Final Decision on the Proposal to Withdraw Approval of Makena
Docket No. FDA-2020-N-2029
April 5, 2023

This document is the final decision of the Food and Drug Administration (FDA), pursuant to Section 506(c)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356(c)(3) (2021))[1] and 21 CFR 314.530 (2022), on the Center for Drug Evaluation and Research's (CDER's) proposal to withdraw approval of Makena (hydroxyprogesterone caproate injection, 250 milligrams (mg) per milliliter (mL), once weekly), new drug application (NDA) 021945, held by Covis Pharma Group/Covis Pharma GmbH (Covis).[2] Robert M. Califf, M.D., Commissioner of Food and Drugs, and Namandjé Bumpus, Ph.D., Chief Scientist, are jointly issuing this decision.

We acknowledge at the outset the serious problems of preterm birth with respect to both maternal and neonatal health and the contribution of institutional forces that have led to health disparities, including preterm birth, among communities of color. It is tragic that the scientific research and medical communities have not yet found a treatment shown to be effective in preventing preterm birth and improving neonatal outcomes. In light of this unmet need, it is imperative that the medical and scientific communities redouble their efforts to find effective treatments, including further research on Makena. Nothing in this opinion today is intended to minimize these concerns – to the contrary, our hope is that this decision will help galvanize further research.

Fundamentally, however, the touchstone of FDA drug approval is a favorable benefit-risk assessment; without that favorable assessment, the drug should not have the status of being FDA-approved. After thoroughly reviewing the record for this matter, we have determined that there is an insufficient demonstration of effectiveness to balance any level of risk. Accordingly, as further explained below and in the referenced attachment, FDA hereby withdraws approval of Makena. We also hereby withdraw the approvals for the abbreviated new drug applications (ANDAs) that reference Makena pursuant to 21 CFR 314.151(b)(3).

[1] Although the Consolidated Appropriations Act, 2023, enacted on December 29, 2022, amended certain procedures for withdrawing accelerated approval of a drug, the legislation states that these revisions do not apply to "ongoing withdrawal proceedings" where, as here, the notice of proposed withdrawal was published before the December 29, 2022 date of enactment of the Act. See Consolidated Appropriations Act, 2023, Pub. L. No. 117-328, § 3210(f) (2022).

[2] AMAG Pharmaceuticals, Inc. (AMAG) was the previous the sponsor of NDA 021945 during some of the relevant time period described in this decision. For efficiency, this decision refers to AMAG as "Covis."

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Background

The background of this proceeding has been described in several documents that are posted in the docket (and some published in the Federal Register)[3] and will only be briefly recounted here. On February 3, 2011, FDA approved the NDA for Makena under the accelerated approval pathway to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth (recurrent sPTB). CDER granted accelerated approval based on the results from the Maternal Fetal Medicine Unit Network trial (referred to as "Trial 002" or "the Meis trial"). CDER determined that the sponsor had demonstrated an effect on an intermediate clinical endpoint (i.e., recurrent sPTB) that was reasonably likely to predict clinical benefit (i.e., an effect on neonatal morbidity and mortality from complications of sPTB).

Consistent with the statute and regulations, CDER's approval letter required that the sponsor complete a postmarketing confirmatory study. Covis conducted the study, referred to as "Trial 003" or "PROLONG," but Trial 003 did not verify the clinical benefit of Makena.

On October 5, 2020, CDER proposed withdrawing accelerated approval of Makena and provided Covis with an opportunity to request a hearing on the proposal. In the proposal, CDER cited two grounds under section 506(c)(3) of the FD&C Act and § 314.530(a) for withdrawing approval:

(1) the confirmatory study failed to verify clinical benefit of the drug; and
(2) the evidence does not establish that the drug is effective under its conditions of use.

Under the statute, the sponsor is entitled to an opportunity for an informal hearing before FDA can withdraw accelerated approval, 21 U.S.C. 356(c)(3), and FDA's implementing regulations provide that the hearing is to be conducted before an advisory committee.[4] On October 14, 2020, Covis timely requested a hearing. By letter to CDER and Covis dated August 18, 2021, FDA's then Chief Scientist RADM Denise Hinton granted Covis's hearing request.[5] In the letter, RADM Hinton designated the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) [6] as the advisory committee to be present at the hearing and to provide advice and recommendations to the Commissioner. The letter appointed Celia M. Witten, Ph.D., M.D., Deputy Director, Center for Biologics Evaluation and Research, as the presiding officer to conduct a hearing in accordance with 21 CFR 314.530(e) (referencing 21 CFR Part 15, which provides for the appointment of a presiding officer in 21 CFR 15.30).

CDER and Covis submitted prehearing briefing materials to the docket, and members of the public—representing public interest and medical advocacy groups, as well as individual medical

[3] See, e.g., Presiding Officer's Written Report Summarizing Public Hearing and Providing Recommendations on CDER's Proposal to Withdraw Approval of MAKENA, Docket No. FDA-2020-N-2029 (Jan. 19, 2023) (PO Report) (attached and available at https://www.regulations.gov/document/FDA-2020-N-2029-0379); Notice of Hearing, 87 FR 50626 (Aug. 17, 2022).
[4] 21 CFR 314.530(e)(1).
[5] The letter explained that then Acting Commissioner for Food and Drugs, Janet Woodcock, M.D., had recused herself from this proceeding based on her previous involvement in CDER's consideration of the matter and had delegated her role in this proceeding to RADM Hinton.
[6] On March 23, 2022, BRUDAC was reconstituted as the Obstetrics, Reproductive and Urologic Drugs Advisory Committee (ORUDAC). 87 Fed. Reg. 16477 (Mar. 23, 2022). The function of the ORUDAC no longer includes osteoporosis and metabolic bone disease.

professional, patients, and patients' families – submitted comments to the docket.[7] The hearing was conducted virtually on October 17 to 19, 2022.[8] CDER and Covis made presentations followed by an opportunity for questions by the other party, the advisory committee, and the Presiding Officer. There were also comments from twenty public commenters, representing a range of backgrounds and perspectives. No ANDA holders elected to make presentations, although some submitted comments to the docket.[9]

On the final day, after each party gave closing presentations, the advisory committee discussed and voted on a series of questions. On the first question ("Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?") all 15 advisory committee members voted "no," and agreed that Trial 003 did not verify the clinical benefit of Makena. On the second question ("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?"), 13 advisory members voted "no," one member voted "yes," and one member "abstained." During the discussion, most advisory committee members did not believe that the two studies taken together demonstrated effectiveness of the labeled indication. On the last question ("[S]hould FDA allow MAKENA to remain on the market while an appropriate confirmatory study is designed and conducted?"), 14 advisory members voted "no," and one member voted "yes." The advisory committee's discussions included whether Makena should remain on the market and whether facilitating further study was a reason to retain it on the market. The advisory committee also considered the benefit-risk profile of Makena, factors related to unmet needs and equity, the evidence in support of a narrower indication, and some additional concerns related to intergenerational safety risks. Most advisory committee members agreed that there was not sufficient evidence that Makena is effective in any population.

Following the hearing, Dr. Witten issued a report, dated January 19, 2023, that summarized the legal and factual background, the content of the hearing, and her analysis and recommendations (PO Report). CDER and Covis submitted post-hearing briefs on March 6, 2023. Pursuant to the process outlined in FDA's regulations, this matter is now ready for a final FDA decision.

Discussion

After reviewing the record for this matter, including the submissions by the parties, comments to the docket, the transcript of the hearing, and the PO Report, we have determined that FDA must withdraw approval of Makena and generic versions of Makena. The PO Report provided a

[7] https://www.regulations.gov/docket/FDA-2020-N-2029.
[8] https://www.regulations.gov/document/FDA-2020-N-2029-0375 (transcript for Oct. 17, 2022); https://www.regulations.gov/document/FDA-2020-N-2029-0376 (transcript for Oct. 18, 2022); https://www.regulations.gov/document/FDA-2020-N-2029-0377 (transcript for Oct. 19, 2022).
[9] As we discussed in our letter granting Covis's request for a hearing, one ANDA holder, American Regent, Inc. had submitted a written comment and request that it be granted status as a nonparty participant. Another company, Beloteca, Inc. had submitted a written comment indicating that it has a pending ANDA referencing the NDA for Makena and requesting that it be granted status as a nonparty participant. After the hearing, ANDA holder Eugia Pharma Specialties, Ltd. (Eugia) requested a wind-down period should its ANDA be withdrawn from the market. Specifically, Eugia requested "at least four (4) months of continued marketing before withdrawal of the ANDA from the US Market."

detailed and thoughtful presentation and analysis of the evidence and the issues relevant to this matter, and we agree with the findings and conclusions of that report. Rather than repeat that analysis here, we are incorporating the PO Report by reference as part of this final decision. We offer a few comments below to highlight the key considerations and address certain questions raised in the post-hearing submissions.

There is no dispute that FDA has grounds under the statute for withdrawing approval of Makena and its generic versions. Indeed, Covis conceded that the PROLONG trial failed to demonstrate clinical benefit. Accordingly, the remaining question is whether FDA *should* withdraw approval, as was the focus for most of the hearing itself. We agree with the Presiding Officer's analysis of the various arguments presented. The bottom line is that, based on current studies, there is an insufficient demonstration of effectiveness to balance any level of risk. Without a favorable benefit-risk assessment, there is no justification for keeping the product on the market, even where there is an unmet need.

In its posthearing submission, Covis argues that the Presiding Officer should have instructed the advisory committee to vote on Covis's proposal to narrow the population in the approved indication to high-risk patients while an additional confirmatory is conducted. Covis asserts that, although the advisory committee could have construed the final voting question ("[S]hould FDA allow Makena to remain on the market while an appropriate confirmatory study is designed and conducted?") to encompass Covis's proposal, the Presiding Officer clarified at the hearing that the final question related to the currently approved indication (as reflected in the approved labeling), not to a hypothetical amendment to the labeling.

The Presiding Officer's clarification was appropriate given the context of this proceeding. FDA approved Makena for patients "with a singleton pregnancy who have a history of singleton spontaneous preterm birth."[10] CDER sought to withdraw that specific approval when it began this proceeding, and whether to withdraw the approval for that indication is the question before us.

But even if the question had been reframed in the manner that Covis would have preferred – to specifically ask whether the approved indication for Makena should be narrowed to the population of high-risk patients – an advisory committee vote on that question would not have affected our decision today. We have made our decision based on our independent review of the record for this proceeding and have concluded that the current data and other available evidence do not establish a favorable benefit-risk assessment of Makena for a narrowed population of high-risk patients.

We have also considered Covis's arguments relating to compounding hydroxyprogesterone caproate (17-OHPC) (the active ingredient in Makena). The current lack of adequate data supporting effectiveness implicates compounded products as well as Makena and its generic versions. However, as a procedural matter, compounded products are not within the scope of this withdrawal proceeding, and the agency must address them through a separate regulatory process.

[10] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021945s012lbl.pdf

Covis requests that we delay the effective date of the withdrawal so that current patients can complete their courses of treatment and for remaining in-channel inventory to be exhausted. We decline to do so. Given our conclusions regarding the unfavorable benefit-risk assessment for Makena as discussed above, FDA's continued approval of Makena and its generic versions is unwarranted and inappropriate.

This decision, however, does not necessarily foreclose FDA's exercise of enforcement discretion. We defer to CDER to determine next steps with respect to implementing this decision, including any appropriate wind down, such as exercising enforcement discretion as to inventory currently in distribution or permitting continued use of Makena for patients currently undergoing treatment. We further defer to CDER on how best to address compounding using 17-OHPC.

We wish to extend our gratitude to the members of the advisory committee for their service and thoughtful consideration of this matter. We also appreciate the participation of the public commenters who brought a range of perspectives and experiences to this proceeding – many of whom expressed heartfelt concerns and recounted personal experiences regarding preterm birth.

In closing, we recognize the impact that preterm birth has on patients and their families and are committed to helping advance the development of effective treatments. Preterm birth is a serious condition with a disparate impact on communities of color. We share the frustration expressed by many of the advisory committee members and public commenters as well as the parties that there is no effective treatment available. But at the same time, exposing patients to the risks of a treatment that is not shown to be effective is not the solution. FDA hopes that in the future, new studies will demonstrate an effective treatment for preventing preterm birth, whether that treatment is Makena or a different therapy. In the meantime, FDA is committed to working together with patients, researchers, and drug developers to advance the development of safe and effective therapies that are urgently needed to treat this serious condition.

Namandje N. Bumpus -S

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Namandjé N. Bumpus, Ph.D.
Chief Scientist

Robert Califf -S

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Robert M. Califf, M.D.
Commissioner of Food and Drugs

Attachment

Presiding Officer's Written Report Summarizing Public Hearing and Providing Recommendations on CDER's Proposal to Withdraw Approval of MAKENA (Jan. 19, 2023).

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

TO: Robert M. Califf, M.D.
Commissioner of Food and Drugs

Namandjé Bumpus, Ph.D.
Chief Scientist

FROM: Celia M. Witten, Ph.D., M.D.
Deputy Director
Center for Biologics Evaluation and Research

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SUBJECT: Presiding Officer's Written Report Summarizing Public Hearing and Providing Recommendations on CDER's Proposal to Withdraw Approval of MAKENA

DATE: January 19, 2023

1. Introduction and Summary

The Food and Drug Administration (FDA) granted a hearing on the Center for Drug Evaluation and Research's (CDER's) proposal to withdraw approval of Makena (hydroxyprogesterone caproate injection, 250 milligrams (mg) per milliliter (mL), once weekly), new drug application (NDA) 021945, held by Covis Pharma Group/Covis Pharma GmbH (Covis). I served as presiding officer at the hearing, which was held virtually October 17 to 19, 2022, and included the presence of the Obstetrics, Reproductive and Urologic Drugs Advisory Committee (ORUDAC, advisory committee, or committee) for purposes of providing advice and recommendations to the Office of the Commissioner. The hearing consisted of presentations by CDER, Covis, and members of the public; opportunities for questions; and discussion and votes by the advisory committee.

This report summarizes the hearing, including relevant background. In the final section, I provide my own advice and recommendations as to whether FDA should withdraw approval of Makena. By March 6, 2023, Covis and CDER may each submit to the docket a brief with arguments and analysis addressing the substance of this report, the presentations and discussions at the hearing, and the committee's advice and recommendations. There is no required format for these optional submissions. The Commissioner and Chief Scientist will consider any such submissions in making the final decision for the agency on CDER's proposal to withdraw approval of Makena.

2. Legal Background

a. Summary of accelerated approval process

Section 506 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356) provides that a drug sponsor may request to expedite the review and approval of a drug intended to treat an unmet need related to a serious or life-threatening disease or condition. Under the accelerated approval pathway, FDA may grant accelerated approval based on the drug's effect on a surrogate or intermediate clinical endpoint. FDA's regulations, at § 314.510 (21 CFR 314.510), require that accelerated approval be subject to a sponsor's engaging in further study "to verify and describe [the drug's] clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome."

b. Summary of withdrawal process including hearing process

Under section 506(c)(3) of the FD&C Act, FDA may withdraw approval of a drug approved under this pathway using expedited procedures if, among other reasons, the required study fails to verify "the predicted effect on irreversibility morbidity or mortality or other clinical benefit." An FDA regulation, 21 CFR § 314.530, outlines the expedited procedures for withdrawing a product approved under accelerated approval.[1] Under § 314.530(a) (21 CFR 314.530(a)), FDA may withdraw accelerated approval of a drug when "[a] postmarketing clinical study fails to verify clinical benefit" or "[o]ther evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use," among other circumstances.

To initiate the process for withdrawing accelerated approval of a drug under 21 CFR § 314.530, the Director of CDER must provide the applicant with notice of an opportunity for a hearing on the proposed grounds for withdrawal under § 314.530(b). To obtain a hearing, the applicant must, pursuant to § 314.530(c), request one within 15 days after receiving CDER's notice and submit "the data and information upon which [it] intends to rely at the hearing" within 30 days thereafter. Pursuant to § 314.530(e)(1), FDA conducts hearings under § 314.530 in accordance with part 15 (21 CFR part 15), with certain modifications. The key modification under § 314.530(e)(1) is that an advisory committee is present at the hearing and provides advice and recommendations to the Commissioner.

Under § 314.530(e)(2), the presiding officer, the members of the advisory committee, and up to three representatives from both the applicant and CDER may ask questions of the presenters at the hearing. The presiding officer, as a matter of discretion, may also permit questions of presenters posed by others participating in the hearing upon submission of such questions in writing. After receiving advice and recommendations from the advisory committee, the agency makes a final decision on whether to withdraw accelerated approval of the drug product at issue.

[1]Although the Consolidated Appropriations Act, 2023, enacted on December 29, 2022, amended certain procedures for withdrawing accelerated approval of a drug, the legislation states that these revisions do not apply to "ongoing withdrawal proceedings" where, as here, the notice of proposed withdrawal was published before the December 29, 2022 date of enactment of the Act. *See* Consolidated Appropriations Act, 2023, Pub. L. No. 117-328, § 3210(f) (2022).

3. Background on Makena

a. Approval of Makena

On February 3, 2011, FDA approved the NDA for Makena under the accelerated approval pathway to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth (recurrent sPTB). As described in CDER's proposal to withdraw approval, the Makena NDA relied on evidence from the Maternal Fetal Medicine Unit Network trial (referred to as "Trial 002" or "the Meis trial") for primary support of efficacy and safety. CDER granted accelerated approval based on the results for Trial 002. Consistent with section 506(c)(2) of the FD&C Act and § 314.510, CDER's approval letter required, *inter alia*, that the sponsor complete a postmarketing confirmatory study, described as "a clinical trial of Makena in women with a singleton pregnancy who had a previous spontaneous preterm birth (Protocol #17P–ES–003)." (This subsequent study is referred to as "Trial 003" or "PROLONG.")

b. Procedural history from CDER's notice to hearing

On October 5, 2020, CDER proposed withdrawing accelerated approval of Makena and provided Covis with an opportunity to request a hearing on the proposal.[2] In the proposal, CDER cited two grounds under section 506(c)(3) of the FD&C Act and § 314.530(a) for withdrawing approval: (1) the confirmatory study failed to verify clinical benefit of the drug and (2) the evidence does not establish that the drug is effective under its conditions of use. CDER's proposal to withdraw approval also provided notice to all holders of approved abbreviated new drug applications (ANDAs) referencing the NDA for Makena (ANDA holders) that, if the Agency withdraws accelerated approval of Makena, CDER would proceed to withdraw approval of the ANDAs under 21 CFR 314.151(b)(3).

On October 14, 2020, Covis timely requested a hearing and sought an additional 30 days in which to submit data and information in support of that request. On December 4, 2020, after receiving an extension of time within which to do so, Covis further responded to CDER's proposal to withdraw accelerated approval of Makena. The response included data and information and incorporated other data and information in FDA's administrative files by reference.

By letter to CDER and Covis dated August 18, 2021, FDA's then Chief Scientist RADM Denise Hinton granted Covis's hearing request. The letter explained that then Acting Commissioner for Food and Drugs, Janet Woodcock, M.D., had recused herself from this proceeding based on her previous involvement in CDER's consideration of the matter and had delegated her role in this proceeding to RADM Hinton. In the letter, RADM Hinton designated the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) as the advisory committee to be present at the hearing and to provide advice and recommendations to the Commissioner and appointed me

[2] AMAG Pharmaceuticals, Inc. (AMAG), the sponsor of NDA 021945 at the time, received this notice. After AMAG requested a hearing, Covis acquired AMAG, including NDA 021945. For efficiency, this report refers to AMAG as "Covis."

as the presiding officer to conduct a hearing in accordance with 21 CFR 314.530(e).[3] The letter addressed certain procedural issues related to the hearing and referred the matter to me to resolve any remaining issues related to the process for the hearing. The letter further noted that CDER had provided notice to the ANDA holders that, if the Agency withdraws accelerated approval of Makena, CDER would proceed to withdraw approval of the ANDAs.

As the docket for this proceeding reflects, over the course of the following year, I engaged with CDER and the sponsor in extensive pre-hearing preparations and exchanges, including responding to disputes over document requests, developing the questions for the advisory committee, providing the framework for prehearing submissions, and resolving other prehearing disputes. In constituting the advisory committee for the hearing, including the selection of temporary voting members, I solicited feedback from CDER and Covis on the scientific disciplines and areas of expertise they believed should be represented on the advisory committee for the hearing. The process for selecting temporary voting members for the advisory committee for this hearing also included contacting professional society organizations for nominations of individuals with the expertise needed for this meeting.

4. Hearing summary

a. Overview

On August 17, 2022, FDA published a Notice of Hearing in the Federal Register announcing that the hearing would be conducted virtually on October 17 to 19, 2022.[4] That notice announced the questions for discussion and vote that would be posed to the advisory committee at the hearing. The notice invited the ANDA holders to submit questions to be asked at the hearing by submitting the questions to the docket in advance of the hearing. The notice also invited members of the public to watch the hearing remotely, to present oral comments at the hearing by registering in advance of the hearing, and to submit written and electronic comments to the docket by November 3, 2022.

The final roster for the advisory committee at the hearing consisted of fifteen voting members and one non-voting member. Nine of the sixteen advisory committee members were temporary members. The advisory committee included ten practicing obstetricians, including eight who specialized in maternal fetal medicine or perinatology. The committee included one expert in biostatistics and one expert in epidemiology. The committee also included one consumer representative, one patient representative, and one industry representative, who was a non-voting member.

At the hearing, CDER and Covis each made presentations followed by an opportunity for questions by the other party, the advisory committee, and the Presiding Officer. There were also comments from twenty public commenters, representing public interest and medical advocacy

[3] On March 23, 2022, BRUDAC was reconstituted as the Obstetrics, Reproductive and Urologic Drugs Advisory Committee (ORUDAC). 87 Fed. Reg. 16477 (Mar. 23, 2022). The function of the ORUDAC no longer includes osteoporosis and metabolic bone disease.

[4] 87 FR 50626 (Aug. 17, 2022). On September 7, 2022, the Agency published a federal register notice changing the deadline for receiving requests for oral presentations by the public from September 6, 2022, to September 14, 2022.

groups as well as individual medical professional and patients. There were no presentations by ANDA holders.

On the final day, after each party gave closing presentations, the advisory committee discussed and voted on a series of questions.

b. Questions and Discussion

This section sets forth each of the questions for discussion and vote by the advisory committee, provides the advisory committee votes, and summarizes the relevant presentations by each party and the committee's discussions and votes with respect to each question.

Question 1. For discussion and vote:

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

The advisory committee voted "no," 15-0.

Background: The original approval of the Makena NDA was based primarily on the results from Trial 002, a randomized placebo controlled clinical trial that studied the effect of Makena in women with a singleton pregnancy and a prior history of sPTB. This study demonstrated a reduction in the proportion of women delivering prior to 37 weeks of gestation; smaller reductions of preterm birth were also observed at 35 and 32 weeks. Trial 002 did not demonstrate a reduction of fetal/neonatal deaths or neonatal morbidity as measured on a neonatal composite index; the trial was not designed to evaluate this clinical outcome. CDER determined that the sponsor had demonstrated an effect on an intermediate clinical endpoint (i.e., recurrent sPTB) that was reasonably likely to predict clinical benefit (i.e., improved neonatal outcomes). CDER granted accelerated approval on the basis of that determination and required the sponsor to complete Trial 003 to verify Makena's clinical benefit. Trial 003 was designed as a randomized trial, with co-primary efficacy endpoints of the proportion of subjects with deliveries at less than 35 weeks of gestation and neonatal morbidity/mortality composite index. The results did not demonstrate a statistically significant treatment effect on either endpoint.

CDER's and Covis's arguments: CDER and Covis agreed that Trial 003 did not verify the clinical benefit of Makena, i.e., an effect on neonatal morbidity and mortality from complications of sPTB.

Highlights from advisory committee discussion: The advisory committee members noted that CDER and Covis agreed that Trial 003 did not verify the clinical benefit of Makena. One member commented that neither study demonstrated clinical benefit, noting, "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." Hearing Transcript (Oct. 19, 2022) at 51 (comment by Dr. Hudak).

Question 2. For discussion and vote:

Does the available evidence demonstrate that Makena is effective for its approved indication of reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth?

One member voted "yes," one member "abstained," and 13 members voted "no."

Background: As noted above, two clinical trials, Trials 002 and 003, were performed in the population under consideration. Trial 002 demonstrated an effect on the proportion of sPTB, at the primary endpoint of 37 weeks, and at secondary endpoints of 32 and 35 weeks. The initial accelerated approval of Makena was based on this trial's effect on these endpoints. In contrast, Trial 003 did not demonstrate an effect on the proportion of sPTB at 35 weeks, the coprimary endpoint. Additionally, no treatment effect for Makena was noted at 32 or 37 weeks. Thus, for the intermediate clinical endpoint that formed the basis for the accelerated approval—the gestational age at delivery—Trial 003 did not show Makena to be effective.

CDER's key points: CDER pointed out that Trial 003 was a large well-designed trial, which enrolled nearly four times the number of patients as Trial 002, and that not only did the trial fail to verify clinical benefit but the effect on the intermediate clinical endpoint, which was the basis for the original approval, was not seen.

CDER's presentation directly addressed many of the reasons offered by Covis in its pre-hearing briefing materials to explain why Trial 003 did not generate results similar to those of Trial 002 with respect to the effectiveness of Makena in reducing the risk of recurrent sPTB. CDER acknowledged that "the populations of Trials 002 and 003 differed in certain prognostic factors (e.g. demographics and socioeconomic factors) for PTB." Briefing Materials Supporting CDER's Proposal to Withdraw Approval of Makena, Docket No. FDA-2020-N-2029 (Sept. 16, 2022) at 32. To address whether these differences in baseline characteristics were responsible for the difference in study outcomes and whether the differences observed could modify the treatment effect of Makena, CDER conducted additional analyses. CDER did not identify any risk factors that were effect modifiers in Trial 002. In particular, whether a subject was Black versus non-Black was not found to be an effect modifier, nor was there an effect modifier by gestational age of qualifying sPTB of less than 34 weeks. CDER also performed a number of exploratory analyses in Trial 003 to examine whether there was an effect seen in any of the prespecified subgroups in Trial 003 or an effect in subgroups defined by more than one risk factor. According to CDER, there was no effect of Makena seen in any of the prespecified subgroups or in the subgroups defined by more than one risk factor. CDER concluded that there was no evidence that the differences in risk factors were responsible for the failure of Trial 003 to demonstrate an effect on gestational age at delivery.

CDER also addressed several other specific considerations to which Covis points in arguing that Trial 003 does not warrant as much weight as Trial 002 in evaluating Makena's effectiveness. Covis raised questions about: (i) the reliability of the determination of the gestational age of the qualifying sPTBs for enrolled subjects in Ukraine and Russia; (ii) the low proportion of subjects

with a short cervix enrolled in Trial 003; and (iii) the differences between the rate of sPTB in the placebo groups between Trials 002 and 003. Regarding the determination of gestational age of the qualifying sPTB for Ukrainian and Russian subjects, CDER noted that there was no evidence that the proportion of neonates with higher-than-expected birth weights when compared to the proportion of US subjects. In addition, treatment groups were balanced in the neonatal weights of the qualifying preterm birth. With respect to the low proportion of subjects with a short cervix enrolled in Trial 003, CDER noted that, as Trial 002 did not identify the number of subjects with a short cervix, a comparison of cervical length between the two trial populations is not possible. Regarding Covis's assertion that the rates of preterm birth were different in the placebo groups in Trial 002 and Trial 003, CDER provided information from epidemiological studies to put in perspective the placebo rates of sPTB seen in Trial 002 and 003, specifically to show that the rates of recurrent sPTB at less than 37 weeks seen in the placebo group for Trial 003 overall, and for the US subgroup, were within the range reported for women in the US with a prior sPTB.

CDER further presented its review of data from medical and scientific literature that could bear on the question of Makena's effectiveness for its labeled indication. This review included observational studies and other randomized clinical trials in related populations. According to CDER, these studies did not provide support for a conclusion that Makena is effective in reducing the risk of recurrent sPTB. In short, looking at available evidence, CDER concluded that Makena lacks substantial evidence of effectiveness for its conditions of use.

CDER provided comments on Covis's new analyses of Trial 003. In attempting to demonstrate a treatment effect, Covis utilized a new endpoint: time from randomization to delivery, capped at 35 weeks. Covis performed an analysis on the subset of 294 women whose gestational age at randomization was less than 20 weeks to demonstrate that in Trial 003 the treatment effect favoring Makena is higher among patients with more severe recent birth history. CDER commented on the lack of robustness of some of the analyses provided by Covis and pointed out their post hoc exploratory nature. CDER also noted some specific issues related to Covis's proposed endpoint; for example, stillbirths and miscarriages would be counted the same as live births. CDER pointed to the analysis provided in slide 83 from Covis as an example to illustrate shortcomings in Covis's exploratory analyses. According to that slide, the treatment effect favoring Makena in Trial 003 was higher among patients with a more severe recent birth history (as defined by the gestational age of the most recent prior spontaneous delivery). CDER applied the same analysis to a similarly defined subset in Trial 002 and did not get the same result. CDER concluded that there was "little evidence that higher risk women have a higher response to Makena in 002 or 003, including from post hoc analyses from Covis." Hearing Transcript (Oct. 17, 2022) at 79 (presentation by Dr. Laura Lee Johnson, CDER).

CDER concluded its presentation by summarizing its determination that the available evidence, including Trials 002 and 003, does not demonstrate Makena's effectiveness for its approved indication, i.e., reducing the risk of recurrent sPTB.

Covis's Key Points: Covis noted that significant treatment outcomes for Makena were observed in Trial 002. Reduction in the proportions of sPTB in all three gestational age endpoints were noted in the overall population and all key subgroups. Acknowledging that the Trial 003 did not show a difference between placebo and Makena groups with respect to the study population as a

whole, Covis noted that it was important, in the case of a trial that failed to show effectiveness, to understand why the trial failed.

The sponsor identified a variety of factors to consider in evaluating why Trial 003 did not demonstrate Makena's effectiveness with respect to the study population as a whole. One of the factors to which Covis pointed was the enrollment of a lower risk patient population for Trial 003 compared to Trial 002. According to Covis, the history of sPTB in the placebo groups was different between trials, and the study populations were different between the trials in terms of obstetrical history, race, marital or partner status, educational history, and substance use during pregnancy. Covis further pointed to differences in where the studies were conducted. Trial 002 was performed in the US; Trial 003 drew most of its subjects from outside the US. Covis raised questions about the methods for evaluating the gestational age of the qualifying birth in Ukraine and Russia. Covis also noted that only 2% of the women in Trial 003 were noted to have a short cervix. Additionally, noting that the preterm birth rates in Trial 003 in the placebo arm were lower than in Trial 002, Covis contended that Trial 003 was underpowered.

In looking at Trials 002 and 003 together, Covis concluded that the results from Trial 003 do not "cancel or invalidate" the findings of Trial 002. Covis Affirmative Presentation at slide 59 (October 18, 2022) (Covis slides available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-information-october-17-19-2022-hearing-announcement-involving-obstetrics-reproductive-and#event-materials). The sponsor identified what it believes to be a higher risk subgroup of 87 subjects within the Trial 003 population and performed an analysis utilizing the continuous endpoint referred to in the previous section, supposedly showing that there was a benefit for Makena in this subgroup with the new endpoint. According to Covis, the same analysis showed a treatment benefit when applied to a similarly selected subgroup in Trial 002. Covis proposed studying this subgroup further and working with the agency to revise the approved labeling of Makena to reflect this narrower population while further study was underway.

Covis commented on the observational studies presented by CDER, noting the limitations of those studies for purposes of drawing conclusions about Makena and its current labeled indication. Covis also noted that the additional randomized studies presented by CDER were not studies performed in the population for which Makena is indicated and therefore merited little to no weight in evaluating the question of whether Makena is effective for its labeled indication.

Highlights from advisory committee's discussion: The advisory committee's discussion addressed several key points, including whether the body of evidence supported effectiveness of Makena with respect to its labeled indication, the explanations of the sponsor regarding the reasons for the results in Trial 003, and committee members' views regarding the need for a new trial.

In its discussion, the advisory committee focused on the evidence provided in Trials 002 and 003. Most members did not believe that the two studies taken together demonstrated effectiveness for the labeled indication. Comments on this topic included the following:

- "[T]he 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." Hearing Transcript (Oct. 19, 2022) at 70 (comment by Dr. Caughey).

- "[T]he body of evidence right now doesn't support its indication." Hearing Transcript (Oct. 19, 2022) at 77 (comment by Dr. Munn).

Some members observed that, although the current evidence did not demonstrate effectiveness, it also did not demonstrate ineffectiveness:

- "[I]t 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. … 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." Hearing Transcript (Oct. 19, 2022) at 72 (comment by Dr. Ellenberg).
- "We don't know if it's effective or not effective because the two trials had different results." Hearing Transcript (Oct. 19, 2022) at 71-72 (comment by Ms. Ellis, patient representative).

One member abstained because in her view the studies did not demonstrate that the product was ineffective with respect to the labeled indication:

- "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." Hearing Transcript (Oct. 19, 2022) at 71 (comment by Dr. Eisenberg).

Although the majority of committee members voted that the drug was not shown to be effective for its labeled indication, one member voted "yes," observing:

- "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." Hearing Transcript (Oct. 19, 2022) at 60-61 (comment by Dr. Henderson).

Several members shared their views on the explanations provided by the sponsor regarding the reasons Trial 003 failed to show an effect on preterm birth. Regarding whether this failure could be attributed to lack of power of the study, one member commented:

- "[Covis's arguments about the power of Trial 003] 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." Hearing Transcript (Oct. 19, 2022) at 59-60 (comment by Dr. Ellenberg).

On the subject of effectiveness for the labeled indication in a subgroup defined by race, another member commented:

- "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." Hearing Transcript (Oct. 19, 2022) at 62 (comment by Dr. McAdams-DeMarco).

Several members shared both their disappointment regarding the results of Trial 003 and their hopes that a new trial evaluating Makena's effectiveness would be conducted. However, as one member observed, "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." Hearing Transcript (Oct. 19, 2022) at 66 (comment by Dr. Hudak). Several members similarly expressed the need for more data in order to determine whether a subgroup that would benefit from Makena could be identified.

Question 3. For discussion:

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 birth?**

For vote:

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?

One member voted "yes," and 14 members voted "no."

Background: The first two questions related to the two grounds for withdrawing accelerated approval of Makena. A finding that either one of the two grounds has been met is sufficient for FDA to withdraw approval. However, the statute and regulations state that if the grounds for withdrawal are met, the FDA "*may* withdraw" approval. See section 506(c)(3) of the FD&C Act; 21 CFR 314.530(a) (emphasis added). Therefore, I asked the advisory committee to discuss their recommendation on whether FDA *should* withdraw accelerated approval of Makena.

CDER's key points: CDER presented its rationale for why the agency should withdraw approval of Makena and emphasized that the benefit-risk profile for Makena was not favorable.
As discussed in connection with Question 2, Trial 003, which was designed as a confirmatory study, did not verify the clinical benefit of Makena in its indicated population, nor did it replicate the effectiveness on the intermediate clinical endpoint of gestational age observed in Trial 002. CDER contended that there was not substantial evidence of effectiveness regarding sPTB in the indicated population, in either the subgroup identified by Covis or other subgroups CDER evaluated.

CDER noted that Makena has known safety risks, including thromboembolic events, allergic reactions, decreased glucose tolerance, and injection site reactions. In addition to the known concerns, CDER discussed the Murphy study, and noted that the study highlights the uncertainty

about intergenerational safety for children exposed to Makena in utero, although this is only a potential risk.[5]

CDER's position, as presented at the hearing, is that, given both the known and potential risks of Makena and the absence of demonstrated benefit, the benefit-risk profile is not favorable for Makena.

CDER also addressed other factors Covis identified for the Agency to consider in deciding whether to withdraw approval. These factors included how best to facilitate additional study, whether compounded versions of Makena would present an additional safety hazard, whether there are health inequities, and whether precedents and the application of regulatory flexibility regarding withdrawal weigh in favor of the Agency's declining to withdraw approval of Makena. CDER did not believe that a study would be easier to perform if the product remained on the market and expressed some skepticism that the survey performed by Makena was informative in that regard based on the information about the survey provided by Covis. CDER provided its view that the compounding issue was not relevant to analyzing whether FDA should withdraw approval. CDER contended that the Agency should withdraw approval of Makena based on its unfavorable benefit-risk profile. According to CDER, removing Makena from the market would not contribute to health inequities. CDER maintained that on the contrary, given the unfavorable benefit-risk profile, it would be a disservice to all women to leave Makena on the market and that leaving it on the market was likely to make it more difficult for sponsors to develop treatments for an indication for which effective treatments are needed. CDER also addressed Covis's arguments that the drugs Proamatine (midodrine hydrochloride) and Iressa (gefitnib) were relevant precedents for allowing drugs to remain on the market. More specifically, CDER provided some additional background on those two examples and highlighted some differences between those examples and Makena.

Covis's key points: As noted in the discussion regarding question 2, Covis contended that Trial 003 enrolled lower risk patients than did Trial 002 and that this difference explains the inability of Trial 003 to confirm the clinical benefit of Makena and the failure to show effectiveness on the gestational age at delivery endpoint. Covis maintained that for this reason the evidence from Trial 002 continues to support Makena's effectiveness in reducing the risk of recurrent sPTB. Covis provided background on the correlation of gestational age with neonatal health and pointed out that, in its view, Trial 002 showed a clinical benefit for neonates at 32 and 35 weeks, as well as the 37 weeks (the primary endpoint). Covis noted the clinical significance for neonates of preventing preterm births at these earlier time points.

In considering benefit-risk, Covis noted there were no new safety concerns identified in Trial 003 and that Trial 003 confirmed the safety of Makena. In relation to the potential intergenerational safety concerns raised by CDER in its discussion of the Murphy article, Covis

[5] *See* Murphy CC, Cirillo PM, Krigbaum NY, Cohn BA. In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. Am. J. Obstet. Gynecol. 2022 Jan;226(1):132.e1–132.e14 (the "Murphy study"). The study reported an increased cancer risk in the children of women treated with hydroxyprogesterone caproate, the active ingredient in Makena. CDER noted that the study had limitations, but they did not dismiss the risk since it raised "the concern that long-term safety in children of women treated with Makena is not fully understood." Hearing Transcript (Oct. 19, 2022) at 29 (statement by Peter Stein, CDER).

highlighted the methodological issues limiting interpretation of the findings and CDER's own assessment that the findings of that study were an indeterminate safety signal.

Additionally, Covis proposed working with FDA to revise Makena's labeling to limit the indication to a higher risk population, as described in the discussion of Question 2. The sponsor asserted that benefit-risk considerations favored leaving the product on the market for the higher risk population it identified.

The sponsor also noted additional considerations, including the risk of compounded versions of Makena, health equity concerns, the views of patient organizations and other stakeholders, and the ability of Covis to conduct a trial if FDA withdrew approval of Makena. Covis argued that the risks of sPTB are borne disproportionately by minority communities and that women in those communities would be left without options if the product were withdrawn from the market. The sponsor contended that compounding would put patients at risk because compounding pharmacies are not subject to good manufacturing practices. In arguing that Makena should remain on the market, the sponsor cited the support of numerous medical organizations and organizations representing the interested minority populations. In addition, the sponsor provided the results of patient and clinician surveys to make the case that a new trial could more easily be performed if Makena remained on the market. Finally, Covis cited the cases of Proamatine (midodrine hydrochloride) and Iressa (gefitnib) as instances when FDA allowed continued marketing of therapies approved under accelerated approval after the failure of confirmatory studies to verify and describe the predicted clinical benefit of the drug.

Highlights from advisory committee's discussions: Topics covered by the advisory committee included whether Makena should remain on the market and whether facilitating further study was a reason to retain it on the market. The advisory committee also considered the benefit-risk profile of Makena, factors related to unmet needs and equity, the evidence in support of a narrower indication, and some additional concerns related to intergenerational safety risks.

Several members commented during the discussion or vote that the benefit-risk profile for Makena did not support retaining the product on the market. Some comments mentioned risk; for example, one member observed:

- "[A]ll medications have some risk associated with them[.] [W]hy 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?" Hearing Transcript (Oct. 19, 2022) at 101 (comment by Dr. Alukal).

Most of the comments, however, focused on the lack of available evidence to establish Makena's effectiveness for its conditions of use:

- "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." Hearing Transcript (Oct. 19, 2022) at 124 (comment by Dr. Gass).
- "[T]he 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." Hearing Transcript (Oct. 19, 2022) at 125 (comment by Dr. Harper).

- "We desperately want a good treatment modality for this overwhelming disease, and it's frustrating that at this time, the evidence and these 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." Hearing Transcript (Oct. 19, 2022) at 130-31 (comment by Dr. Obican).

Several members noted they believed that the decision of whether Makena should remain on the market should not be based on whether maintaining the status quo would facilitate additional study:

- "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." Hearing Transcript (Oct. 19, 2022) at 89-90 (comment by Dr. Fox, industry representative).
- "When a drug is approved by the FDA, there is an expectation that it's both safe and effective." Hearing Transcript (Oct. 19, 2022) at 106-07 (comment by Dr. McAdams-DeMarco).
- "[E]ssentially 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." Hearing Transcript (Oct. 19, 2022) at 107-08 (comment by Dr. Gass).
- "[If Makena] 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, particular 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." Hearing Transcript (Oct. 19, 2022) at 132 (comment by Dr. Shields, the consumer representative).

The member who voted in favor of retaining Makena on the market also discussed issues of benefit and risk and their role in this determination:

- "I think the trial with the highest risk group in the Meis demonstrated that there is some signal of effectiveness." Hearing Transcript (Oct. 19, 2022) at 125 (comment by Dr. Henderson).

That member also expressed concern that women and babies would be exposed to risk from compounding pharmacies if the product were withdrawn. *Id*. at 126. She additionally expressed concerns about the potential for intergenerational risk and the need to have patients informed about this potential risk. *Id*.

Responding to the concerns regarding access and unmet need relative to withdrawing approval of Makena, several members shared their views:

- "[U]nmet 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." Hearing Transcript (Oct. 19, 2022) at 97 (comment by Dr. Ellenberg).

- "[J]ust because we think this condition disproportionately burdens certain populations does not mean that we have to push to provide any treatment in those populations, we may be doing harm as opposed to good, even though our intentions are good." Hearing Transcript (Oct. 19, 2022) at 118 (comment by Dr. Alukal).

One member expressed his view on whether Makena should remain on the market for a high-risk population:

- "[W]hile 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." Hearing Transcript (Oct. 19, 2022) at 121 (comment by Dr. Caughey).

There were comments regarding the question of whether a study would be hampered by withdrawing approval of Makena:

- "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 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." Hearing Transcript (Oct. 19, 2022) at 121 (comment by Dr. Alukal).
- "I don't really think that withdrawing it should be preventing people from enrolling in a trial. "Hearing Transcript (Oct. 19, 2022) at 90 (comment by Dr. Fox, industry representative).
- "I do think 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." Hearing Transcript (Oct. 19, 2022) at 130 (comment by Dr. Munn).

The patient representative added the following on this point:

- "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." Hearing Transcript (Oct. 19, 2022) at 105 (comment by Ms. Ellis).

However, not all members believed that withdrawing approval of Makena would help facilitate recruitment for a clinical trial:

- "If the drug is taken off the market, then people will question whether to go on it, and [that] will make it extraordinarily difficult to recruit patients for the study… [and]you may have compounding pharmacies that come into the picture." Hearing Transcript (Oct. 19, 2022) at 81 (comment by Dr. Eisenberg).

c. Public comments

As noted above, twenty people participated in the open hearing to provide their views on behalf of themselves or their organizations. Many of the concerns echoed themes raised by CDER, Covis, and the advisory committee members.

Several individuals provided their personal experiences. Some patients described the benefit they attributed to being treated with Makena. One speaker, who testified about potential safety issues associated with the use of a synthetic sex steroid in utero, shared her experiences with

infantile hemangioma. Hearing Transcript (Oct. 18, 2022) at 25-33 (presentation by Amy Romano, Primary Maternity Care). She shared her questions regarding whether her experience may have been related to in utero exposure to progesterone and her uncertainty as to whether she was, in fact, exposed.

Several other speakers noted concerns about Makena's safety, citing the experience with DES, the Murphy study on delalutin, and animal studies demonstrating neurobehavioral consequences to animals exposed in utero. Several speakers questioned the long-term intergenerational safety. For example:

- "Why do we assume it's safe to expose a developing fetus to synthetic hormones? Is there a reassuring track record of safety with doing that? Why would we make an assumption of developmental, and especially neurodevelopmental, safety? . . . DES was given to pregnant women for over 30 years, and it led to tragic consequences." Hearing Transcript (Oct. 17, 2022) at 288, 290 (presentation by Dr. Adam Urato, MetroWest Medical Center).

In contrast, other speakers believed that safety was not an issue. For example:

- "[Y]ou may also hear that the benefits of Makena don't outweigh the risks. This implies that there are safety issues with the therapy, but the published evidence, both from clinical trials and ongoing safety surveillance, doesn't bear this out." Hearing Transcript (Oct. 17, 2022) at 259 (presentation by Sally Greenberg, National Consumers League).

Some speakers commented on the available data for evaluating the safety and effectiveness of Makena. Some believed the data do not support effectiveness, and others felt that the data support keeping the product on the market. Several speakers felt that the data are sufficient to support shared decision making between patients and physicians.

Commenters expressed divergent views on the topic of health equity. One of the speakers, representing her organization, expressed her view that Makena should not be withdrawn from the market:

- "Removing[Makena] and its generics will not affect all women equally. … [T]he proposal to withdraw seems to be based on the results of the confirmatory trial, PROLONG, which was conducted primarily outside of the U.S. among mostly white European women, and which found Makena to not have the same level of efficacy as in the Meis trial. … [E]vidence of efficacy for women of color in the U.S. should be more determinative than the lack of demonstrated efficacy on white women in Europe." Hearing Transcript (Oct. 18, 2022) at 19-23 (presentation by Milena Berhane, Preterm Birth Prevention Alliance).

Another member of the public expressed a similar view, quoting a statement from an article in the New England Journal of Medicine:

- "When the majority of a population achieves little benefit from a drug, but a minority demographic group at greatest risk for a serious medical morbidity appears to obtain significant benefits, any decision that will ultimately make it impossible to obtain the drug should be undertaken cautiously." Hearing Transcript (Oct. 18, 2022) at 65 (presentation by Washington Hill, CenterPlace Health) (quoting Michael F. Greene, Mark A. Klebanoff, & David Harrington, *Preterm Birth and 17OHP — Why the FDA Should Not Withdraw Approval*, 383 N. Engl. J. Med. e130, e130(3) (2020)).

Another point of view was expressed by an assistant professor with a background in clinical maternal health research and certified nurse midwife. She maintained that leaving Makena on the market "sidesteps important conversations that are at the root of why disparities exist in the first place." Hearing Transcript (Oct. 18, 2022) at 58 (presentation by Dr. Elise Erickson, University of Arizona). She commented that "race is a social construct rather than a biologically informed one"; that racism has been a factor in health disparities; and that currently there is a lack of access to comprehensive reproductive health care. *Id.* at 58-59. She contended that, given these factors, we cannot draw conclusions that access to Makena is appropriate for Black populations without more data: "When we say Makena could be a treatment specifically for high-risk groups, and Black populations in particular, I think we need to dig much deeper into this proposal and consider how race is actually playing a role in this association. We also need to answer why we think exogenous hydroxyprogestorone is the best intervention to address these disparities; in short, we need more data." *Id.* at 59. Given the need for more data, she noted the need for collecting these data in an ethical manner:

> Black individuals have been subjected to experimentation without consent for centuries, particularly in obstetrics. The American College of Obstetrics and Gynecology outlines this history on its website. … The bar needs to be higher than shared decision making. ... [O]ur nation's most vulnerable communities deserve better from all of us than what is afforded to them by prior generations. Let's not make the mistake of ignoring history by assuming an exogenous hormone is innocuous to a fetus, particularly the ones that were never going to be born preterm, but also let's not assume it's universally effective because of one's race. Studying this drug in high-risk communities can be done ethically, but people have to be told that they're being studied, and they have to have a choice not to participate. One of the speakers yesterday mentioned that women with prior preterm births are often so traumatized by the first experience that they "would have done anything" to avoid it again. This is the definition of a vulnerable population, and we all have the duty to protect these people by ensuring that the principles of autonomy and justice are upheld. *Id.* at 59-61.

A number of speakers commented on financial motives of the firm or on unacknowledged conflicts of interest on the part of certain other speakers.

5. Presiding Officer's Advice and Recommendations

This part of the report conveys my views on the matters discussed at hearing. First, I will review CDER's proposed grounds for withdrawing approval of Makena. Second, I will provide my recommendation regarding whether FDA *should* withdraw approval.

a. Grounds for withdrawal: CDER proposed to withdraw approval of Makena on two grounds: (1) the confirmatory study (Trial 003) failed to verify clinical benefit of the drug, and (2) the evidence does not establish that the drug is effective under its conditions of use.

(1) The confirmatory study (Trial 003) failed to verify clinical benefit of the drug.

This proposed ground for withdrawing approval of Makena has been met. Trial 003 failed to meet its coprimary endpoints, one of which was a neonatal morbidity/mortality composite index to evaluate clinical benefit. CDER and the sponsor, as well as the ORUDAC, agreed that the study failed to verify clinical benefit of the drug.

(2) The evidence does not establish that the drug is effective under its conditions of use.

This proposed ground for withdrawing approval has also been met. The basis for accelerated approval of Makena was the effect on gestational age seen in Trial 002. Trial 003 had a co-primary endpoint of gestational age at delivery. Trial 003 failed to meet this endpoint. Covis provided an extensive discussion of additional analyses to explain the difference in results between Trials 002 and 003 with respect to Makena's effectiveness for its intended use. While it is true that there are differences in where the trials were conducted and in the baseline characteristics of the population, the analyses provided by CDER that evaluated the effect of Makena in various subpopulations, and the analyses that evaluated whether risk factors such as race were effect modifiers, did not support Covis's attempts to explain the failure of Trial 003 to demonstrate an effect of the drug on recurrent sPTB. As one of the committee members noted, the argument that Trial 003 was underpowered due to the low rate of sPTB in the placebo arm is not supported by the results of the trial. Trial 003 was a large, randomized trial, with 1708 patients. It was almost four times as large as Trial 002, and it is not possible to dismiss the results of this trial. As several members of the committee noted, Trial 003 did not prove that Makena is ineffective for its labeled indication, but the trial did call into question the results of Trial 002 with respect to Makena's effect on reducing the risk of recurrent sPTB.

b. Recommendations regarding whether FDA should allow Makena to remain on the market while a new confirmatory study is performed.

Both the statute and the regulation provide that FDA "may" withdraw approval based on those grounds, but withdrawal is not mandatory. During the three-day hearing and in submissions to the docket, CDER, Covis, and members of the public raised several issues for consideration in evaluating whether FDA should withdraw approval of Makena, many of which the advisory committee members discussed. Below I provide my views on each significant factor discussed at the hearing.

(1) Benefit-risk in the overall population

The first two grounds for withdrawing approval speak to the question of benefit of the drug in the indicated population. I believe, as explained above, that the existing evidence for Makena does not establish either a clinical benefit or a treatment effect on the intermediate endpoint that was the original basis for accelerated approval. On the other hand, there are established risks, as

listed in the product label and described by CDER at the hearing. In addition, various speakers raised the potential intergenerational risks, such as cancer in individuals exposed in utero. (As CDER acknowledged, the data on this potential risk are currently indeterminate, but several speakers advocated for further study.) Absent a benefit to patients, the benefit-risk balance is not favorable for Makena.

(2) Benefit-risk in a narrowed population

The sponsor proposed retaining the product on the market with a narrowed indication. Covis itself characterized the analyses provided to arrive at their conclusion as "hypothesis generating." The subset identified comprises 87 out of 1708 subjects in Trial 003. Covis proposed conducting a new randomized controlled trial to confirm Makena's effect on reducing the risk of recurrent sPTB in that population.[6] However, in Trial 002, it did not appear that the treatment effect of Makena relative to sPTB was any different in Black or non-Black women or for women with a history of a qualifying sPTB of less than 34 weeks, as compared to those without that history. In the analyses of Trial 003 presented by CDER, there was no benefit suggested in any prespecified subgroup. I agree with Covis and CDER that the analysis of the 87-subject subset used to identify a high-risk group, which is fewer than five percent of the patients in the overall study, is hypothesis generating.

I agree with the committee member who commented that there is not good evidence that Makena is effective in reducing the risk of recurrent sPTB in any subgroup. See Hearing Transcript (Oct. 19, 2022) at 121 (comment by Dr. Caughey). For this reason, I do not feel that the benefit-risk profile is favorable in a narrowed indication.

(3) Ability to conduct a randomized trial

Covis asserted that it would be more likely to successfully conduct a randomized controlled trial of Makena if it remained on the market as an FDA-approved drug and put forward several surveys to support this position. The advisory committee discussed this issue extensively. Most, but not all, of the committee members felt that it would be more difficult to recruit patients if Makena was on the market because patients might not want to be randomized. One member commented on the difficulty of explaining the situation to a patient. Hearing Transcript (Oct. 19, 2022) at 109 (comment by Dr. Obican) (questioning "how to have that personal conversation with patients [about the trial when] we truly have equipoise"). The patient representative commented that, rather than participating in a randomized trial as a subject, she would find a way to get the drug if it remained on the market. Hearing Transcript (Oct. 19, 2022) at 105 (comment by Ms. Ellis). On the limited question of whether it would be easier or more difficult to conduct a trial if Makena remained on the market, I agree that it would be more difficult if it was on the market and in particular, as noted by Dr.Obican, it would be difficult to explain the trial to patients. However, I do not believe the question of whether it is more or less difficult to perform a study if the drug is retained on the market is the right question on which to base a decision on

[6] I note that the randomized study proposed by Covis would be aimed at evaluating the effect of Makena on the intermediate endpoint that formed the basis of the accelerated approval. Although Covis proposed an additional observational study to validate the intermediate endpoint and its ability to predict a positive effect on neonatal health, the proposed randomized study would not meet the objectives of a confirmatory study to verify clinical benefit.

whether to withdraw approval. That decision should be based primarily on a benefit-risk assessment.

(4) Safety issues related to drug product compounding

Covis argues that, if Makena is removed from the market, patients will be at risk for safety issues related to drug-product compounding because compounding might increase to fill in the gap and the safety concerns surrounding compounding are greater than the safety concerns regarding the marketed product. I think it is difficult to predict whether the compounding will be more or less than it is currently. For example, we have heard from the sponsor that the utilization of this treatment has decreased by 45 percent since Trial 003 was published, and it is possible that market withdrawal of Makena will decrease compounding rather than increase it. But, in any case, I don't think the potential effect on compounding should be the key factor in making this decision. Maintaining Makena's approval is not the right tool to address a concern about a potential increase in compounding.

(5) Health equity

There is no dispute that preterm birth is a particular problem in the minority population. Covis brought up the need for treatments and argued that withdrawing approval of Makena would leave this population without treatment options. There were several comments from the public expressing concern that FDA might withdraw approval based on a study that was conducted in a primarily non-Black population, even though the results of a study performed in the US showed an effect. However, based on the analyses presented at the hearing, I do not believe effectiveness has been demonstrated in any subgroup and think that for this reason the benefit-risk considerations do not favor keeping Makena on the market to preserve access. I also share the view that maintaining an ineffective treatment on the market may impede development of other products for Makena's labeled indication, which will not serve the cause of furthering health equity.

c. Summary and conclusion

The advisory committee recommended, by their vote of 14 to 1 on question 3, that Makena should not remain on the market while a new study was being performed. The principal reason that the committee members cited was that Makena was not shown to be effective for its labeled indication. The one member who voted in favor of retaining Makena on the market believed that Trial 003 did not undercut the effectiveness with respect to reducing the risk recurrent sPTB shown in Trial 002.

I do not believe that Makena has been shown to be effective, either in the currently indicated population, or in the more limited population proposed by Covis. In addition, there are known risks, and a potential for other risks, including intergenerational safety risks. For these reasons, I do not think there is a favorable benefit-risk profile to support Makena's remaining on the market and recommend approval be withdrawn. There is equipoise for a new study, which I hope will be feasible to conduct.

In summary, I agree with the following comment from one of the advisory committee members:

> The compulsion to do something is strong…there needs to be another trial because I want to believe that there is a solution for preterm birth…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. (Hearing Transcript (Oct. 19, 2022) at 115-17 (comment by Dr. Kaimal)).