the opportunity to explain your votes after the voting process.

The voting will now begin. You have 30 seconds before the vote closes. Thank you.

(Voting.)

DR. CHOI: You have 15 seconds before the vote closes.

DR. WITTEN: We're missing one vote.

Is there someone who needs help?

MR. KAWCZYNSKI: Michael, is that you again?

DR. LINDSAY: Yes.

MR. KAWCZYNSKI: Just log out again and come back in again. Okay, sir?

(Pause.)

DR. CHOI: Voting has closed and is now complete. Once the vote results have been displayed, I will read the votes into the record.

(Pause.)

DR. CHOI: For the record, 1 yes, 14 no, and no abstentions.

Dr. Caughey voted no; Dr. Kaimal voted no; Ms. Ellis voted no; Dr. Henderson voted yes; Dr. Eisenberg voted no; Dr. Alukal voted no; Dr. Shields voted no; Dr. Harper voted no; Dr. McAdams-DeMarco voted no; Dr. Gass voted no; Dr. Hudak voted no; Dr. Munn voted no; Dr. Lindsay

voted no; Dr. Obican voted no; and Dr. Ellenberg voted no.

Thank you.

DR. WITTEN: Thank you.

I will now call the members one at a time to state your vote and explain the reasons behind your vote.

Dr. Alukal?

(No response.)

DR. KAIMAL: Sorry. Anjali Kaimal. I have struggled with this mightily, and I'm very appreciative of all the information that was presented. There was a speaker yesterday that said the most terrifying thing you can tell that patient is that there's nothing to do and, unfortunately, in obstetrics there are many situations where I find myself in that situation. The compulsion to do something is strong, both on the part of the patient and on the part of the provider.

I wasn't sure whether I should share this or not, but I also had a preterm baby. I had a baby in the NICU, and then had a subsequent pregnancy

where I had to think about what to do. So having participated in that conversation so many times as a provider and to also have the experience as a patient, it just brought home what I had seen on the faces of so many people that I have taken care of before.

But while I think that there are not significant harms that have been shown with Makena, there are still costs to continuing to have it on the market while we try to figure out who it might work for, and I do think that that's a very important question to answer, and the additional study is needed. In no way does my no vote say that that is not what needs to happen.

One hundred percent, there needs to be another trial because I want to believe that there is a solution for preterm birth, and that this might be part of what our instruments could be to try to help people. But I think that when we leave something on the market that hasn't been shown to be effective, we lose out on other investigations that might be pursued. We spend money that could

be spent elsewhere for all of the many problems in maternal and child health that need our attention.

And the last thing I would say is that, again, faced with that powerless feeling, is false hope really any hope at all? So I hope that in the future, we are able to do a study that shows us who the population is that will benefit from this medication, if any, and when we have that evidence, we're able to go to that patient population confidently and say this is the thing that I think will help you.

I also want to believe better of my colleagues when we talk about saying, well, we need to have something to do so that we don't do other things that might be more harmful. We do have an evidence base in obstetrics. It's not the same as maybe in some other fields, but I hope that we will turn to our evidence and that our professional societies will guide us in thinking about how best to take care of patients with the evidence and interventions that we have available.

It is very weighty to think about the most

vulnerable populations that we take care of and concern about not giving them access to a treatment that might help them. But in the same conversation, to think that I'm going to give a very vulnerable population an ineffective treatment also just doesn't seem like the right thing to do.

So I know lots of others have struggled with this question as well, but those are the reasons why I voted no. Thank you.

DR. WITTEN: Thank you.

Dr. Alukal?

DR. ALUKAL: Thank you. Dr. Alukal.

I couldn't agree more with what Dr. Kaimal just said. I think that last point, that just because we don't have a treatment, and just because we think this condition disproportionately burdens certain populations does not mean that we have to rush to provide any treatment in those populations, we may be doing harm as opposed to good, even though our intentions are good.

So I think doing the necessary study to get us some answers about this particular intervention

that's, I think, absolutely in agreement by everyone. We've all stated that in different ways, and I think even with the drug not on the market without an indication, that study can be performed, and I hope it will be performed.

I really hope Covis as the sponsor continues to participate in that effort, and enrollment may be easier than everybody believes at first glance, again, because there appear to be no other options, so then this problem will persist. So hopefully we'll be able to recruit patients rapidly and get some answers.

I think the second part of the question that's up there, obviously, a prospective one, a controlled trial in a high-risk population would be one part of this, and I think the other, in parallel, should be an observational cohort study of infants born after treatment of the mother with Makena.

I was curious about that, again, not knowing a lot about both the clinical condition and the drug. It appears the drug is available overseas

under a different name, and it made me curious as to whether or not there's any published data on safety with regard to newborns, and then any follow-up of those newborns in database studies from overseas in the national health registry. There doesn't appear to be, although that's my cursory lit search. That also represents a potential for further research, but obviously that's going to be a longer term study and will take more time unless you were to simply analyze whatever retrospective data exists.

But it's a hugely important question, and I echo everyone. Thanks for all the people who have come forth and shared their own experiences with this, obviously, incredibly difficult clinical question, and hopefully we can find a way through to getting some much needed answers as soon as possible.

DR. WITTEN: Thank you.

Dr. Caughey?

DR. CAUGHEY: Hi. This is Aaron Caughey. Can you hear me?

DR. WITTEN: Yes.

DR. CAUGHEY: Great.

I would strongly agree with what Dr. Kaimal said and was really impressed by her commentary. I worked with Dr. Kaimal in the past, and she clearly has superseded anything I would have to say.

I guess the one thing I might add in this setting was that while I did think that there might be a case made to consider approval of this medication for some really high-risk group, that case was not made from an evidentiary standpoint, so I don't see how I could vote to approve it continue in the market.

I really appreciate that it's an incredibly important area, one of great impact to patients, and I really liked the frame that Dr. Kaimal said, of that feeling of desperation is one that is important, but we do have other tools. And the idea that we will leave women to just going back to prescribing bed rest I think is not a fair characterization of where the field is at the moment. We do have other things we can do at this

moment in time in terms of following these patients clinically.

We do certainly need medications, and this medication may be a benefit in the highest risk populations, and such studies need to be conducted to elucidate the populations of which benefit will be affected. So I'll leave it there. That will be my last comment. Thank you so much.

DR. WITTEN: Thank you so much.

Dr Eisenberg?

DR. EISENBERG: I voted no, but I still am very conflicted because this is a very, very difficult question. I don't feel that the studies to date have demonstrated absolute effectiveness, but they have also not demonstrated ineffectiveness depending on the population. I think that the difficulty is identifying the population that would benefit.

I took to heart Dr. Stein's comments, yet on the other hand I do pose the question, at what point do you remove the accelerated approval if that secondary study -- I mean, are you allowed to

do another study to try to identify the benefit if the study that was done was flawed? That is really a question I have.

I definitely encourage an additional study to be done, probably not only a randomized placebo-controlled trial, but if, what the last speaker just said, there are other treatments, then I would recommend a comparative effectiveness trial because it would be much easier to recruit for that type of trial. Basically, this is just a really very difficult question, it's a difficult problem, and I think we all wish we had solutions.

DR. WITTEN: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: Susan Ellenberg. I voted no for the reasons that I stated before. I would also be supportive of studies that follow up on some of the hypotheses that were generated in the prior studies. Ideally, such a study would be able to identify an effect on neonatal morbidity and mortality, which I think is the ultimate goal of preventing preterm pregnancy. That would require a

larger and longer study, I understand, but that is really what we are interested in here. But for the reasons that I said before and which other members of the committee have also stated, I do not favor leaving this on the market. Thank you.

DR. WITTEN: Thank you.

Ms. Ellis?

MS. ELLIS: I voted no. If I had the opportunity to vote with my heart, it might have been yes, but I had to vote with my head and stay within the guardrail of the question and what I know to be true on the regulatory side. So that's why I had to vote no. Thank you.

DR. WITTEN: Thank you.

Dr. Gass?

(No response.)

DR. WITTEN: I think you're on mute.

DR. GASS: I voted no because if we allow Makena to remain on the market, it implies that the FDA looked at a large study, found no benefit, and yet allowed this drug to stay on the market. I think that's a bad precedent. So I do hope to

encourage Covis to continue their work quickly and come up with a new study so we have something to look forward to. Thanks.

DR. WITTEN: Thank you.

Dr. Harper?

DR. HARPER: Thank you. Lorie Harper. I voted no. I would just echo what Dr. Kaimal said. I think she really said it very clearly. But I think that the fact that we believe that we have equipoise to further study this medication in a high-risk population to determine its effect leaves me to believe that there is not currently enough evidence to leave it on the market to state that it's efficacious. So that's why I voted no. Thank you.

DR. WITTEN: Thank you.

Dr. Henderson?

DR. HENDERSON: Thank you.

I voted yes, and it goes along with my vote for question 2. I think the trial with the highest risk group in the Meis demonstrated that there is some signals of effectiveness. I think the second

trial did not include a high-risk group, although the percentage of the Black population was pretty similar.

As I discussed the other day, I think that race in the U.S. is really a surrogate for the structural determinants of health, as we talked about during the meeting, and I think that hasn't been done in the second trial. I think taking it off the market will, again, just ratchet up the compounding pharmacies, and then we're in a condition where fetuses are being exposed to substances that we don't understand. We don't know. We don't know what's in them. There's no GMC [ph] in those products, so I'm concerned about what women will then be subjected to getting injected with if Makena is not available, so I voted yes.

DR. WITTEN: Thank you.

Dr. Hudak?

DR. HUDAK: Well, again, I voted no. I think the information presented by both sides was very compelling. I really appreciate Dr. Kaimal

and Ms. Ellis relating their personal experiences, and I will say as a physician who deals with this vulnerable population of mothers who deliver preterm babies on a daily basis, it's a very, very challenging emotional journey, that both the parents and professionals who are treating these babies and families go through.

So I very much empathize with this internal debate that we conduct all the time between our heart and our mind, and it is difficult. I'm sometimes called a therapeutic nihilist. I like to say that rather than being a nihilist, I like to ground my approach in evidence. And looking at the evidence here, and looking at the regulatory structure, and looking at the potential to create, as I said, a bad precedent and regulatory chaos, I think that we have to recommend that this product be taken off the market. In my view, that will only facilitate the very much needed further study in the subpopulations of interest.

I further comment that I don't think that the 003 trial was flawed. I think it was very

carefully constructed. It was similar to the design of 002. It was a much larger trial. The 87 patients in the subanalysis of the 1700 patients in the trial, which is a signal of efficacy, very much is intriguing and in need of being pursued in further rigorous studies, as I said, with endpoints that are accepted and that are likely to show efficacy in a very meaningful way, in the fewest number of patients as possible, so those are my thoughts.

DR. WITTEN: Thank you.

Dr. Lindsay?

DR. LINDSAY: I voted no, based on the totality of the evidence, but as I said earlier, I would encourage additional clinical trials. I would encourage both the sponsor and the FDA to use the information that they learned from the Meis trial and the PROLONG trial to come up with a trial that will address some of the limitations that were pointed out in the trials, and also include the expertise from our academic community across the U.S. Those are my comments.

DR. WITTEN: Thank you.

Dr. McAdams-DeMarco?

DR. McADAMS-DeMARCO: Hi. This is Dr. McAdams-DeMarco, and I voted no for a lot of the reasons that have already previously been stated. I would, however, make two suggestions for sponsor.

I would first encourage them to use not only the randomized-controlled trial data, but also pharmaco-epi studies to help identify a truly high-risk population that you expect to have a differential response to the drug, and this would be based on biologic traits. I think this is an important ground-level stage to informing the design of your subsequent RCT.

I would also encourage the sponsor to work with the Office of Surveillance and Epidemiology at the FDA to design a high-quality retrospective cohort study to investigate the risk of intergenerational outcome. Thank you.

DR. WITTEN: Dr. Munn?

DR. MUNN: Hey. This is Dr. Munn, and I

voted no as well. This, like for many others, was very difficult for me. I live and work in Alabama, and I take care of those highest at risk for preterm birth, so this was very difficult. I do think that our patients deserve an answer, and I think that they deserve that well-designed clinical trial, and I think that taking the drug off the market is going to allow that. I think our patients are amazing and wonderful, and they'll be willing to participate in something going forward, so I look forward to the future. Thank you.

DR. WITTEN: Thank you.

Dr. Obican?

DR. OBICAN: Thank you. This is Sarah Obican, University of South Florida, maternal-fetal medicine. As others have echoed, I had a difficult time making this decision, and it was certainly heavy, but I voted no. And the difficulty comes in how our patients are going to see this, and also for my obstetric colleagues.

We desperately want a good treatment modality for this overwhelming disease, and it's

frustrating that at this time, the evidence and this subsequent analyses have not shown effectiveness, and that's difficult certainly to bear.

Certainly, I would also support another trial to be done in the populations with an appropriate discussion of risk and benefits for those patients, but at this time, given the evidence that we have, my vote was no. Thank you.

DR. WITTEN: Thank you.

Dr. Shields?

DR. SHIELDS: Yes. Hi. I voted no as well. It's been an excellent discussion of the pros and cons of this decision. There are so many elements at play. I voted no for all of the reasons cited by my colleagues. I disagree with this sponsor that Makena would need to stay on the market in order for them to do a clinical trial. I actually believe the opposite, that women with high-risk pregnancies would be more likely to participate, or if that's the only way they can get the drug, I don't think that would prevent them from enrolling.

I think that FDA needs to follow the expedited approval rules that have been set out and require a confirmatory study in order for the product to stay on the market. I think that's really important. I'm afraid that if it remains on the market, it will be used by women for whom there is no confirmation of efficacy and would be exposing them to harm, both known side effects and potential side effects, particularly to the baby.

So I don't think it's for the FDA to keep the product on the market in order to assist the sponsor to conduct the study that could be conducted with the product off the market. Thank you.

Adjournment

DR. WITTEN: Thank you.

So that concludes polling the advisory committee members. I'm just going to summarize, the vote was 14 votes no, 1 vote yes, so there wasn't consensus about everything.

I think in the sense of the discussion, though, there's clearly a need for treatment for

these patients, and also it will be important to identify who would actually benefit, but this benefit needs to be there in order for this to be available for treatment.

There was general agreement, at least from most of the comments, that the ability to do a study would be not improved by the product staying on the market. There were also some concerns raised about compounding and what the effect of market withdrawal could be, and there were some comments about specifically what might need to be done in further studies to identify subpopulation, as well as a comment about looking at epidemiological studies to examine the question about intergenerational safety effects, potential effects of the product.

So this concludes our discussion. I'll just say in closing, these are really difficult and challenging issues that we've been discussing over the last couple days, so there's obviously a real clinical need for treatment for these patients. As I noted in my opening statement, the vote is not

going to decide the issues. The discussions at this hearing, including the votes and your comments before and after the votes, will be reviewed by FDA before a final decision is issued.

I really would like to thank everyone who participated in this hearing, the advisory committee, the sponsor, the CDER participants, the Commissioner's team that has helped with the logistics behind the scene, and everyone else who has helped to have this meeting. So the hearing is now adjourned. Thank you.

(Whereupon, at 11:21 a.m., the hearing was adjourned.)