CENTER FOR DRUG EVALUATION AND RESEARCH

U.S. Food and Drug Administration

Post-Hearing Submission Supporting CDER's Proposal to Withdraw Approval of Makena

Docket No. FDA-2020-N-2029

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I. INTRODUCTION

Patients, clinicians, regulators, and industry agree that premature birth is a serious public health problem for which there is an urgent need for safe and effective treatment. This serious condition disproportionately affects some of our nation's most at-risk women, children, and families. The Center for Drug Evaluation and Research (CDER) recognizes the importance of the forthcoming decision of the Commissioner of Food and Drugs and the Chief Scientist regarding the approval status of Makena and appreciates the voices of all participants in the hearing on CDER's proposal to withdraw approval.

In the interest of the public health, Makena's approval should be withdrawn. Makena is no longer shown to be effective for its approved indication, and its benefit-risk profile is unfavorable. The Obstetrics, Reproductive, and Urologic Drugs Advisory Committee recognized the adverse public health consequences of retaining Makena's approval, voting 14 to 1 in agreement with CDER's proposal to withdraw approval. The Presiding Officer and many public commenters also agreed. The legal standard for withdrawal has been met, and Makena should be withdrawn.

As discussed in this submission, FDA approved Makena under the accelerated approval pathway to reduce the risk of preterm birth (PTB) in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth (sPTB). In support of efficacy, the new drug application (NDA) relied on data from a single trial, known as Trial 002, in which, compared to placebo, Makena reduced the proportion of women delivering prior to 37 weeks gestation.[1] CDER concluded that gestational age of delivery < 37 weeks was an intermediate clinical endpoint that was reasonably likely to predict Makena's clinical benefit—reduction in neonatal morbidity and mortality resulting from complications of premature birth. Because the approval was based on a prediction, rather than a direct measurement, of clinical benefit, FDA required, as a condition of the approval, that the sponsor conduct a postmarketing confirmatory trial (Trial 003) to verify Makena's predicted clinical benefit.

Trial 003 was a well-designed and well-executed randomized, placebo-controlled clinical trial nearly four times larger than Trial 002. This confirmatory trial evaluated two co-primary endpoints: (a) delivery < 35 weeks gestation and (b) a neonatal morbidity/mortality composite index. The results of the trial failed to demonstrate a statistically significant treatment effect on either endpoint.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations authorize FDA to expedite withdrawal of a drug under the accelerated approval framework if at least one of six

[1] Makena's effect on gestational age at delivery either < 35 weeks or < 32 weeks in Trial 002 was not statistically persuasive enough to support substantial evidence of effectiveness based on a single clinical trial.

grounds for withdrawal is present.[2] As relevant here, FDA has statutory authority to use expedited procedures to withdraw approval of a drug product that has received accelerated approval if, among other reasons, "a study required to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the product fails to verify and describe such effect or benefit,"[3] or "other evidence demonstrates that the product is not safe or effective under the conditions of use."[4] FDA regulations similarly provide that FDA may withdraw approval of a drug product approved under the accelerated approval pathway when, among other circumstances, "[a] postmarketing clinical study fails to verify clinical benefit[,]"[5] or "[o]ther evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use."[6]

Although only one ground for withdrawal needs to be present, two independent grounds are satisfied here. First, Makena's confirmatory trial failed to verify the predicted clinical benefit of reducing neonatal morbidity and mortality from complications of preterm birth.[7] Second, based on the available evidence, Makena is no longer shown to be effective at reducing the risk of recurrent sPTB in women with a singleton pregnancy who have a history of sPTB.[8] As noted previously, Makena's confirmatory trial, Trial 003, which was required as a condition of the approval, failed to verify the predicted clinical benefit to the neonate and did not even show an effect on the intermediate clinical endpoint of gestational age that was the basis of the approval. Covis Pharma GmbH (Covis) has agreed that the confirmatory trial failed to verify the predicted clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth;[9] thus, there is no dispute that the legal standard for withdrawal is satisfied.

During the hearing on CDER's proposal to withdraw approval of Makena, CDER and Covis delivered affirmative presentations and were questioned by each other, members of the advisory committee, and the Presiding Officer.[10] Members of the public presented their views, and the

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[2] *See* section 506(c)(3) of the FD&C Act; 21 CFR 314.530. Throughout this submission, references to the FD&C Act refer to the statute prior to the enactment of the Consolidated Appropriations Act, 2023, which amended section 506(c) of the FD&C Act and expressly states that "[n]othing in this section (including the amendments made this section) shall be construed to affect ongoing withdrawal proceedings for products approved pursuant to section 506(c) of the [FD&C Act] for which a notice of proposed withdrawal has been published in the Federal Register prior to the date of enactment of this Act." Consolidated Appropriations Act, 2023, Pub. L. No. 117-328, section 3210(f) (2022).

[3] Section 506(c)(3)(B) of the FD&C Act.

[4] Section 506(c)(3)(C) of the FD&C Act. Conditions of use include use for the indication described in the labeling, which includes the patient population. *See, e.g.*, FDA's guidance for industry, *Medical Product Communications That Are Consistent With the FDA-Required Labeling Questions and Answers* (June 2018) at 4-5.

[5] 21 CFR 314.530(a)(1).

[6] 21 CFR 314.530(a)(6).

[7] *See* Section 506(c)(3)(B) of the FD&C Act; 21 CFR 314.530(a)(1).

[8] *See* Section 506(c)(3)(C) of the FD&C Act; 21 CFR 314.530(a)(6).

[9] *See* Letter from Rebecca Wood to Dr. Celia Witten and Christine Hunt (July 1, 2022) (stating that "we propose to stipulate that the findings from Trial 003 (PROLONG) do not verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth").

[10] Throughout the proceedings leading up to the hearing, correspondence between the Presiding Officer, CDER, and Covis, as well as the parties' briefing materials, were posted to a public docket: No. FDA-2020-N-2029. The

advisory committee members deliberated and voted on each voting question presented to them. Sponsors of abbreviated new drug applications (ANDAs) and the public also had opportunities to submit comments to the docket and participate in the hearing.

In response to the first voting question, whether the findings from Trial 003 verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth, the advisory committee unanimously voted "No," 15 to 0.[11] In response to the second voting question, whether the available evidence demonstrates that Makena is effective for its approved indication of reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth, one committee member voted "Yes," one member "abstained," and thirteen members voted "No."[12] In response to the third voting question, whether FDA should allow Makena to remain on the market while an appropriate confirmatory study is designed and conducted, fourteen advisory committee members voted "No," that Makena should not be allowed to remain on the market pending completion of another confirmatory trial. Only one advisory committee member voted "Yes."[13]

On January 19, 2023, Dr. Celia Witten, Presiding Officer, issued the "Presiding Officer's Written Report Summarizing Public Hearing and Providing Recommendations on CDER's Proposal to Withdraw Approval of MAKENA" (Presiding Officer's Report or Report). The Report states:

> 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.[14]

The Presiding Officer thus agrees with CDER that FDA should withdraw approval of Makena because its benefit-risk profile is not favorable. Here, where clinical benefit has not been demonstrated and the drug is no longer shown to be effective for its approved indication, retaining approval would unnecessarily expose pregnant patients to the risks associated with this drug product, including serious risks. Additionally, retaining approval of such a drug product, even though the legal standard for withdrawal is met and the benefit-risk profile is unfavorable, would also undermine the integrity of the accelerated approval framework and jeopardize the important public health benefits associated with this pathway.

Presiding Officer afforded the parties extensive opportunities to provide input before she made decisions, including on the scope and format of the hearing. CDER is not aware of any data or information that Covis sought, but did not obtain permission from the Presiding Officer, to introduce. In addition, to CDER's knowledge, the Presiding Officer did not limit the content that Covis sought to address in its briefing materials.

[11] Tr. (Oct. 19, 2022) at 54.

[12] Tr. (Oct. 19, 2022) at 68.

[13] Tr. (Oct. 19, 2022) at 114.

[14] Presiding Officer's Report at 19.

CDER appreciates the opportunity to address the substance of the Presiding Officer's Report, the presentations and discussions at the hearing, and the advisory committee's advice and recommendations. CDER presented in briefing materials submitted to the docket in advance of the hearing, and in presentations during the hearing, the reasons for its position that Makena should be withdrawn and responses to Covis' arguments that it should not. CDER is not restating all of this information in this post-hearing submission, but rather is using this opportunity to address certain topics raised at the hearing and in the Presiding Officer's Report, to clarify and highlight aspects of CDER's position.[15]

II. FDA SHOULD WITHDRAW APPROVAL OF MAKENA

It is undisputed that the legal standard for withdrawal of Makena has been satisfied.[16] Accordingly, we focus on the disputed issue: whether FDA *should* withdraw approval. As CDER stated, the "benefit-risk balance from Makena is not favorable and does not support leaving the drug on the market."[17] The Presiding Officer agreed, explaining "that the existing evidence for Makena does not establish either a clinical benefit or a treatment effect on the intermediate clinical endpoint that was the basis for accelerated approval" and that "[a]bsent a benefit to patients, the benefit-risk balance is not favorable for Makena."[18]

In its discussion of the third voting question regarding whether Makena should remain on the market, the Presiding Officer's Report identifies several areas of discussion by the advisory committee. CDER agrees with the Report's overall assessments regarding these areas, and would like to further address certain information raised in the presentations and discussion during the hearing.

[15] For example, the Presiding Officer's Report summarizes Covis' assertion that CDER's proposal to withdraw Makena is not consistent with how CDER has addressed certain other drugs approved under the accelerated approval pathway. CDER has already addressed this argument in its briefing materials and during the hearing. *See e.g.*, Tr. (Oct. 17, 2022) at 110 (presentation of Dr. Christine Nguyen) (explaining that the "decision about withdrawal of a drug is based on each drug's own merits, and the same holds true for Makena"). As another example, the Presiding Officer's Report concludes that "[m]aintaining Makena's approval is not the right tool to address a concern about a potential increase in compounding" and that "the potential effect on compounding should [not] be the key factor in making this decision." Presiding Officer's Report at 19. This conclusion is consistent with CDER's position, explained in its briefing materials and during the hearing. *See, e.g.*, CDER's Briefing Materials Supporting CDER's Proposal to Withdraw Approval of Makena, Docket No. FDA-2020-N-2029 (Sept. 16, 2022) ("CDER Briefing Materials") at 76-77; Tr. (Oct. 17, 2022) at 109-110 (presentation of Dr. Nguyen).

[16] Indeed, by proposing to stipulate to the first voting question, Covis has acknowledged that at least one legal ground for withdrawal is present.

[17] Tr. (Oct. 19, 2022) at30 (statement of Dr. Peter Stein).

[18] Presiding Officer's Report at 17-18.

A. Makena is No Longer Shown to be Effective Under Its Approved Conditions of Use

When CDER evaluated the benefit-risk profile of Makena resulting in the proposal to withdraw, CDER considered the available evidence of effectiveness and information about risks of the drug product. Makena is no longer shown to be effective under its conditions of use, and it carries risks, including some serious risks. Below, we address discussion from the hearing regarding the effectiveness of Makena under its approved conditions of use.

1. Trial 003 was a well-designed and well-executed study to evaluate Makena's effectiveness.

CDER and Covis agree that Trial 003, the only randomized, placebo-controlled trial designed to evaluate Makena's predicted clinical benefit, was negative on its prespecified endpoints of gestational age at delivery and neonatal morbidity and mortality outcomes.[19] When considering the negative efficacy results of Trial 003, hearing participants discussed the reliability of the trial design and the weight to afford its outcome. CDER explained that "Trial 003 was specifically designed by the sponsor to verify Makena's clinical benefit," and it "failed to confirm [Trial] 002" or verify clinical benefit.[20] Covis argued that because Trial 003 "enrolled a lower risk population compared with [Trial 002]," it was underpowered and "was not capable of confirming the benefits of Makena in a population of patients similar to those enrolled in [Trial 002]."[21]

CDER—and the Presiding Officer—disagree with Covis that Trial 003 has limitations that preclude a conclusion that Makena is no longer shown to be effective for its approved indication. As the Presiding Officer explained, "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."[22] A member of the advisory committee similarly observed that Trial 003 "was very carefully constructed."[23] Further, Trial 003 was not underpowered. It was adequately powered to reveal statistically significant reductions in preterm birth, with a sample size adequate to rule out the expected treatment effect on the rate of preterm births before 37 weeks.[24]

With respect to Covis' concern about the differences between the populations in Trial 002 and Trial 003, although these populations differed in certain prognostic factors (e.g., demographics and socioeconomic factors) that may place women at higher risk of preterm birth,[25] these

[19] *See, e.g.,* Letter from Rebecca Wood to Dr. Celia Witten and Christine Hunt (July 1, 2022) (stating that "we propose to stipulate that the findings from Trial 003 (PROLONG) do not verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth"); Tr. (Oct. 19, 2022) at 42, 45 (statement of Dr. Raghav Chari).
[20] Tr. (Oct. 17, 2022) at 69 (presentation of Dr. Laura Lee Johnson).
[21] Tr. (Oct. 19, 2022) at 43 (statement of Dr. Chari); Tr. (Oct. 18, 2022) at 134 (presentation of Dr. Michael Greene).
[22] Presiding Officer's Report at 17.
[23] Tr. (Oct. 19, 2022) at 127-128 (comment by Dr. Mark Hudak).
[24] Tr. (Oct. 17, 2022) at 81-83 (statement of Dr. Johnson).
[25] CDER Briefing Materials at 32, referenced in the Presiding Officer's Report at 6.

differences do not explain the difference in study outcomes between Trials 002 and 003.[26] CDER's analyses did not show that the presence of one or more of these risk factors influence how a woman responds to Makena. In Trials 002 and 003, for each trial's primary endpoints, there was no evidence that the drug had any better or any worse effect dependent on a woman's baseline risk.[27] CDER's extensive analyses did not find any risk factors, including race, that meaningfully modified the response to Makena in Trial 002 on its primary endpoint.[28] CDER's interaction and subgroup analyses of Trial 003[29] did not show a differential response to Makena, compared to placebo, between groups with or without the risk factors (or combinations of these risk factors), or between groups with lower and higher baseline recurrent PTB risk.[30]

In particular, there was extensive discussion at the hearing about whether Makena might be effective in Black women, with Covis suggesting that the negative results of Trial 003 could be explained in part by low enrollment of Black women.[31] In the U.S. subgroup of Trial 003, 29% of the subjects were Black.[32] Further, although CDER agrees that Black women are at greatest risk for PTB compared to other racial and ethnic groups in the U.S., Makena was not shown in Trial 003 to reduce recurrent PTB in Black women or any other identified subgroup.[33] Accordingly, there is no indication that the outcome of Trial 003 might have been different if it had higher enrollment of Black women.

2. The overall body of evidence available today demonstrates that Makena is not shown to be effective under its approved conditions of use.

The randomized, placebo-controlled trials specifically designed to evaluate Makena's approved use in the intended population—Trials 002 and 003—provide the most rigorous and relevant evidence to evaluate Makena's efficacy for its approved use.[34]

But Trial 003 is not the only study that failed to show a treatment effect on gestational age of delivery. The overall body of evidence concerning Makena, which is now far more substantial than at the time of approval in 2011, supports CDER's conclusion that Makena is no longer

[26] *See, e.g*., CDER Briefing Materials at Tables 4-6, and Figures 8-15.
[27] *See, e.g.*, CDER Briefing Materials at 53.
[28] Tr. (Oct. 19, 2022) at 21 (statement of Dr. Stein). *See also* Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, et al. Prevention of recurrent preterm delivery by 17-alpha-hydroxyprogesterone caproate. N. Engl. J. Med. 2003;348:2379–85 ("More than half the women enrolled [in Trial 002] were black. The reduction in the rate of preterm delivery [before 37 weeks of gestation] with 17P among the black women was very similar to that among nonblack women (Table 2).").
[29] These analyses included but were not limited to analyses based on region, race, number of prior sPTB, gestational age of prior sPTB, prior full term births, and composite risk based on the sponsor's identified five factors (history of > 1 prior sPTB, Black race, substance use in current pregnancy, ≤ 12 years of education, unmarried with no partner). To look at composite risk, CDER undertook analyses for the efficacy endpoints, defining subjects as having none, one, or at least two of a composite's risk factors.
[30] CDER Briefing Materials at 53.
[31] Tr. (Oct. 18, 2021) at 124 (presentation of Dr. Blackwell).
[32] CDER Briefing Materials at 29.
[33] *Id*. at 81.
[34] *Id*. at 62.

shown to be effective under its conditions of use. CDER thoroughly explored available evidence of effectiveness, including the EPPPIC meta-analysis; five observational studies with hydroxyprogesterone caproate (HPC) in Makena's indicated population; three randomized, placebo-controlled trials described by Covis as supporting safety of HPC in other groups at high-risk for PTB; and three additional studies that Covis identified as supporting the Trial 002 results. CDER concluded that these studies, both individually and collectively, fail to provide evidence of effectiveness of Makena in reducing PTB.[35]

During the hearing, Covis questioned the reliability of the observational studies that CDER discussed. These five studies provided exploratory evidence about HPC's effect for its approved use, and none of these studies suggested a treatment effect of HPC in reducing the rate of recurrent PTB.[36] Specifically, Covis questioned why CDER would consider "any of the observational studies measuring, particularly, preterm birth as an endpoint [ ] as appropriate to include in the benefit-risk assessment" and whether CDER would "agree that, in general, findings from these observational studies are not reliable for preterm birth as an endpoint."[37] As CDER explained in response, although there are significant limitations to observational studies (such that a double-blind, placebo-controlled, randomized clinical trial would be necessary to confirm treatment effect on the endpoints of gestational age and neonatal outcomes), it was relevant that the five observational studies that CDER discussed were consistent in their negative result. Indeed, when considering the available evidence concerning effectiveness of Makena for its approved indication, it is important supporting information that all five of these observational studies consistently showed no evidence of a treatment effect. It is the totality of the data from these and other studies that is informative; the findings from these observational studies, which collected information on HPC's use in real world conditions, supplement the already-compelling body of evidence that Makena is no longer shown to be effective for its approved indication.

3. Makena is no longer shown to be effective under its conditions of use; a demonstration of "ineffectiveness" is not the standard.

There was discussion amongst the advisory committee members regarding whether Trial 003 definitively demonstrated that Makena is ineffective for its approved indication.[38] The FD&C Act and its regulations provide that the Agency may withdraw approval of a drug under the accelerated approval pathway if, among other things, the drug is not shown to be effective under its approved conditions of use.[39] A showing of "ineffectiveness" is not the standard for withdrawal of approval.

[35] *Id.*at 62; *See, e.g.*, Tr. (Oct. 17, 2022) at 86-89 (presentation of Dr. Johnson).
[36] Tr. (Oct. 19, 2022) at 27 (statement of Dr. Stein).
[37] Tr. (Oct. 17, 2022) at 167-168 (comment of Dr. Chari).
[38] *See, e.g.*, Tr. (Oct. 19, 2022) at 72 (comment by Dr. Susan Ellenberg); Tr. (Oct. 19, 2022) at 71 (comment by Dr. Esther Eisenberg); Tr. (Oct. 19, 2022) at 71-72 (comment by Ms. Annie Ellis).
[39] *See* section 506(c)(3)(C); 21 CFR 314.530(a)(6).

Requiring CDER to make such a showing of "ineffectiveness" to withdraw approval would be inconsistent with the statutory approval standard, which places the burden of demonstrating safety and effectiveness upon the sponsor. It would also inappropriately impose on CDER a burden of proof that would be virtually impossible as a practical matter. Clinical trials—including Trials 002 and 003—are designed to provide evidence of the drug's effectiveness. Failure of a trial—or even failure of more than one trial—to meet the trial's primary endpoints generally does not prove ineffectiveness.

Makena is no longer shown to be effective under its approved conditions of use, and there are safety risks associated with its use. In the absence of demonstrated benefit, all patients are left with is risk.

4. Trial 003 was necessary to assess Makena's clinical benefit; the results of Trial 002 did not support traditional approval.

Covis has suggested that the confirmatory trial—Trial 003—was not necessary because Trial 002 should have, alone, supported traditional approval. Covis asserted that "the primary outcome results [of Trial 002] showed that Makena reduced the risk of preterm birth prior to 37 weeks gestation" and "reduced delivery at less than 35 weeks … and… at less than 32 weeks."[40] Covis stated that "in its briefing book, CDER explicitly states that gestational age of delivery is an intermediate clinical endpoint, which is itself a measure of therapeutic effect."[41] Covis continued, "Medical and scientific communities agree that gestational age of delivery is strongly correlated with neonatal health because it is related to the development of the fetus."[42]

CDER disagrees that Trial 002 demonstrated treatment effect on neonatal outcomes from complications of preterm birth—the clinical benefit of interest. Although Trial 002 did provide substantial evidence of Makena's effectiveness in reducing the risk of recurrent preterm delivery of < 37 weeks,[43] this is an intermediate clinical endpoint that was only reasonably likely, but not known, to predict clinical benefit.[44] Accordingly, Makena was granted accelerated approval based on the treatment effect on gestational age of delivery < 37 weeks in Trial 002. Because of the uncertainty concerning the predictive value of the gestational age < 37 weeks endpoint,

[40] Tr. (Oct. 18, 2022) at 111 (presentation of Dr. Baha Sibai); *see also* Presiding Officer's Report at 11.
[41] Tr. (Oct. 18, 2022) at 88 (presentation by Dr. Chari).
[42] *Ibid.*
[43] Trial 002 did *not* provide substantial evidence of effectiveness on the other two gestational age endpoints (< 32 and < 35 weeks) evaluated in the study. Makena's effect on these two endpoints was not sufficiently statistically persuasive to provide substantial evidence of benefit with only one adequate well-controlled trial.
[44] As CDER explained at the hearing, the pathophysiology and causes of PTB are poorly understood. Although longer natural pregnancies generally correlate with better neonatal outcomes, it is not clear whether this is true of drug-induced prolongation of pregnancy. Spontaneous preterm labor leading to PTB could be an appropriate response to an adverse condition, such as subclinical infection, subclinical uteroplacental insufficiency, or fetal reasons. Under such adverse conditions, remaining in utero longer may result in greater harm to the neonate than if delivery were allowed to occur spontaneously. In such a case, pharmacologically induced prolongation of pregnancy may result in worse neonatal outcomes than spontaneous PTB. CDER is not aware of reliable evidence indicating reducing PTB < 37 weeks with pharmacotherapy improves neonatal outcomes compared to spontaneous PTB < 37 weeks.

FDA's approval of Makena required the sponsor to conduct a confirmatory trial to verify clinical benefit to neonates.

This confirmatory trial, Trial 003, was entirely negative. Accordingly, Covis' question as to whether Trial 002 could have supported traditional approval is moot because the findings from both Trials 002 and 003 are available to us today. There is no longer substantial evidence of effectiveness for Makena's approved indication. If CDER had access to the data from both Trials 002 and 003 in 2006–2011, at the time the application was being considered, together with all the other evidence available today, it would have concluded that efficacy had not been shown, and it would not have approved the drug under either the accelerated or traditional approval pathways.

B. Makena is Not Shown to Be Effective in Any Subgroup

As discussed in section II.A.1, CDER performed numerous exploratory analyses to assess consistency of treatment effect and explore factors that could explain the differences between the outcomes of Trials 002 and 003.[45] These analyses did not show that race, other variables, or combinations of the variables played a role in the differences in efficacy outcomes. Nor was there evidence of differences in effect by region (U.S. versus non-U.S.) or by number of prior spontaneous preterm births in Trial 003. As CDER explained during the hearing, it found "little evidence that higher risk women have a higher response to Makena in [Trials] 002 or 003, including from post hoc analysis from Covis."[46]

Covis also performed certain post-hoc exploratory analyses of Trial 003 data; it acknowledged these analyses were not pre-specified, subject to multiple comparison issues (multiple subgroups, multiple endpoints), and were hypothesis-generating.[47] Using new endpoints (including continuous time from randomization to delivery capped at 35 weeks) and subgroup definitions, and a new linear regression analysis model, Covis sought to demonstrate that in Trial 003, there was a treatment effect among patients with more severe recent birth history.[48] Additionally, Covis hypothesized that there could be a treatment effect in certain subgroups based on race or history of sPTB of less than 34 weeks.[49] At the hearing, Covis identified a subset of 87 out of 1708 subjects in Trial 003, suggesting that these 87 patients represented a "high-risk" subgroup for which there may be evidence of a treatment effect.[50] Covis recommended that FDA "align the labeling of Makena with this higher risk subset of patients" while it conducts further study.[51]

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[45] Tr. (Oct. 17, 2022) at 72 (presentation of Dr. Johnson).
[46] *Id*. at 79.
[47] Tr. (Oct. 18, 2022) at 141 (presentation of Dr. Eugene Poggio).
[48] Presiding Officer's Report at 7.
[49] *See, e.g.*, Covis Briefing Materials In Response To The Center for Drug Research and Evaluation's Notice Of Opportunity For A Hearing And Proposal To Withdraw Approval Of MAKENA®, Docket No. FDA-2020-N-2029 (Sept. 16, 2022) at 53, 111-112, Appendix at 3.
[50] *See, e.g.*, Covis affirmative presentation, slides 9 and 88-89 (with slide 89 noting an N of 87). *See also* Tr. (Oct. 18, 2022) at 93 (presentation of Dr. Chari).
[51] Tr. (Oct. 19, 2022) at 44 (statement of Dr. Chari).

These post hoc exploratory analyses lacked sufficient robustness to demonstrate a meaningful or reliable treatment effect. The Presiding Officer "agree[d] 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."[52] The Presiding Officer also observed that "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 in women with a history of qualifying sPTB of less than 34 weeks, as compared to those without that history."[53] The Presiding Officer further observed that "[i]n the analyses of Trial 003 presented by CDER, there was no benefit suggested in any prespecified subgroup."[54]

Even in the face of a considerable body of evidence that fails to show effectiveness for Makena's approved indication, Covis asks FDA to retain approval based on a hypothesis. This would expose patients to the risks—including serious risks—associated with Makena while Covis explores a theory that there could potentially be a treatment effect in a certain subset of patients. As CDER cautioned in its closing statement, "such a post hoc speculation is helpful in raising hypothes[es] to test, but should worry us if we are using such speculation as the basis for a regulatory decision."[55] Retaining approval on this basis would be particularly concerning here given that Covis' subgroup analyses suggesting a treatment effect "were not prespecified, not controlled for multiplicity, not consistent between trials, and not consistent in U.S. versus ex-US women[.]"[56]

We also note that identifying people in the "higher-risk target population" that Covis discussed at the hearing involves a two-part test examining up to five separate factors.[57] Covis described this test as:

- *Women with ≥ 1 recent prior spontaneous preterm birth < 35 weeks* ***and***
- *≥ 1 additional risk factor such as*
  - *Prior spontaneous preterm birth < 32 weeks*
  - *Multiple spontaneous preterm births < 37 weeks*
  - *Last pregnancy within 2 years*
  - *Other social determinants of preterm birth*.[58]

Even if there were robust evidence that Makena is effective in this subgroup, which there is not, it would likely be challenging to apply this multi-part test in practice. Additionally, it

[52] Presiding Officer's Report at 18.
[53] *Ibid*.
[54] *Ibid*.
[55] Tr. (Oct. 19, 2022) at 25 (statement of Dr. Stein).
[56] Tr. (Oct. 19, 2022) at 23-24 (statement of Dr. Stein).
[57] Covis affirmative presentation, slides 9 and 88. *See also* Tr. (Oct. 18, 2022) at 93 (presentation of Dr. Chari).
[58] Covis affirmative presentation, slide 9. Covis alternately describes the final factor as "Other social determinants of preterm birth," without specifying determinants, or "Women Who are Black." Covis affirmative presentation, slides 9 and 88.

presumably required numerous analyses for Covis to identify this subgroup, which dramatically increases of the probability of a false positive finding.

As CDER explained in its closing statement:

> 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 hypothes[es] 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.[59]

As one advisory committee member similarly observed, "we know these can be false positive when you have a big database and you hunt through for signals."[60] Patients should not be exposed to serious risks of a drug based on a theory.

As CDER stated at the hearing, Covis' "post hoc, non-prespecified analyses do not constitute substantial evidence and do not demonstrate the effectiveness of the drug for any narrowed indication."[61] CDER agrees with the advisory committee member who stated that "while . . . 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[.]"[62] Covis has not shown there is substantial evidence of effectiveness under different, limited conditions of use.

CDER cautions that any new post hoc exploratory analyses that Covis may advance in its post-hearing submission concerning Trial 002 and Trial 003 data are just that—exploratory. Such analyses may present interesting hypotheses for potential further study, but they are not capable of demonstrating a reliable treatment effect to show that Makena is effective under its approved conditions of use or under different conditions of use. If Covis intends to explore its hypotheses about a treatment effect in a particular subgroup, CDER welcomes a proposed study that evaluates impact on neonatal outcomes. If, based on further study, Covis or any other party believes it has developed substantial evidence of effectiveness for a certain indication, CDER welcomes a marketing application for that indication.

C. Makena has Known and Potential Safety Risks

Makena has known risks—including serious risks—as well as potential safety issues, including intergenerational safety issues.[63] Makena's known risks include thromboembolic events (i.e., blood clots), allergic reactions that can be serious, decreased glucose tolerance that can exacerbate gestational diabetes, fluid retention that may worsen maternal conditions such as pre-

[59] Tr. (Oct. 19, 2022) at 18-19 (statement of Dr. Stein).
[60] Tr. (Oct. 19, 2022) at 60 (comment of Dr. Ellenberg).
[61] Tr. (Oct. 19, 2022) at 88 (comment of Dr. Stein).
[62] Tr. (Oct. 19, 2022) at 121 (comment of Dr. Aaron Caughey).
[63] Tr. (Oct. 17, 2022) at 94-95 (presentation of Dr. Nguyen).

eclampsia, and depression.[64] Women may also experience injection site reactions over the course of up to twenty injections throughout pregnancy, which can cause pain, swelling, and nodules.[65]

CDER also has questions about the long-term safety of Makena, meriting further surveillance. Specifically, after a careful review of an article by Murphy et al. reporting increased cancer risk in the children of women treated with HPC,[66] considering the strengths and limitations of the study, CDER concluded that the study "highlights uncertainty regarding the intergenerational safety to children exposed to Makena in the second and third trimesters of pregnancy while fetal development is ongoing."[67] Covis disagreed, arguing that the study "has a number of methodological flaws that make it difficult to interpret and inconclusive not only in regard to Makena."[68]

CDER believes that the Murphy study is, in fact, relevant to the benefit-risk profile of Makena. As CDER explained during the hearing:

> We didn't conclude that this was a risk that we could base regulatory actions [on], such as changing labeling or even removing the drug from the market if the risk was of great enough concern, but we neither dismissed this. And I think what we pointed out is that it raises an uncertainty about intergenerational risk.[69]

The Murphy study is relevant to the overall benefit-risk analysis in that "there may be long-term risks that are not fully understood[.]"[70] In sum, "given that Makena's benefit has not been demonstrated, this signal of an intergenerational cancer risk associated with HPC . . . makes the overall benefit-risk balance for Makena even more unfavorable."[71]

D. Makena Should Not Remain on the Market While Further Studies Are Conducted[72]

CDER and Covis agree that developing effective therapies for preterm birth is a public health priority. In CDER's view, retaining approval of Makena would hinder such development because "patients and providers will be extremely unlikely to risk having patients randomized to placebo in [a randomized controlled trial] when the patient would be guaranteed treatment with

[64] Tr. (Oct. 17, 2022) at 95 (presentation of Dr. Nguyen).
[65] *Ibid*.
[66] 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.
[67] Tr. (Oct. 17, 2022) at 96 (presentation of Dr. Nguyen).
[68] Tr. (Oct. 18, 2022) at 155 (presentation of Dr. Chari).
[69] Tr. (Oct. 17, 2022) at 143 (comment of Dr. Stein).
[70] Tr. (Oct. 17, 2022) at 128 (presentation of Dr. Stein).
[71] Tr. (Oct. 17, 2022) at 96 (presentation of Dr. Nguyen).
[72] *See* Presiding Officer's Report at 18-19 ("(3) Ability to conduct a randomized trial").

Makena by not enrolling in such a trial."[73] Covis contends that "providers will be more likely to refer patients to a trial with an approved product compared to a trial of a withdrawn product[,]" based in part on surveys Covis conducted.[74]

Covis concluded that "enrolling a clinical trial following withdrawal is likely to face more significant challenges than if the product would remain on the market."[75] For the reasons CDER discussed during the hearing, including that Covis did not do qualitative work to ensure that the participants understood the survey questions, the survey results Covis uses to support its position are deeply flawed.[76] Instead, as CDER explained:

> The best predictor for timely enrollment of a new trial is a prior experience of a similar trial under similar circumstances, and we already know what happened in Trial 003, where enrollment in the United States decreased by 70 percent after Makena was approved.[77]

The Presiding Officer agreed with CDER, concluding that "it would be more difficult" to conduct a trial if Makena was on the market.[78] Many advisory committee members also agreed with that assessment. For example, one advisory committee member stated that she "disagree[d] with this sponsor that Makena would need to stay on the market in order for them to do a clinical trial," but rather understood "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, . . . that would [not] prevent them from enrolling."[79]

With regard to Covis' concerns about enrolling patients in a trial studying a drug that was withdrawn from the market for reasons of effectiveness, it is reasonable to expect that patients would enroll in a trial designed to assess effectiveness for a different indication than that of the

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[73] Tr. (Oct. 17, 2022) at 100, 116 (presentation of Dr. Nguyen). The Presiding Officer advised that the withdrawal decision "should be based primarily on a benefit-risk assessment," rather than on feasibility to perform a study if the drug remains on the market. Presiding Officer's Report at 18-19. CDER agrees. Nevertheless, we discuss our position in this submission because the advisory committee extensively discussed feasibility of a new trial during the hearing.

[74] Tr. (Oct. 19, 2022) at 40 (statement of Dr. Chari). To support its position, Covis presented survey results that "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," while "[i]n contrast, only 15 percent would consider referring patients if the product had its marketing authorization for this indication is withdrawn." *Ibid.*

[75] *Ibid*.

[76] Tr. (Oct. 17, 2022) at 100 (presentation of Dr. Nguyen); *see also* CDER briefing materials at 73.

[77] Tr. (Oct. 17, 2022) at 99-100 (presentation of Dr. Nguyen).

[78] Presiding Officer's Report at 18.

[79] Tr. (Oct. 19, 2022) at 131 (comment of Dr. Kristine Shields); *see also* Tr. (Oct. 19, 2022) at 98 (comment by Dr. Ellenberg) (If Makena remains approved, "[p]eople will be able to get it then, and may not choose to be in the study."); Tr. (Oct. 19, 2022) at 100 (comment by Dr. Joseph Alukal) (There are "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."); Tr. (Oct. 19, 2022) at 105 (comment by Ms. Ellis) (If "presented with participation in a clinical trial and randomization, if [Makena] was on the market, [she] would find a way to get it."); Tr. (Oct. 19, 2022) at 127 (comment by Dr. Hudak) (If Makena is withdrawn, "that will only facilitate the very much needed further study in the subpopulations of interest.").

drug product that was withdrawn. As CDER explained during the hearing, "it would be a recruitable, feasible study not replicating [Trial 003], but learning from it, and going on to the next set of hypotheses that research should be done on."[80]

Most importantly, CDER agrees with the Presiding Officer that the Agency's decision about whether to withdraw approval should be based on the benefit-risk profile of the drug, and not the feasibility of any future studies.[81] Because the legal standard for withdrawal is met and Makena's benefit-risk profile is unfavorable, Makena should not remain approved while Covis designs and conducts a new trial.[82] The advisory committee overwhelmingly voted (14-1) in agreement with this position, and the Presiding Officer concurred.

E. Retaining Approval of Makena Would Not Mitigate Health Disparities[83]

Continued approval of Makena would not diminish health disparities. It would expose women most likely to experience preterm birth to only risks—with no counterbalancing evidence of benefit. As the Presiding Officer concluded, "preterm birth is a particular problem in the minority population[,]" but retaining approval of a drug that is no longer shown to be effective in reducing the risk of preterm birth "will not serve the cause of furthering health equity."[84] Instead, retaining approval of Makena "may impede development of other products for Makena's labeled indication."[85]

Covis observed that "preterm birth disproportionately impacts women who are Black and other minorities in the United States."[86] Covis argued that "[t]hese and other social determinants of risk are factors in defining the higher risk population where Makena is most likely to be effective."[87] Although CDER agrees that Black women are among those at greatest risk for preterm birth, for the reasons discussed in section II.A.1, Makena is no longer shown to be effective in this or any other identified subgroup.[88]

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[80] Hearing Transcript (Oct. 17, 2022) at 218-219 (comment by Dr. Stein).
[81] *See* Presiding Officer's Report at 18-19.
[82] Covis has not even proposed conducting a trial that would evaluate whether Makena confers its intended clinical benefit—improvement of neonatal morbidity or mortality outcomes associated with premature birth. During the hearing, Covis suggested that, if Makena were to remain FDA approved, it would conduct a clinical trial that "would be sufficient to confirm benefit." Tr. (Oct. 19, 2022) at 39 (statement of Dr. Chari). Yet, "[t]he primary endpoint" of this study "would evaluate the mean increase in time from randomization to birth capped at 35 weeks for Makena-treated patients compared with placebo." *Ibid*. This study still would not evaluate whether Makena has an effect on the clinical benefit of interest. To evaluate "the relationship between gestational age and neonatal outcomes in treated versus untreated patients," Covis suggested that it would be "open to conducting an observational study." Tr. (Oct. 19, 2022) at 41-42 (statement of Dr. Chari). But only a randomized, double-blind, placebo-controlled trial could be capable of overcoming the negative trial result of Trial 003 and verifying Makena's clinical benefit—that is, demonstrating improved neonatal outcomes.
[83] Presiding Officer's Report at 19 ("(5) Health equity").
[84] *Ibid.*
[85] *Ibid*.
[86] Tr. (Oct. 19, 2022) at 38-39 (statement of Dr. Chari).
[87] Tr. (Oct. 19, 2022) at 39 (statement of Dr. Chari).
[88] *See, e.g.*, CDER Briefing Materials at 81.

As one advisory committee member observed, "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[.]" The advisory member continued, "[W]e may be doing harm as opposed to good, even though our intentions are good."[89]

Women at highest risk for PTB, including minority women, deserve a treatment with proven clinical benefit. As stated at the hearing, CDER believes that withdrawing approval of Makena "would protect women at risk for recurrent preterm birth, and especially women at high risk for a drug that [is] not shown to be effective and only has risks and uncertainties."[90]

III. APPROVAL OF ANDAS REFERENCING MAKENA SHOULD BE WITHDRAWN

As acknowledged in the Presiding Officer's Report, if the Agency withdraws accelerated approval of Makena, FDA would also withdraw approval of the ANDAs referencing Makena under 21 CFR 314.151(b)(3).[91] In accordance with 21 CFR 314.151(b)(3), if the Commissioner and Chief Scientist issue a final decision withdrawing approval of the Makena NDA, approval of the ANDAs identified in the notice of opportunity for hearing will also be withdrawn.[92] Upon issuance of such a final decision, CDER would proceed to publish a *Federal Register* notice announcing the removal of the Makena NDA and the ANDAs referencing Makena from the list of approved drugs effective on the date of withdrawal set forth in the final decision.[93] This process would fulfill the governing regulations for withdrawals, which state that when the Agency withdraws approval of an application or abbreviated application for a new drug, FDA will also publish a notice in the *Federal Register* announcing the withdrawal of approval.[94] For clarity of the administrative record, if the Commissioner and Chief Scientist decide to withdraw Makena's approval, CDER strongly encourages that the final decision also state that, pursuant to

[89] Tr. (Oct. 19, 2022) at 118 (comment of Dr. Alukal).
[90] Tr. (Oct. 17, 2022) at 113 (presentation of Dr. Nguyen).
[91] *See* Presiding Officer's Report at 3.
[92] *See* 21 CFR 314.151(b)(3) (stating that "…the approval of an abbreviated new drug application for a drug product identified in the notice of opportunity for hearing on the withdrawal of a listed drug will be withdrawn when the agency has completed the withdrawal of approval of the listed drug").
[93] *See* 21 CFR 314.162(b). This proposed process is consistent with the process that CDER utilized in the Avastin proceeding, wherein the Commissioner issued its final decision withdrawing Avastin's breast cancer indication on November 18, 2011, and CDER published a Federal Register notice on February 27, 2012, announcing the availability of the final decision withdrawing approval of the breast cancer indication for Avastin (Bevacizumab). https://www.federalregister.gov/documents/2012/02/27/2012-4424/final-decision-on-withdrawal-of-breast-cancer-indication-for-avastin-bevacizumab-following-public. The Federal Register notice announced that the withdrawal of Avastin's breast cancer indication was effective November 18, 2011, the date of the Commissioner's final decision. *Id.*
[94] *See* 21 CFR 314.152.

21 CFR 314.151(b)(3), the approvals of the ANDAs identified in the notice of opportunity for hearing are also withdrawn.

CDER's proposed process for withdrawing approval of ANDAs referencing Makena at the same time as the reference listed drug follows the governing regulations for withdrawals, as the ANDA holders have been provided notice and an opportunity to respond to the proposed withdrawal of their applications. CDER's notice of opportunity for hearing concerning its proposal to withdraw approval of Makena provided notice to all of the holders of approved ANDAs referencing the Makena NDA that, if FDA withdraws accelerated approval of Makena, FDA would also withdraw approval of the ANDAs under 21 CFR 314.151(b)(3). CDER's withdrawal proposal invited the ANDA holders to submit written comments on the proposal to withdraw approval and indicated that, if a hearing is held, FDA would permit the ANDA holders that submitted timely comments to participate in the hearing as nonparty participants. Prior to the issuance of the notice of hearing, one ANDA holder, American Regent, Inc., submitted a written comment and requested that it be granted status as a nonparty participant.[95] Another company, Beloteca, Inc., also submitted a written comment indicating that it had a pending ANDA referencing Makena and requested that it be treated the same as holders of approved ANDAs and granted the status of a nonparty participant in the hearing.[96] In a letter granting Covis' hearing request, FDA's then-Chief-Scientist, RADM Denise Hinton, declined to grant any ANDA holders the status of a nonparty participant because those requests were premature, explaining that ANDA holders could instead file a written notice of participation in the hearing once the notice of hearing was issued.[97] No ANDA holders filed a written notice of participation in the hearing once notice of hearing was issued. There were no presentations at the hearing by ANDA holders, and no ANDA holders submitted questions to be posed during the hearing.[98] After the hearing and the advisory committee's 14 to 1 vote that Makena should be withdrawn from the market, one ANDA holder, Eugia Pharma Specialties, US, LLC, submitted a comment

[95] *See* Comment from American Regent, Inc., Document ID no. FDA-2020-N-2029-0020 (Oct. 26, 2020), available at https://www.regulations.gov/comment/FDA-2020-N-2029-0020.

[96] *See* Comment from Beloteca, Inc., Document ID no. FDA-2020-N-2029-0025 (Nov. 3, 2020), available at https://www.regulations.gov/comment/FDA-2020-N-2029-0025.

[97] *See* Letter from Dr. Denise M. Hinton to Rebecca K. Wood and Vincent Amatrudo at 8 (Aug. 18, 2021), which states "…21 CFR 15.21(a) sets forth a specific process for providing any person an opportunity to file a written notice of participation in a hearing under 21 CFR part 15. Although the submissions by American Regent and Beloteca request participation, those requests are premature as "notice[s] of participation" under the process in 21 CFR 15.21(a), which requires such notices to contain the information specified in the "notice of hearing." I nonetheless note their requests, and the presiding officer will send copies of the notice of hearing once issued to both companies to enable them to provide the necessary information in a notice of participation."

[98] The Notice of Hearing stated that requests to make a presentation during the session for public participation at the hearing had to be submitted as a comment to the docket for the hearing by September 6, 2022. Similarly, the Notice of Hearing stated that requests by ANDA holders to propose a question to either CDER or Covis at the hearing also had to be submitted by September 6, 2022. *See* Notice of Hearing; Proposal to Withdraw Approval of Makena, https://www.federalregister.gov/documents/2022/08/17/2022-17715/proposal-to-withdraw-approval-of-makena-hearing. These deadlines were subsequently extended to September 14, 2022, as noted on FDA's advisory committee webpage at https://www fda.gov/advisory-committees/advisory-committee-calendar/updated-information-october-17-19-2022-hearing-announcement-involving-obstetrics-reproductive-and.

requesting a wind-down period for its products should the Makena NDA and associated ANDAs be withdrawn from the market.[99]

IV. CDER'S RECOMMENDED TIMELINE FOR WITHDRAWAL

Should the Commissioner determine that Makena and its generics should be withdrawn, the withdrawal should be immediately effective. As we have explained above, absent demonstrated benefit, treatment with Makena and its generics unnecessarily exposes patients to only risks. This unfavorable benefit-risk balance also applies to patients who are currently taking Makena in pregnancy; CDER has not identified evidence of harm from discontinuing Makena, such as signs or symptoms of withdrawal, prior to reaching 37 weeks gestation.[100]

V. CONCLUSION

CDER acknowledges and shares the concern of hearing participants regarding the need for an effective and safe treatment for premature birth, and the hope that such an effective treatment will be found. However, retaining approval of a drug simply to be able to offer *something* to patients, regardless of effectiveness, would be contrary to public health.

Allowing Makena to remain on the market in the hope that it may eventually be shown to be effective would undermine the integrity of the accelerated approval pathway. As CDER stated during the hearing, "[t]he accelerated approval pathway is a two-way street. The balance of approval and withdrawal are needed to make the program work, and thereby protect patients and the public health."[101] As one advisory committee member commented, "essentially disregarding a large study" and "allowing [Makena] to continue on the market . . . would reflect very poorly on the FDA and our advisory committee."[102]

Another advisory committee member reflected on concern from a public speaker that "the most terrifying thing you can tell [a] patient is that there's nothing to do and, unfortunately, in

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[99] *See* Comment from Eugia, US, LLC, Document ID no. FDA-2020-N-2029-0343 (Oct. 25, 2022), available at https://www.regulations.gov/document/FDA-2020-N-2029-0343. This comment was submitted after the hearing was held, and after the September 14, 2022 deadline.

[100] However, if the Commissioner and Chief Scientist would like to allow patients who are currently on treatment to finish the course of treatment, CDER recommends that the Commissioner and Chief Scientist permit a wind-down period for the discontinuance of marketing of Makena and the ANDAs no greater than 21 weeks from the date of the Agency's final decision. A wind-down period of 21 weeks would allow all patients taking Makena at the time of the decision to continue taking Makena until week 37 of gestation or delivery. *See* FDA-approved prescribing information for Makena (INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021945s013lbl.pdf (patients taking Makena may "… begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation…[and] [c]ontinue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first (2.1)").

[101] Tr. (Oct. 17, 2022) at 47 (statement of Ms. Sara Rothman).

[102] Tr. (Oct. 19, 2022) at 108 (comment of Dr. Margery Gass).

obstetrics there are many situations where I find myself in that situation."[103] The advisory committee member acknowledged "that powerless feeling," but asked, "[I]s false hope really hope at all?"[104]

As CDER explained in its closing remarks, during the hearing,

> some practitioners [stated] that no treatment is the worst outcome. [CDER] disagrees. It is clearly worse to provide a drug requiring weekly injections, exposing patients to serious risks, both established and [uncertain], 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.[105]

Preterm birth is a serious condition for which effective treatment is urgently needed. CDER shares the view that at "a human level, it is brutally painful [that] there's nothing available."[106] But exposing patients to the risks—including serious risks—of a treatment that is not shown to be effective is not a solution. CDER shares the hope of an advisory committee member 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[.]"[107] CDER, the Presiding Officer, and the vast majority of advisory committee members agree that a new study designed to assess Makena's clinical benefit would be most feasible if Makena is withdrawn from the market. CDER is committed to taking action, within its regulatory authority, to encourage promising research and development initiatives, and to collaborate with sponsors on such efforts. In the meantime, patients must not be exposed to the risks of this drug product without counterbalancing evidence of benefit.

In the interest of public health, CDER asks the Commissioner and Chief Scientist to issue a decision withdrawing approval of Makena and the generic drug applications that reference Makena.

[103] Tr. (Oct. 19, 2022) at 115 (comment of Dr. Anjali Kaimal).
[104] *Id*. at 117 (comment of Dr. Kaimal).
[105] Tr. (Oct. 19, 2022) at 34-35 (statement of Dr. Stein).
[106] Tr. (Oct. 19, 2022) at 103 (comment of Ms. Ellis).
[107] Tr. (Oct. 19, 2022) at 117 (comment of Dr. Kaimal).