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March 6, 2023

By Electronic Submission

Robert M. Califf, M.D.
Commissioner of Food and Drugs
Namandjé N. Bumpus, Ph.D.
Chief Scientist
Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20909

Re: Docket No. FDA-2020-N-2029
Makena (hydroxyprogesterone caproate injection)

Dear Commissioner Califf and Chief Scientist Bumpus:

Covis Pharma GmbH (Covis) submits this response to the Presiding Officer's Written Report of January 19, 2023 (Presiding Officer's Report)[1] and pursuant to her October 7, 2022 letter,[2] which provided Covis and CDER until March 6, 2023, to submit comments for your consideration.

First and foremost, Covis appreciates the attention FDA has directed to this important matter. FDA's granting of a hearing, the many stakeholders who participated in the comment and hearing process, and the considered attention and engagement of the Advisory Committee, reflect the complexity of the issues and the difficulty of deciding to withdraw a drug with mixed efficacy data and a positive safety profile. The proposed withdrawal of Makena raises complex issues of science, public health, and law, including unmet medical need, disproportionate impacts on historically disadvantaged patients, conflicting clinical trial results, a favorable safety profile, inconclusive secondary data, continued physician and patient support for keeping the product on the market, and an environment in which the accelerated approval pathway itself was questioned. The hearing process allowed for an orderly airing of these many issues that was not fully reflected in the ultimate voting questions and vote of the Advisory Committee. We review some of these factors here for the record and to commend FDA for providing a forum for this important, multifaceted discussion.

Covis appreciates the opportunity it was afforded at the hearing to present its view that the relevant safety and efficacy data continue to support the approval of Makena, at least in a narrower

[1] Presiding Officer's Written Report Summarizing Public Hearing and Providing Recommendations on CDER's Proposal to Withdraw Approval of Makena, Dkt. No. FDA-2020-N-2029-0379 (Jan. 19, 2023), https://www.regulations.gov/document/FDA-2020-N-2029-0379 [hereinafter, Presiding Officer's Report].

[2] Letter from Celia Witten, Ph.D., M.D. to Rebecca Wood and Christine Hunt, Dkt. No. FDA-2020-N-2029-0314 (Oct. 7, 2022), https://www.regulations.gov/document/FDA-2020-N-2029-0314.

indication, while additional study is undertaken. Like FDA, Covis invested significant resources and effort in working to understand the conflicting clinical trial results and dedicated itself to working with experts to design additional studies that would be feasible and could be conducted on a timely basis to better characterize the population in which Makena has demonstrated efficacy. Covis continues to believe in Makena's favorable benefit-risk profile, including its efficacy in women at highest risk of preterm birth.

Covis has concerns about the way in which the ultimate question—Question 3, addressing whether Makena should remain on the market while an appropriate confirmatory study is designed and conducted—was changed during the hearing. Unfortunately, as explained below in Section II.d, the question was not presented as written and may well have skewed the resulting vote and not fully reflected the robust discussion at the hearing. In particular, we believe that the revisions to Question 3 limited the ability of the committee members to vote on whether Makena should remain on the market with a narrowed indication for higher-risk women.

At the same time, Covis respects the recommendations provided by Obstetrics, Reproductive and Urologic Drugs Advisory Committee (ORUDAC) and the public process that culminated in ORUDAC's vote. It is for that reason that, shortly following the hearing, on October 31, 2022, Covis outlined a plan of orderly voluntary withdrawal that would have obviated the need for further proceedings by the Presiding Officer or before the Office of the Commissioner. CDER was not, however, in agreement with the plan outlined by Covis. Covis remains willing to voluntarily withdraw the product and to work cooperatively with the Agency to effectuate an orderly wind-down. We outline our suggestions for this process below.

I. The Withdrawal Of Makena Raises A Number Of Difficult Public Health Issues

Withdrawing an approved drug product takes away an available therapy and, as such, invariably raises a range of important public health issues, particularly where withdrawal would lead to unmet medical need, the safety profile is positive, and the benefit-risk profile remains favorable in at least certain populations. The proposed withdrawal of Makena is no different. As acknowledged by CDER and the Presiding Officer's Report, the Federal Food, Drug, and Cosmetic Act (FDCA) states that FDA "may" withdraw (rather than "shall" withdraw, as stated in other sections of the statute) accelerated approval, making clear that FDA has discretion to permit the drug to stay on the market pending further study.[3] The accelerated approval framework is designed to allow discretion when the public health benefits from flexibility rather than constraint, with the purpose of addressing unmet medical needs for serious or life-threatening diseases or conditions. Indeed, over the life of the accelerated approval program, FDA has exercised regulatory flexibility to allow the continued marketing of numerous therapies even after the failure of confirmatory studies to verify and describe the predicted clinical benefit of the drug.[4] It is worth revisiting the complex array of factors bearing on the withdrawal of Makena, as this regulatory process nears its end.

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[3] *E.g.*, Hearing Involving the Obstetrics, Reproductive and Urologic Drugs Advisory Committee Transcript, at 137:22-138:01 (Oct. 17, 2022), https://www.regulations.gov/document/FDA-2020-N-2029-0375 [hereinafter, Oct. 17, 2022 Transcript], answer by Sara Rothman, OCC ("Under the law, FDA's decision about withdrawal of Makena is discretionary . . ."); Presiding Officer's Report at 2.

[4] The hearing transcript and Section V of Covis' Final Briefing Materials provide a detailed discussion of how FDA's precedent and practice support maintaining approval for Makena while additional data are developed,

The active ingredient of Makena, 17-OHPC,[5] has a long history of therapeutic use, dating at least to the 1950s, for different gynecologic and obstetrical conditions. 17-OHPC became the standard of care in the U.S. during the second and third trimester for women with history of previous spontaneous birth based on the results of the Meis trial—a multi-site, randomized, double-blind, placebo-controlled clinical trial conducted by the Maternal Fetal Medicine Units (MFMU) Network and sponsored by the National Institute of Child Health and Human Development (NICHD)—even before Makena's accelerated approval. Over 350,000 women have been treated with Makena to date.[6] Even now, Makena and its five generics are the only FDA-approved drugs indicated for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. As such, during the hearing, ORUDAC members and public participants expressed their concerns that the withdrawal of Makena would take away the only FDA-approved treatment option:

- "[A]s someone who's been a practicing MFM [maternal fetal medicine specialist] during this time, and then also in thinking about, we really only have two FDA-approved medications for pregnancy complications, right? Right now we have Makena and we have Diclegis."[7]

- "I think women need this in their life. It gives them hope. Withdrawing it would be devastating to a lot of women. What else is out there? Nothing."[8]

- "I'm aware there are questions here of efficacy, but the thought of taking away the one safe, readily available treatment that might help prevent premature delivery seems unacceptably dangerous without a ready alternative."[9]

- "We would be the ones receiving calls from desperate and disheartened moms if they were to learn from their physician that the one questionable study took away her only treatment option, and potentially her chance of a good birth outcome. What is the most terrifying thing you can tell any patient? There is nothing we can do."[10]

Similarly, Dr. Sean Blackwell—an MFM specialist who served as the president of the Society for Maternal-Fetal Medicine (SMFM) and as a principal investigator with the NICHD MFMU—noted that

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including the examples of PROAMATINE (midodrine hydrochloride) and IRESSA (gefitinib). *See* Hearing Involving the Obstetrics, Reproductive and Urologic Drugs Advisory Committee Transcript, at 101:02-102:20 and 249:21-252:05 (Oct. 18, 2022), https://www.regulations.gov/document/FDA-2020-N-2029-0376 [hereinafter Oct. 18, 2022 Transcript]; Covis Pharma GmbH's 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, Dkt. No. FDA-2020-N-2029-0303, at Section V (Sept. 16, 2022), https://www.regulations.gov/document/FDA-2020-N-2029-0303 [hereinafter, Covis' Final Briefing Materials].

[5] Makena (hydroxyprogesterone caproate injection) is sometimes referred to as 17-OHPC, 17 α-Hydroxy-progesterone Caproate, 17-HPC, or 17P.

[6] Covis Pharma GmbH, Periodic Safety Update Report (PSUR), Makena® (Hydroxyprogesterone Caproate Injection), at 9 (Apr. 1, 2022).

[7] Oct. 17, 2022 Transcript at 210:11-16, comment by ORUDAC member, Dr. Anjali Kaimal.

[8] *Id.* at 255:11-14, public participation by Crystal Mullins.

[9] *Id.* at 269:15-20, public participation by Patricia Joseph.

[10] Oct. 18, 2022 Transcript at 54:10-16, public participation by Sidelines.

"[t]here remain no other evidence-based treatment options for this population" and that "[v]aginal progesterone, cervical cerclage, and cervical pessary have all been tested and found ineffective."[11]

- **A serious condition and unmet clinical need**

Preterm birth, defined as birth before the 37th week of gestation, is one of the most difficult challenges faced in obstetrics. It is the leading cause of neonatal and infant mortality, as well as the cause of short- and long-term complications for those infants who survive. Despite years of research and investigation, preterm birth remains a complex syndrome with its causes not well-understood. The causes are likely multifactorial, including different genetic, environmental, and/or behavioral factors.

The U.S. lags significantly behind other industrialized, high-income nations with respect to the preterm birth rate,[12] and the impact of preterm birth is disproportionately borne by Black and other minority women as well as socioeconomically disadvantaged populations. According to the March of Dimes 2022 report, the preterm birth rate among Black women is 14.4 percent, which is 52 percent higher than the rate among all other women in the United States.[13]

Other available options to prevent or treat preterm birth are not satisfactory as explained, for example, by Dr. Baha Sibai, an MFM specialist who served as a principal investigator and an alternate principal investigator in the NICHD MFMU Network for more than 20 years and was one of the investigators of the Meis trial.[14] According to Dr. Sibai, there would be only three options available to physicians if Makena were withdrawn, none of which are safe and effective:

> I think there will be three options; doing nothing. And for us as physicians and for the patients, it will be very difficult to sit across from our patient to tell her, "I don't have anything to offer you," yet she's at risk for having a preterm birth at 24 weeks or 26 weeks.
>
> The second option is to put the patient on bed rest, but that has never been shown to be effective. It really takes away the life, the real normal life of a woman. She cannot go to work. She cannot do any house activity, and in essence, really, we made her disabled. The other option is really cerclage.

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[11] Oct. 18, 2022 Transcript at 174:01-05. Dr. Blackwell serves as Chair and Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at the McGovern Medical School, University of Texas, Houston. Dr. Blackwell served as a presenter for Covis during the hearing, but he was not compensated by Covis for his time and has no financial interest in the outcome of this proceeding.

[12] *See* WHO, Born Too Soon, The Global Action Report on Preterm Birth (2012), https://apps.who.int/iris/rest/bitstreams/53412/retrieve; Hannah Blencowe et al., *National, Regional, and Worldwide Estimates of Preterm Birth Rates in the Year 2010 with Time Trends Since 1990 for Selected Countries: A Systematic Analysis and Implications*, 379 LANCET 2162-72 (Jun. 9, 2012), https://pubmed.ncbi.nlm.nih.gov/22682464/.

[13] March of Dimes, 2022 March of Dimes Report Card at 12, https://www.marchofdimes.org/sites/default/files/2022-11/March-of-Dimes-2022-Full-Report-Card.pdf.

[14] Dr. Sibai is also a Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at the McGovern Medical School, University of Texas, Houston.

> In my opinion, these are the only three options we'll be left with if Makena is not on the market.[15]

Regarding cerclage, both Drs. Sibai and Blackwell stated that the surgical procedure is generally ineffective for this indication and that it would put women at risk of complications and more surgery in all subsequent pregnancies. Furthermore, cerclage is a costly procedure and can itself lead to preterm births when not indicated.[16]

In all likelihood, as several ORUDAC members and public participants explicitly acknowledged, withdrawing Makena and its generics could expose at-risk pregnant women, already a vulnerable population, to *compounded* versions of 17-OHPC.[17] It is well known that compounded products lack robust regulatory oversight and have a history of quality and safety concerns, especially compounded versions of sterile injectable products.[18]

As we have previously shown,[19] if Makena is withdrawn, the statute would require FDA to bar further compounding of 17-OHPC,[20] for the same reason that FDA must withdraw its approval for generic versions of Makena.[21] Although CDER has addressed generic versions of Makena through this proceeding, it has not yet taken the steps necessary to prohibit the continued compounding of the same molecule. Based on the discussions around this topic at the hearing, it appears that compounded 17-OHPC is likely to still be available at least for some time after these proceedings, if not indefinitely.[22]

Covis' own recent survey of approximately 400 obstetricians, gynecologists, and MFM specialists revealed that more than a quarter of physicians would very likely recommend compounded

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[15] Oct. 18, 2022 Transcript at 288:02-17.

[16] *Id.* at 110:10-13; 174:03-05; 225:09-12.

[17] *See, e.g.*, Oct. 18, 2022 Transcript at 65:18-21, public presentation by Dr. Washington Hill ("Withdrawal can mean returning to the use of compounded formulations, which have potential safety issues and unreachable out-of-pocket costs"); Hearing Involving the Obstetrics, Reproductive and Urologic Drugs Advisory Committee Transcript, at 81:13-14 (Oct. 19, 2022), https://www.regulations.gov/document/FDA-2020-N-2029-0377 [hereinafter Oct. 19, 2022 Transcript], comment by Dr. Esther Eisenberg ("you may have compounding pharmacies that come into the picture"); 112:13-14, comment by Dr. Cassandra Henderson ("I think if this is taken off the market, my concern is that the compounding will increase").

[18] Between 2013 and 2019, a period of just seven years, for compounded 17-OHPC specifically, there were at least 26 recalls for reasons including lack of sterility assurance, product contamination, and adverse events from bacteria and fungi in product suspension fluid. *See* David L. Gandell et al., *FDA Approved vs. Pharmacy Compounded 17-OHPC – Current Issues for Obstetricians to Consider in Reducing Recurrent Preterm Birth*, 36 CURR. MED. RES. OPIN. 1393-1401 (Jun. 7, 2020), https://pubmed.ncbi.nlm.nih.gov/32544354/. For additional details on potential risks posed by compounded 17-OHPC, please see Section VII.C.1 of Covis' Final Briefing Materials.

[19] *See* Section VII.C.1 of Covis' Final Briefing Materials.

[20] 21 U.S.C. § 353a(b)(1)(C); § 353b(a)(4); *see also* 21 C.F.R. § 216.24.

[21] 21 U.S.C. § 355(j)(6).

[22] *See* Oct. 17, 2022 Transcript at 148:15-19, answer by Ms. Rothman, OCC ("Currently, 17p may be eligible for compounding if the conditions described in Section 503A or 503B are met, as well as other applicable requirements of the Federal Food, Drug, and Cosmetic Act"); October 17-19, 2022 Hearing of the Obstetrics Reproductive and Urologic Drugs Advisory Committee – FDA Final Presentation Slides Shown, at 107, https://www.fda.gov/media/162308/download ("HPC may be eligible for compounding provided certain conditions in the FDCA are met").

medication if there are no approved alternatives.[23] These results indicate that withdrawing approval for Makena and its generics will not end the utilization of 17-OHPC in this field. Instead, the withdrawal will likely result in a shift of utilization to a demonstrably *less safe* type of product. For these reasons, Covis cannot agree with CDER's position, which was reiterated in the Presiding Officer's report, that the availability of compounded 17-OHPC is irrelevant.[24]

- **Compelling evidence of safety and efficacy in the initial study that included predominantly higher-risk pregnant women**

The results of the Meis trial were so compelling in establishing the efficacy of Makena that enrollment was halted at the second planned interim analysis (conducted when 463 patients had undergone randomization and outcome data were available for 351 patients). At the time, an independent data and safety monitoring committee reviewed the study data and determined that the risk of delivery prior to 37 weeks of gestation was significantly reduced in the patients treated with 17-OHPC compared to the placebo arm, with a p-value that was below the pre-specified value in stopping rules (p=0.015). Enrollment was therefore halted as it was deemed unethical to continue treating with placebo considering the robust efficacy observed.[25]

Although the American Black population generally is underrepresented in clinical trial research,[26] the Meis study enrolled a high proportion of Black women (59% of total participants), reflecting the reality that the risk of preterm birth is substantially higher in this population. An additional 14.9% of the participants were Hispanic or Latino women. These figures stand in stark contrast to the 8% and 11% averages, reported by FDA of Black and Hispanic participation of clinical trials for new molecular entities and biological products approved by CDER in 2020.[27] As described below in Section II, Meis included a high-risk population with 26.1% of participants reporting substance use during pregnancy and 71.3%

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[23] *See* Covis' Final Briefing Materials at Attachment A to the Appendix.

[24] *See* The Presiding Officer's Report at 19 ("I think it is difficult to predict whether the compounding will be more or less than it is currently. . . . 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"); *see also* Oct. 17, 2022 Transcript at 109:21-110:01, presentation by Dr. Christine Nguyen, CDER ("the potential availability of lack of availability of compounded drugs is not the basis to conclude that Makena should remain approved").

[25] *See* CDER, NDA 21945 Statistical Review and Evaluation, Clinical Studies at 11 (Oct. 19, 2006), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf; Paul J. Meis et al., *Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate*, 348 N. ENGL. J. MED. 2379 (Jun. 12, 2003); CDER, Office of Drug Evaluation III, Division Reproductive and Urologic Products, Division Director Summary Review for Regulatory Action, NDA 021945 at 7 (Feb. 3, 2011), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000SumR.pdf [hereinafter, NDA 21945 Summary Review].

[26] *See* FDA, 2020 Drug Trials Snapshots Summary Report at 3, https://www.fda.gov/media/145718/download.

[27] *See id.*; *see also* Isabelle Yates et al., *Representation in Clinical Trials: A Review on Reaching Underrepresented Populations in Research*, CLINICAL RESEARCHER (Aug. 10, 2020) ("In a recent report from the U.S. Food and Drug Administration (FDA) on its 2018 Drug Trial Snapshots, there is a significant imbalance in representation of minorities in clinical research. Whites make up 67% of the U.S. population, but are 83% of research participants. Black/African Americans make up 13.4% of the U.S. population, but only 5% of trial participants. Hispanic/Latinos represent 18.1% of the U.S. population, but less than 1% of trial participants"), https://acrpnet.org/2020/08/10/representation-in-clinical-trials-a-review-on-reaching-underrepresented-populations-in-research/.

having ≤ 12 years of education. All of these traits are surrogates that have been linked to higher preterm birth rate.

In such an extraordinary circumstance, where compelling evidence of efficacy is observed in a trial population whose majority is composed of minority women, and where the confirmatory trial was performed in a less high-risk population, a decision to withdraw the drug should be given even greater care. As stated aptly by Dr. Michael Greene and his co-authors in their 2020 editorial in the *New England Journal of Medicine*—quoted by Dr. Washington Hill during the hearing—"[w]hen the majority of a population achieves little benefit from a drug, but a minority demographic group at greatest risk for a serious medical problem appears to obtain significant benefit, any decision that will ultimately make it impossible to obtain the drug should be undertaken cautiously."[28] Dr. Greene is Professor Emeritus at Harvard Medical School and Associate Editor of the *New England Journal of Medicine*.[29] Dr. Hill is an MFM specialist at CenterPlace Health and a member of the National Medical Association and SMFM.[30]

Several public participants voiced similar concerns as Drs. Greene and Hill, stating that FDA must "do[] everything possible to understand which population [17-OHPC] is most effective in treating before taking it off the market entirely"[31] and "at least consider the harm that could be created by prematurely removing a treatment that might have the merit for a smaller subset like at-risk women with a history of spontaneous preterm birth."[32] One of the ORUDAC members, Dr. Cassandra Henderson, was similarly concerned about having insufficient representation of minority women in the confirmatory trial, PROLONG, and stated that "if we don't focus on that target population [of Black women in the U.S.], we may miss the opportunity to show a benefit of Makena."[33]

- **Makena's favorable safety profile for high-risk pregnant women and their offspring**

The Meis trial demonstrated the positive safety profile of Makena, and in CDER's own words, "[t]here were no safety findings," as noted in the Center's review of the trial at the time.[34] The most common type of adverse event (AE) reported during the Meis study was injection site reactions, a reaction that is unsurprising in patients receiving weekly intramuscular injections. The follow-up study (Study 17P-FU), which examined outcome data at two years of age or greater on the children born to women treated in the Meis study, also revealed no differences in developmental delays, safety concerns related to overall health or physical development, or genital or reproductive anomalies between children with in utero exposure to placebo versus 17-OHPC. The authors of the follow-up study therefore

[28] Michael F. Greene et al., *Preterm Birth and 17OHP —Why the FDA Should Not Withdraw Approval*, N. ENGL. J. MED. (Nov. 3, 2020), https://pubmed.ncbi.nlm.nih.gov/33140924/.

[29] Dr. Greene served as a presenter for Covis during the hearing, but he was not compensated by Covis for his time, and he has no financial interest in the outcome of this proceeding. *See* Oct. 18, 2022 Transcript at 128:21-129:01.

[30] *See id.* at 61:12-18.

[31] *Id*. at 21:13-16, public participation by Preterm Birth Prevention Alliance).

[32] Oct. 17, 2022 Transcript at 296:06-10, public participation by Dr. Hugh Miller).

[33] Oct. 19, 2022 Transcript at 61:10-11.

[34] CDER, NDA 21945 Medical Review at 63, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125514Orig1s000MedR.pdf [hereinafter, NDA 21945 Medical Review].

concluded, "this study provides reassurance that 17 α- hydroxyprogesterone caproate is safe for the fetus when administered in the second and third trimesters."[35]

Although PROLONG did not confirm 17-OHPC's efficacy, it did reaffirm the favorable maternal and fetal safety profile of 17-OHPC by meeting the key safety objective, which was to rule out a doubling in the risk of fetal and early infant death in the 17-OHPC group compared to placebo.[36] Indeed, CDER acknowledged in the October 2019 Briefing materials: "Although the number of fetal and neonatal deaths are too low to draw definitive conclusions, the findings of this safety outcome appear to be similar between placebo and Makena."[37]

In addition to these trials, more than a decade of real-world use supports the positive safety profile of Makena. As is required for all FDA-approved drugs, Covis and its predecessors have maintained post-marketing surveillance throughout the life of the drug. Among the more than 350,000 women treated with Makena, no new safety concerns, signals, or risks have been identified in more than 10 years of use. The known potential risk of Makena are already described in its labeling, and the reported adverse event rates in real-world use are consistent with the as-labeled safety profile of the product.

Indeed, Dr. Peter Stein, Director of CDER's Office of New Drugs, agreed during the hearing that Makena's safety profile did not prompt the Center to seek withdrawal, in response to a clarification question from one of the advisory committee members, Dr. Anjali Kaimal:

> Dr. Kaimal: . . . My second clarifying question is just to also say, from CDER's perspective, it seems that the major issue is lack of benefit. Of course we never want to take on any harm in the absence of benefit, and I understand how that changes the calculus, but *it doesn't seem that we have significant concerns, the intergenerational piece and the lack of understanding of that at this point, notwithstanding*.
>
> *We do not have significant concerns about the harms of this treatment*. Really what we're mostly focused on is the fact that we've not been able to demonstrate the benefit that we had hoped that it would have. Would you say that's a proper characterization of your viewpoint?
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> Dr. Stein: Yes. . . . . Yes, I think that's a fair characterization. . . .[38]

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[35] Northen et al., *Follow-Up of Children Exposed In Utero to 17 alpha-Hydroxyprogesterone Caproate Compared With Placebo*, 110 OBSTET. GYNECOL. 865-72 (2007), https://pubmed.ncbi.nlm.nih.gov/17906021/.

[36] A "doubling of risk" was selected and agreed upon with FDA based on sample size consideration as well as clinical relevance given the expected low rate of the outcome.

[37] FDA Briefing Document, "NDA 021945 Hydroxyprogesterone Caproate Injection (trade name Makena)," Bone, Reproductive, and Urologic Drugs Advisory Committee Meeting at 45 (Oct. 29, 2019), https://www.fda.gov/media/132003/download [hereinafter, FDA 2019 Briefing Document].

[38] Oct. 17, 2022 Transcript at 208:11-209:06 (emphasis added). Although the transcript erroneously referenced the above quote as stating "We do have significant concerns about the harms of this treatment," as the video recording makes clear, the question actually states "We do *not* have significant concerns about the harms of this treatment," which also is clear from the context of the question. *See* Makena Hearing involving the Obstetrics, Reproductive, and Urologic Drugs Advisory Committee - Day 1 at 4:27:17, https://www.youtube.com/watch?v=EEm7pM_LgsM.

Dr. Stein went on to state, "this is not a high-risk drug by any means" and that the risks associated with Makena "are not by any means substantial worrisome risks."[39] Instead, Dr. Stein repeated what has been CDER's argument throughout this proceeding—i.e., that the results from PROLONG allegedly *cancel out* the Meis trial such that Makena's benefits allegedly are *zero* and capable of being outweighed by *any* risk, no matter how insignificant.[40]

- **Flawed confirmatory study that failed to confirm benefit**

The strength of the Meis trial results made constructing a confirmatory study that mirrored the trial's higher-risk population exceedingly difficult. With 17-OHPC quickly established as the standard of care in the United States, even though PROLONG was initiated and partially enrolled before the approval of Makena, providers were unwilling to enroll patients in a trial of 17-OHPC where they might be given a placebo instead. As a result, PROLONG was conducted largely outside the U.S. and primarily enrolled patients in Ukraine and Russia. Ultimately, patients from the Ukraine and Russia made up 61% of the study participants (79% of the ex-US population), versus 23% of study participants from the U.S.

Significantly, PROLONG enrolled a less risky patient population than Meis. PROLONG may have had an unintentional selection bias against enrolling higher-risk patients in the U.S., likely due to desire by physicians to treat their highest risk patients with therapy rather than risk the patients being randomized to placebo. Dr. Annie Dude, an MFM physician at the University of North Carolina Chapel Hill and hearing participant, made this point during the hearing, stating, "[g]iven that such an FDA-approved treatment was available for the prevention of preterm birth, and patients were either overtly or subconsciously steered towards that treatment if they had a high risk of the outcome."[41] Consequently, the U.S. PROLONG participants had lower risk factors for preterm birth than the participants in the Meis trial. There were also fewer Black women in particular in PROLONG: Black women comprised 59% of the Meis population compared to only 6.7% for PROLONG. And the Black women in Meis were higher-risk patients than the Black women enrolled in PROLONG. In fact, only 87 subjects in the PROLONG-U.S. population met Covis' criteria for higher-risk population,[42] in contrast to as many as 164 women in the Meis trial. These numbers therefore indicate that the Meis trial was composed of a much higher

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[39] *Id.* at 211:21-212:06.

[40] *Id.* at 210:03-09 ("In the absence of benefit, all you're left with is risk, and even infrequent risk. Even if the risk is 1 in 10,000, and you end up treating 100,000 women, you're going to get a number of really impactful events in a woman's life. So we don't discount them, but I also would say we don't overemphasize them if there's benefit); *see also* CDER, Briefing Materials Supporting CDER's Proposal to Withdraw Approval of Makena, Dkt. No. FDA-2020-N-2029-0274 at 16 (Sept. 16, 2022), https://www.regulations.gov/document/FDA-2020-N-2029-0274 ("Not only did the postmarketing confirmatory trial fail to verify clinical benefit to neonates, but it also showed no effect on the gestational-age endpoint that was the basis of the initial approval. Considering all evidence available today, the benefit-risk profile of Makena is unfavorable . . . Any amount of risk is unacceptable without countervailing benefit") [hereinafter, CDER's Final Briefing Materials].

[41] Oct. 18, 2022 Transcript at 74:04-08. Dr. Dude stated during the hearing that she has not received any fees from Covis and that she has no financial interest in this proceeding. *See id.* at 73:03-05.

[42] These criteria consisted of women with ≥1 recent prior spontaneous preterm birth <35 weeks and ≥1 additional risk factor, such as (1) prior spontaneous preterm birth <32 weeks; (2) multiple spontaneous preterm births <37 weeks; (3) last pregnancy within 2 years; and/or (4) women who are Black. *See* October 17-19, 2022 Hearing of the Obstetrics Reproductive and Urologic Drugs Advisory Committee – Covis Affirmative Presentation at 88, https://www.fda.gov/media/162303/download [hereinafter, Covis' Affirmative Presentation Deck]. As explained below in Section II.b, these criteria were developed based on Covis' literature analyses and post hoc analyses of women who demonstrated consistent benefit from Makena in Meis and PROLONG trials.

percentage of women at high risk of preterm birth (i.e., 164 of 463 women or ~35.4%) compared to PROLONG (a total of 1,708 women with 351 from the U.S. and 1317 outside of the U.S.).

As a result of its lower-risk population being located primarily outside the U.S., PROLONG had much lower event rates in both the placebo and treatment arms than the Meis trial. Dr. Greene attributed the discordant results of the two studies, in part, to the "significantly lower risk" women that were enrolled in PROLONG and "substantially different" baseline rates of preterm birth in the two trials.[43] This perspective was echoed by physicians such as Dr. Hill, who stated during the hearing: "[e]xperts and clinicians, including myself, as you have heard and will hear today, believe that the differences in outcomes could very well have been due to the differences in study populations. Treatment, efficacy, and high risk, in especially Blacks, have not been excluded."[44]

PROLONG is therefore flawed in its lack of inclusion of patients at higher risk of preterm birth, including American Black women and other minority women, as well as according to Covis' criteria for higher-risk patient populations. Consequently, PROLONG is neither comparable to the Meis population nor generalizable to the subset of the U.S. population that may most benefit from treatment. As such, Covis does not believe that PROLONG should be the basis for withdrawing approval. Dr. Esther Eisenberg from the ORUDAC succinctly captured this point in posing the core question of the proceeding: "the question that I have is, at what point does one remove the accelerated approval if . . . the study that has been done was flawed and is unable to answer the question?"[45]

Interpreting the conflicting results of the Meis trial and PROLONG is made more difficult by the dearth of secondary literature bearing on the efficacy of Makena. For example, CDER's Figure 1 in its Final Briefing Materials provides a forest plot of relative risk of preterm delivery in eight studies (Meis, PROLONG, Price, Rouse, Caritis, Hakim, Wang and Massa) in an effort to depict the Meis trial as an "outlier."[46] As explained by Dr. Greene during the hearing, however, this approach fails upon a closer examination of the studies listed.

These studies were not conducted in the indicated population for Makena. The Rouse and Caritis studies were randomized controlled trials (RCT) evaluating 17-OHPC in women carrying twins and triplets, respectively, meaning the findings are not relevant to women with single pregnancies, the indicated use of Makena. The Price study was an RCT in pregnant women with HIV in Zambia, in which women with a history of previous spontaneous preterm delivery—the indicated population for Makena—were excluded from the study under the exclusion criteria.[47] Further, Hakim, Wang, and Massa studies are all observational studies and by their design, are not sufficiently persuasive evidence of Makena's efficacy.[48]

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[43] Oct. 18, 2022 Transcript at 132:02-134:03.

[44] Oct. 18, 2022 Transcript at 64:04-09.

[45] Oct. 19, 2022 Transcript at 110:19-111:01.

[46] CDER's Final Briefing Materials at 14-15.

[47] Makena's labeling explicitly states: "Makena is not intended for use in women with multiple gestations or other risk factors for preterm birth." Makena Prescribing Information at 1 (Feb. 2011), https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021945s000lbl.pdf.

[48] CDER has also acknowledged that observational studies are not reliable, stating in its briefing materials, "[i]nherent limitations to observational studies or externally controlled trials, whether retrospective or prospective . .

Ultimately, as acknowledged by Dr. Stein during the hearing, "the right population to extract the most robust information about the effect in the indicated population, well, of course it's in studies that are of the indicated population or subsets thereof," and the other studies discussed above would provide only "supportive" information but "aren't definitive in precluding a benefit."[49] Therefore, as stated by Dr. Greene, "[w]hat's left is just Meis and PROLONG,"[50] one study with compelling evidence of efficacy (the Meis trial), and a failed confirmatory study (PROLONG).

- **Professional society, physician, and patient support**

CDER's proposal to withdraw Makena from the market also stands in contrast with the statements of major professional societies—including the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM)—following the publication of PROLONG and CDER's notice of opportunity for a hearing (NOOH), and patient support for keeping the drug on the market. Following publication of the PROLONG results, ACOG stated that it would maintain its current recommendation to use progesterone supplementation in women with prior spontaneous preterm birth.[51] ACOG reaffirmed that its "recommendations remain unchanged" after CDER proposed to withdraw Makena and that "[c]urrent guidelines in the United States recommend the use of progesterone supplementation in women with prior spontaneous preterm birth." [52] ACOG further added that, "[c]onsideration for offering 17-OHPC to women at risk of recurrent preterm birth should continue to take into account the body of evidence for progesterone supplementation, the values and preferences of the pregnant woman and the resources available."[53]

Similarly, the SMFM stated, "[o]n the basis of the evidence of effectiveness in the Meis study, with the largest number of US patients, and given the lack of demonstrated safety concerns, SMFM believes that it is reasonable for providers to use 17-OHPC in women with a profile more representative of the very-high-risk population reported in the Meis trial."[54] Notably, SMFM specifically acknowledged that "substantial differences in the study populations likely account for the different baseline rates of recurrent [preterm birth] and potentially explain some of the contrasting results observed in the Meis and PROLONG trials." SMFM also emphasized that the physician and patient's "risk/benefit discussion should incorporate a shared decision-making approach, taking into account the lack of short-term safety

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. preclude the use of these study designs to obtain reliable evidence of Makena's efficacy." CDER's Final Briefing Materials at 16.

[49] Oct. 17, 2022 Transcript at 187:08-12 and 187:18-22.

[50] Oct. 18, 2022 Transcript at 131.

[51] ACOG, *ACOG Statement on 17p Hydroxyprogesterone Caproate* (Oct. 25, 2019), https://www.acog.org/en/news/news-releases/2019/10/acog-statement-on-17p-hydroxyprogesterone-caproate; ACOG, *Practice Advisory: Clinical Guidance for Integration of the Findings of the PROLONG Trial: Progestin's Role in Optimizing Neonatal Gestation* (Oct. 25, 2019), http://web.archive.org/web/20201023110456/https:/www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2019/10/clinical-guidance-for-integration-of-the-findings-of-the-prolong-study.

[52] ACOG, *Statement on FDA Proposal to Withdraw 17p Hydroxyprogesterone Caproate* (Oct. 7, 2020), https://www.acog.org/news/news-releases/2020/10/acog-statement-on-fda-proposal-to-withdraw-17p-hydroxyprogesterone-caproate.

[53] *Id*.

[54] SMFM, *SMFM Statement: Use of 17-Alpha Hydroxyprogesterone Caproate for Prevention of Recurrent Preterm Birth,* at 3, https://www.smfm.org/publications/280-smfm-statement-use-of-17-alpha-hydroxyprogesterone-caproate-for-prevention-of-recurrent-preterm-birth (Jul. 2020).

concerns but uncertainty regarding benefit." SMFM also released a statement following CDER's NOOH, reaffirming its support for the use of 17-OHPC and maintaining its previous recommendations as outlined in its October 2019 statement.[55]

Dr. Dude, one of the public participants during the recent hearing, shared in her presentation that she had served on the SMFM publications committee that drafted the society's guidelines that were issued after PROLONG.[56] At the hearing, she re-emphasized the importance of shared decision-making between physician and the patient and expressed her belief in patients' ability to contribute to that process:

> [A]s a clinician, I strongly believe that patients can make decisions for themselves, and then having shared decision-making discussions regarding our safety data, our efficacy data, possible benefits in their particular situation, and taking into account the act that over the past 10 years, many patients now themselves have lived experience of using Makena as a treatment. I strongly believe patients can make decisions in conjunction with their doctors for themselves.[57]

Numerous patients echoed this point in comments to the docket urging FDA to leave Makena on the market, to preserve the option of treatment.[58]

- **A sponsor engaged and willing to invest in further clinical study**

FDA has acknowledged that when a confirmatory trial fails, as occurred here, that does not end the inquiry. Instead, the Agency is obliged to understand *why* the trial failed and what implications, if any, that failure has for maintaining access to the therapy. For example, as Dr. Richard Pazdur has stated, "[t]o remove a drug from the market or even an indication is a big deal and not in the public's best interest if you can understand why that trial failed."[59]

After it became the sponsor of Makena in 2021, Covis worked diligently, expending significant time and resources, to further understand the PROLONG trial in an effort to design a further confirmatory study. While these analyses were post hoc and exploratory, they provided important insights on key questions, e.g., whether there is a subset of higher-risk pregnant women who consistently demonstrate treatment effect in both trials, and whether the lessons from PROLONG could inform design decisions of

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[55] *See* SMFM, *SMFM Responds to the FDA's Proposal that Makena and Generic Equivalents be Withdrawn from the Market* (Oct. 5, 2020), https://s3.amazonaws.com/cdn.smfm.org/media/2543/Makena,_10.5.pdf.

[56] Oct. 18, 2022 Transcript at 76:01-06.

[57] *Id.* at 76:06-16.

[58] *See, e.g.,* Comment from Nida Bajwa, Docket No. FDA-2020-N-2029-0064 (Mar. 8, 2021), https://www.regulations.gov/comment/FDA-2020-N-2029-0064 ("The thought of Makena or generic no longer being approved and available to women at high risk for preterm labor is shocking and terrifying, especially because I am currently pregnant and was fully expecting the Makena shot to be part of my medical care. Please do not remove this option for women in need"); Comment from Jamila Almonte, Docket No. FDA-2020-N-2029-0058 (Dec. 10, 2020), https://www.regulations.gov/comment/FDA-2020-N-2029-0058 ("It's scary to think that if it weren't for Makena I may not have been given the chance to be a mother. I truly feel that Makena was a major contributing factor to delivering my healthy full-term babies").

[59] Derrick Gingery, US FDA Pushes Back Against Critics: Breakthrough Is Not A Drug 'Beauty Contest,' THE PINK SHEET (Dec. 10, 2019), https://pink.pharmaintelligence.informa.com/PS141340/US-FDA-Pushes-Back-Against-Critics-Breakthrough-Is-Not-A-Drug-Beauty-Contest.

future studies of Makena. Covis also conducted research into three databases, including the Dorsata database (discussed below), as well as the Meis and PROLONG populations, to identify risk factors that appear to be the strongest predictors of subsequent preterm birth. Covis enlisted recognized expert biostatisticians and clinical trialists, many of whom have significant FDA experience, to develop study proposals that could further confirm the efficacy of Makena. Lastly, Covis conducted extensive, thorough surveys of relevant physician and patient populations to understand their willingness to participate in a confirmatory study.

Together, all of these steps made clear to Covis that there was ample opportunity to further explore the benefit of Makena in high-risk patients, while the product remained available on the market. As explained in Section II.b below, the willingness of the company to narrow the labeling and to undertake further study meant there was a path forward while continuing to make the product available to at-risk women.

- **Questions about accelerated approval generally**

The hearing and potential withdrawal of Makena have taken place at a time where the accelerated approval pathway is the subject of renewed scrutiny, especially in circumstances where—unlike here—the sponsor did not complete a confirmatory study or did not enroll a confirmatory study prior to approval.

Here, the confirmatory study, PROLONG, was initiated prior to the approval of Makena. As of two months before the approval date, as many as 185 subjects (over 10% of the total planned population) had been enrolled in the study, with at least 145 from the U.S. or Canadian sites.[60] CDER granted Makena approval and stated that there was "a high likelihood" that PROLONG would be completed under its planned schedule.[61] Thereafter, the previous sponsors of Makena regularly reported on the progress of the study to FDA and received extensions to complete enrollment. FDA's own documents and correspondence reveal that the agency itself anticipated significant challenges in recruitment, as this study was to be conducted in an orphan population of pregnant women, and healthcare providers as well as patients would be unwilling to participate in the trial due to the possibility of receiving the placebo.[62] CDER has never suggested that there was a lack of due diligence as a reason for its proposal to withdraw Makena, although it has the authority to invoke this basis for withdrawal of accelerated approval.[63]

Covis acquired the previous Makena sponsor, AMAG Pharmaceuticals, Inc., in late 2020 and became the sponsor of Makena in March of 2021. This acquisition occurred after the 2019 Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) meeting convened to discuss PROLONG data and following CDER's proposal to withdraw Makena from the market. Covis became involved with Makena because it saw the critical importance of this therapy in reducing the risk of preterm birth and recognized that there was disagreement among scientific and medical experts with respect to the PROLONG's implications on Makena's efficacy profile. Covis therefore exercised its right to request a hearing, and, in granting the hearing, FDA recognized that this request "provide[d] specific challenges to the factual and scientific bases underlying CDER's proposal" and "raise[d] genuine and

[60] *See, e.g.,* NDA 021945 Summary Review at 32-33.

[61] *Id*. at 33.

[62] *Id.*

[63] Under 21 U.S.C. § 356(c)(3)(A), FDA "may withdraw approval of a product approved under accelerated approval . . . if the sponsor fails to conduct any required postapproval study of the drug with due diligence."

substantial issues of fact appropriate for a hearing."[64] Moreover, Covis timely requested the hearing at the end of 2020 and had no control over the time the Agency took to determine whether to grant the hearing or when to hold the hearing.

II. Covis Showed At The Hearing That Makena Has A Favorable Benefit-Risk Profile Meriting Further Study Rather Than Withdrawal

As Covis demonstrated in its prior submissions and at the hearing, Makena has a favorable benefit-risk profile. For brevity, this letter focuses on Covis' key arguments, incorporating discussions from the recent public hearing and the Presiding Officer's Report.[65]

Makena was granted accelerated approval for the indication of reduction of the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.[66] This approval was based on the Meis trial, which demonstrated a compelling effect on reduction in the risk of preterm births <37 weeks gestation. This is an intermediate clinical endpoint, rather than a surrogate endpoint which is more commonly used for accelerated approval.[67]

The Meis trial also demonstrated statistically significant reductions in the risk of preterm birth at <35 weeks and at <32 weeks gestational age, both "established surrogate endpoints" strongly correlated with a reduction in neonatal morbidity and mortality.[68]

Specifically, the Meis trial found that 17-OHPC:[69]

- Reduced preterm birth prior to 37 weeks gestation from 54.9% to 36.3% with a relative risk (RR) of 0.66 (95% confidence interval (CI): 0.54-0.81; p<0.001), translating to a 34% reduction in the primary outcome; and
- Reduced preterm birth at earlier gestational ages, compared to placebo:
  - For delivery <35 weeks gestation: 0.67 (0.48-0.93), p=0.02
  - For delivery <32 weeks gestation: 0.58 (0.37-0.91), p=0.02

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[64] *See* Letter from RADM Hinton to Rebecca Wood and Vincent Amatrudo, Docket No. FDA-2020-N-2029-0072 at 5 (Aug. 18, 2021), https://www.regulations.gov/document/FDA-2020-N-2029-0072.

[65] For more details on Covis' arguments, we refer you to Covis' Final Briefing Materials and its presentation during the public hearing. *See* Covis' Final Briefing Materials; Oct. 18, 2022 Transcript.

[66] Makena Prescribing Information (Feb. 2011).

[67] FDA, Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics at 18 (May 2014), https://www.fda.gov/media/86377/download (CDER recognizing that an intermediate clinical endpoint is itself "a measurement of a therapeutic effect").

[68] CDER, NDA 21945 Clinical Review at 15, https://www.fda.gov/media/80892/download [hereinafter, Clinical Review]; FDA 2019 Briefing Document at 20, ("FDA determined that further study was needed to provide confirmatory evidence of the drug's efficacy in terms of direct clinical benefit on neonatal outcomes or through an established surrogate such as the rate of preterm birth prior to 35 and 32 weeks gestation").

[69] *See* Meis, *supra* n.25 at 2382-83.

The Meis trial was immediately recognized as a major advance in the field of obstetrics. The results of the Meis trial were so compelling that following publication, ACOG issued a Committee Opinion recognizing that the trial was stopped early because the results showed a "significant protection against recurrent preterm birth for all races of women who received [17-OHPC]."[70] ACOG also issued a Committee Opinion in 2008 establishing 17-OHPC as the de facto standard of care: "Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes."[71]

At the time of approval, CDER stated that the Meis trial was "adequate, well-controlled and very persuasive," and provided "compelling" evidence of clinical benefit.[72] CDER has also more recently recognized that the Meis trial is "sufficiently persuasive to support drug approval based on the findings of a single adequate and well-controlled trial."[73]

Significantly, the Meis population was diverse and composed mainly of patients at higher risk of preterm birth in the U.S. Of the 463 women in the Meis trial, 59% of the trial participants were Black women and 14.9% were Hispanic or Latinos, who are severely underrepresented in clinical trial research in the United States. The Meis population further included a great number of women with certain social determinants of health, which in this context include socioeconomic status, education, marital status, substance use, etc. Such enrollment was likely possible because the Meis trial enrolled exclusively at 19 university-affiliated Network centers in the U.S., which often represent "safety net" hospitals that provide care for the most under-served populations. Clinicians are well aware that a combination of these social determinants places women at higher risk of recurrent preterm birth. The Meis trial population, therefore, represented the higher risk population where Makena is most likely to be effective.

In contrast to the Meis trial, PROLONG studied a vastly different patient population, at significantly lower underlying risk of preterm birth and with markedly different social and demographic characteristics from the Meis trial.[74] The difference between the two populations is best shown by the actual observed rates of preterm birth in the placebo groups in both trials. In the Meis trial, the rate of preterm birth less than 35 weeks in the placebo group was 31%, whereas in PROLONG, it was 9.7% outside of the U.S. and 18% in patients enrolled in the U.S., for an overall rate of 11.5%. These numbers clearly demonstrate that the placebo-treated patients were substantially different between the two trials. The table below further compares the demographics between Meis and PROLONG/PROLONG-U.S.:

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[70] ACOG Committee Opinion, Number 291, *Use of Progesterone to Reduce Preterm Birth*, 102 OBSTET. GYNECOL. 1115 (2003), https://pubmed.ncbi.nlm.nih.gov/14672496/.

[71] ACOG Committee Opinion, Number 419, *Use of Progesterone to Reduce Preterm Birth*, 112 OBSTET. GYNECOL. 963 (2008), https://pubmed.ncbi.nlm.nih.gov/18827143/; *see also* NDA 21945 Medical Review at 16-17 ("This sentence is unambiguous, and has been interpreted as an attempt to create a standard of care.").

[72] FDA 2019 Briefing Document at 11, 21.

[73] *Id*. at 8.

[74] *See* Baha Sibai et al., *Re-examining the Meis Trial for Evidence of False-Positive Results*, 136 OBSTET. GYNECOL. 622, 625 (2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7431135/.

Different Social and Demographic Characteristics Across PROLONG and Meis Trials

Demographics/Baseline Characteristics	**Meis (N=463) %**	**U.S. PROLONG (N=391) %**	**PROLONG (N=1708) %**
Age (years), mean ± SD	26.2 ± 5.6	27.6 ± 5.1	30.0 ± 5.2
>1 previous SPTB	28.9	27.4	14.5
GA of prior SPTB (median)	32 wks	34 wks	33 wks
Black/African American	59.0	28.9	6.7
Hispanic or Latino	14.9	13.8	9.1
Unmarried with no partner	50.3	30.7	10.1
Educational status (≤ 12 years)	71.3	50.5	43.7
Any substance use during pregnancy	26.1	28.4	9.3

Covis' criteria for a higher-risk patient population, developed based on its post hoc analyses, offers another way to understand how the Meis population was higher risk than PROLONG-U.S. and helps to explain why the event rate in PROLONG-US was markedly lower than that of Meis.[75] As explained above, a significantly greater number of women in Meis met Covis' criteria for higher-risk population than in PROLONG. While only 87 women in the PROLONG-U.S. population qualified as higher-risk, as many as 164 women, or more than a third, of the Meis population did. These criteria were developed based on published literature[76] as well as Covis' post hoc analyses of women in Meis and PROLONG that demonstrated consistent benefit from Makena.

Specifically, Covis calculated the treatment effect (expressed as weeks gained by 17-OHPC relative to placebo) from randomization to delivery[77] for the PROLONG-U.S. women by their most recent prior spontaneous delivery (mrpGA) and mean gestational age (mGA) of all prior spontaneous deliveries.[78] Covis' analyses showed a clear increase in weeks gained by 17-OHPC versus placebo for subgroups that met a larger number of Covis' criteria. As Dr. Sibai affirmed during the hearing, this increase in weeks gained is clinically significant as the addition of 1-2 weeks of gestational age prior to week 35 is associated with marked reduction in neonatal morbidities:

> . . . Gestational age at delivery is an indication whether the baby is going to be admitted to a neonatal intensive care unit. At our institution, and I will say most institutions in the United States, being born at less than 35 weeks gestation means you are going to be admitted to a neonatal intensive care unit by policy and protocol.

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[75] *See supra* n.42. Covis' criteria consisted of women with ≥1 recent prior spontaneous preterm birth <35 weeks and ≥1 additional risk factor, such as (1) prior spontaneous preterm birth <32 weeks; (2) multiple spontaneous preterm births <37 weeks; (3) last pregnancy within 2 years; and/or (4) women who are Black.

[76] *See*, *e.g.*, Spong et al., *Progesterone for Prevention of Recurrent Preterm Birth: Impact of Gestational Age at Previous Delivery*, 193 A. J. OBSTET. GYNECOL. 1127 (2005), https://pubmed.ncbi.nlm.nih.gov/16157124/; Mercer et al., *Are Women with Recurrent Spontaneous Preterm Births Different from Those Without Such History?*, 194 A. J. OBSTET. GYNECOL. (2006), https://pubmed.ncbi.nlm.nih.gov/16580328/.

[77] This was capped at 35 weeks, meaning that the endpoint for all analyses was time (weeks) from randomization until the earlier of delivery or 35 weeks gestation. This cap was imposed to focus on the period of gestation viewed as most beneficial to the fetus from the perspective of increased time in utero.

[78] *See* Covis' Affirmative Presentation Deck at 83-84; Covis' Final Briefing Materials at Section VII.A.3.e.

> . . . [I]f you are born at less than 34 weeks, the number of days spent in the neonatal intensive care unit will be markedly increased. . . .
>
> When we push it down to less than 28 and less than 24 weeks, which is really the fetal viability area, then every day matters because babies born at less than 28 weeks have a significantly increased risk for intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, and cerebral palsy. . . .
>
> . . . For those who are at risk, 24 weeks, I do rounds every day, and when I go back, I have several of them waiting for me on the floor. The first thing I tell the patient is, "Congratulations. You have gained one more day." For me, getting one day in utero translates to probably a reduction, somewhere about 2 to 3 days, in the neonatal intensive care unit at this early gestational age.[79]

There is also extensive literature supporting the association of weeks gained with a marked reduction in neonatal morbidities.[80] For example, Manuck et al.'s analysis of an obstetric cohort of 115,502 women and their neonates publication in 2016 demonstrates that incidence rates of death, major neonatal morbidity, and minor neonatal morbidity decline significantly with each advancing week of gestation.[81] Therefore, even a week of gestation gained from 17-OHPC has a significant impact on the rate of neonatal morbidities.

While "CDER agrees with Covis that the populations of Trials 002 [Meis] and 003 [PROLONG] differed in certain prognostic factors (e.g., demographics and socioeconomic factors) for PTB,"[82] CDER argued in its briefing materials and during the hearing that Makena shows no differential treatment effect in any subgroup, including race.[83] But such an effect *was* seen, according to CDER's own materials. Table 22 in CDER's briefing book for the 2019 BRUDAC meeting acknowledged that in the Meis trial, 35.6% of non-Hispanic Black women had a preterm birth <35 weeks in the placebo arm versus 21.3% in the Makena treatment arm, representing a 40% reduction in the event rate in contrast to an 8% reduction for non-Hispanic non-Black women (22.0% vs. 23.8%):

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[79] Oct. 18, 2022 Transcript at 289:12-291:06.

[80] *See, e.g.,* Tracy A. Manuck et al., *Preterm Neonatal Morbidity and Mortality by Gestational Age: A Contemporary Cohort*, 215 A. J. OBSTET. GYNECOL. 103.e1–103.e14 (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4921282/; Lindsay A. Richter et al., *Temporal Trends in Neonatal Mortality and Morbidity Following Spontaneous and Clinician-Initiated Preterm Birth in Washington State, USA: A Population-Based Study*, 9 BMJ OPEN e023004 (2019), https://pubmed.ncbi.nlm.nih.gov/30782691/. As mentioned in its final briefing materials, Covis has also performed an exhaustive literature search regarding preterm morbidity incidences at various gestational ages and can provide additional information as well as validation of the tables contained herein at the Agency's request. *See* Covis' Final Briefing Materials at Appendix, at 15 n.15.

[81] *See* Manuck et al., *supra* n.80.

[82] CDER's Final Briefing Materials at 32; *see also* Presiding Officer's Report at 6 ("CDER acknowledged that 'the populations of Trials 002 and 003 differed in certain prognostic factors (e.g., demographics and socioeconomic factors) for PTB").

[83] *See* Oct. 17, 2022 Transcript at 156:17-157:03; CDER's Final Briefing Materials at Section C.

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CDER's Table 22 from its 2019 Briefing Book: Summary of PTB < 35⁰ Weeks by Subgroup

Stratification Groups, n/N (%)	Trial 003 Makena (N=1130)	Trial 003 Placebo (N=578)	Trial 003 U.S. Subset Makena (N=258)	Trial 003 U.S. Subset Placebo (N=133)	Trial 02 Makena (N=310)	Trial 02 Placebo (N=153)
Any substance use during pregnancy, N (%)						
Yes	19/105 (18.1)	13/51 (25.5)	11/69 (15.9)	10/40 (25.0)	16/85 (18.8)	
No	103/1008 (10.2)	53/523 (10.1)	29/187 (15.5)	13/91 (14.3)	47/221 (21.3)	
Smoking						
Yes	18/92 (19.6)	11/40 (27.5)	10/58 (17.2)	8/30 (26.7)	13/70 (18.6)	
No	104/1021 (10.2)	55/534 (10.3)	30/198 (15.2)	15/101 (14.9)	50/236 (21.2)	
Alcohol						
Yes	1/23 (4.3)	5/18 (27.8)	1/19 (5.3)	4/16 (25.0)	5/27 (18.5)	2/10 (20.0)
No	121/1090 (11.1)	61/556 (11.0)	39/237 (16.5)	19/115 (16.5)	58/279 (20.8)	45/143 (31.5)
Illicit drugs	2/15 (13.3)	3/8 (37.5)	2/14 (14.3)	3/8 (37.5)	2/11 (18.2)	0/4 (0)
Yes						
No	120/1098 (10.9)	63/566 (11.1)	38/242 (15.7)	20/123(16.3)	61/295 (20.7)	47/149 (31.5)
Race						
Non-Hispanic black	17/72 (23.6)	8/40 (20.0)	16/71 (22.5)	8/40 (20.0)	39/183 (21.3)	32/90 (35.6)
Non-Hispanic non-black	92/940 (9.8)	50/480 (10.4)	19/154 (12.3)	10/68 (14.7)	28/127 (22.0)	15/63 (23.8)
Ethnicity						
Hispanic	13/101 (12.9)	8/54 (14.8)	5/31 (16.1)	5/23 (21.7)	10/41 (24.4)	4/26 (15.4)
Non-Hispanic	109/1012 (10.8)	58/520 (11.2)	35/225 (15.6)	18/108 (16.7)	53/265 (20.0)	43/127 (33.9)
Years of education						
≤12	64/474 (13.5)	40/256 (15.6)	24/120 (20.0)	18/74 (24.3)	49/223 (22.0)	32/103 (31.1)
>12	58/639 (9.1)	26/318 (8.2)	16/136 (11.8)	5/57 (8.8)	14/83 (16.9)	15/50 (30.0)

39/183 (21.3) 32/90 (35.6)
28/127 (22.0) 15/63 (23.8)

* If more than one prior delivery was sPTB, qualifying delivery was the most recent.
** The earliest PTB may be indicated or spontaneous.
***Cervical length measurement was not captured for all subjects in a treatment group.
GA = gestational age
NA = not available
Source: Applicant Analysis. ‡FDA Analysis.

FDA Briefing Document 2019 (https://www.fda.gov/media/132003/download)

When Covis questioned CDER about these figures during the Q&A section of the hearing, CDER conceded and stated that certain analyses revealed Black race to be an effect modifier, including the Center's own analysis at 35 weeks.[84]

In short, PROLONG was flawed in that it failed to enroll a population at similarly high risk for preterm birth as was enrolled in the Meis trial. The lower risk of the patients resulted in a lower event rate and as such, undercuts the use of PROLONG to justify conclusions about the efficacy of 17-OHPC in the higher risk population of Meis. Because PROLONG was not capable of confirming the benefits of Makena given the differences in risk in the populations studied, from a position of hindsight, it is not surprising that PROLONG ultimately did not meet its objective of showing a reduction in preterm birth <35 weeks and neonatal morbidity/mortality.

a. Numerous Experts Agree That PROLONG Could Not And Did Not Negate The Meis Trial

After PROLONG was concluded, the interpretation of PROLONG data and its implications for Makena's benefit-risk profile became the subject of much discussion within the ob/gyn and MFM community. Many renowned physicians and trialists have combed through the two study populations and results, exposing and analyzing their substantive differences, and disagreeing on how to interpret the trial findings. FDA's 2019 BRUDAC also reached a divided conclusion after extensive discussion, with nine members recommending withdrawing Makena approval and seven members recommending leaving Makena on the market with the requirement that new confirmatory data be generated. The recent public

[84] Oct. 17, 2022 Transcript at 153:15-154:18.

hearing before ORUDAC further illustrates the ongoing disagreement over how to interpret the PROLONG data and Makena's benefit-risk profile.

CDER has argued that a single positive trial such as Meis, even if well-conducted, may have bias or may reflect a chance finding—a position that has been refuted in peer-reviewed literature and also during the recent hearing.[85] As Dr. Hugh Miller—an MFM specialist who served as a participating investigator in the PROLONG trial—made clear during the hearing, "[w]hile it is possible that the results of the Meis trial may represent a false positive result, it is unlikely given the quality and the size of the study."[86] Critically, however, CDER does not acknowledge the converse—that PROLONG could be a false negative.

Moreover, CDER has suggested that PROLONG undermines the strength of the Meis findings, in part, because PROLONG was a larger trial (four times larger) than Meis. Significantly, the differences in size is not at all a sufficient answer because, as many renowned scientists and physicians have pointed out—and as conceded by CDER—the two trials were significantly different with respect to risk factors and the incidence of preterm birth.[87] This is particularly true in the case of PROLONG where the low event rate markedly impacted the study's power and led to an increased chance of a false negative.

Multiple practitioners agreed at the hearing that PROLONG does not negate Meis and does not disprove the significant benefits of reducing preterm birth demonstrated in the Meis trial in a higher risk patient population in the U.S. For example, Dr. Dude stated, "I am bothered that a priori environments were very different in these two studies and that one study is being used to negate the effects of the other. This is not to say that the Meis study is the final word on using Makena to prevent spontaneous preterm birth, but I do not think it is justified to use the PROLONG trial to refute the outcomes of the Meis trial."[88] Dr. Miller further "urge[d] the committee, at a minimum, to consider that [the differences in study populations] could account for the divergent outcomes of these two trials."[89]

Dr. Hill also questioned, "[f]rom the studies published, are we convinced Makena is not safe and effective, especially in Black and other vulnerable women with previous spontaneous births? I and other clinicians believe no. We have not answered that question. A well-designed randomized trial by the sponsor, which they are willing to do, needs to be done to answer this unanswered question."[90]

As the Presiding Officer's report notes, similar concerns were echoed during the deliberation of ORUDAC members on the last day of the hearing, when several members noted that the currently available evidence did not demonstrate ineffectiveness.[91] For instance, Dr. Susan Ellenberg stated, "[t]here is no way that studies can ever definitively prove that a drug had no effect. Even if we had two definitively negative studies, it would be possible. There's always uncertainty in these issues. So that's not what we're saying. *I wouldn't say that there's proof that it's ineffective*, but I think we're basically back to square zero, where we were before anything was studied."[92] These concerns also led Dr.

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[85] *See* Sibai et al., *supra* n.74; Oct. 18, 2022 Transcript at 113:04-15, statement by Dr. Sibai.

[86] Oct. 17, 2022 Transcript at 295:22-296:03.

[87] *See supra* n.82.

[88] Oct. 18, 2022 Transcript at 75:15-22.

[89] Oct. 17, 2022 Transcript at 295:17-20.

[90] Oct. 18, 2022 Transcript at 67:10-17.

[91] Presiding Officer's Report at 9.

[92] Oct. 19, 2022 Transcript at 72:14-73:01 (emphasis added).

Eisenberg to abstain from the second voting question 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."[93]

While Dr. Eisenberg voted 'no' for the last voting question, she added that she was "still . . . very conflicted" regarding her vote and stated, "I don't feel that the studies to date have demonstrated absolute effectiveness, but they have also not demonstrated ineffectiveness depending on the population. I think that the difficulty is identifying the population that would benefit."[94] Even Dr. Mark Hudak, who voted "no" to all three questions, acknowledged that his votes "[did] not close out the possibility that the drug may be effective in certain situations or certain populations."[95] Lastly, Dr. Henderson, who voted "yes" to both the second and third voting questions, also stated, "I don't think that the 003 [PROLONG] negates Meis" and "I think the trial with the highest risk group in the Meis [trial] demonstrated that there is some signal of effectiveness."[96]

b. Covis' Proposal To Further Confirm The Clinical Benefit Of Makena

At the hearing, Covis expressed its commitment to conducting an additional trial to confirm the clinical benefit of Makena if it remained on the market and proposed a three-tiered approach to address the outstanding questions and concerns raised by the PROLONG trial, while at the same time, continuing to meet the critical need of the higher-risk group of patients. Rather than to simply repeat PROLONG or a similar trial, Covis was determined to learn from the experience and design a better and faster trial that evaluates a truly high-risk population.

Covis' proposals were the outcome of extensive collaboration with Dorsata[97] as well as consultation with a multidisciplinary scientific advisory panel, convened with the purpose of proposing frameworks for and evaluating the feasibility of future studies that could confirm Makena's clinical benefit in high-risk women. The scientific advisory panel included leaders in the fields of obstetrics, gynecology, biostatistics, epidemiology, clinical trials, oncology and drug development, who collectively have decades of experience at FDA and on FDA advisory committees.

First, Covis proposed a narrowing of the labeling to use in a higher-risk target population identified through its analysis of Meis and PROLONG. Based on Covis' post hoc analyses of the Meis and PROLONG trials, Covis defined the higher-risk population to have the following criteria, based on the women from Meis and PROLONG trials that demonstrated consistent benefit from Makena:[98]

- Women with ≥1 recent prior spontaneous preterm birth ≤35 weeks, and

[93] Oct. 19, 2022 Transcript at 71:03-06.

[94] *Id.* at 122:11-18.

[95] *Id.* at 75:14-16.

[96] *Id.* at 61:02 and 125:20-22.

[97] Dorsata is a healthcare technology company with a maternity care management software platform used for decision support, documentation, obstetrical care plans, order entry, and clinical data reporting, among other things. Most relevantly, Dorsata's current database contains over 210,000 pregnancies, enabling Covis to perform deep-dive analyses of preterm birth and insights to inform clinical trial development.

[98] Section VII.D and Appendix of Covis' Final Briefing Materials provide greater detail on Covis' exploratory post-hoc analyses.

- ≥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

These criteria were suggested based on extensive analyses of three datasets—Dorsata, Meis and PROLONG—and would represent a significant narrowing of Makena's indicated population.

Second, Covis proposed an RCT to confirm Makena's effect in the identified higher-risk target patient population. Covis proposed to randomize approximately 400 patients in a 2:1 ratio between Makena and placebo. As for the primary endpoint, after examining a range of different endpoints, Covis proposed to study increase in time from randomization to birth, capped at 35 weeks gestation, rather than a conventional categorial endpoint of preterm birth rate at specific cutoffs (e.g., <37, <35, <32 weeks). This was because Covis' analyses showed the continuous endpoint to be more sensitive than the categorial endpoints, teasing out a signal where the categorial endpoints did not show an effect. Covis also believes that the concept of added weeks of gestation had a clearer clinical interpretation in comparison to a categorical endpoint such as the rate of preterm birth at a given cutoff such as 35 weeks. Further, by picking the cut point at which Covis capped weeks gained, any difference between the treatment arms would be focused on a time window that is clinically relevant for neonatal development. 35 weeks was chosen because literature suggested that incidence rates of death, major neonatal morbidity, and minor neonatal morbidity declined significantly with each advancing week of gestation, with the biggest decline in risk occurring up to 35 weeks. Covis estimated that this RCT would take 4-6 years to be completed.

Third and lastly, Covis proposed an observational study whose goal would be to establish the relationship between gestational age and neonatal outcomes in treated vs. untreated patients. The study would be designed to specifically demonstrate that pharmacological prolongation of gestation with 17-OHPC accrues similar benefits to the neonate as is already seen with spontaneous births at corresponding gestational ages.

In terms of feasibility, as detailed at the hearing, Covis' analyses suggest that the withdrawal of Makena would likely render another RCT unfeasible. Covis undertook an extensive feasibility assessment of a potential RCT, including outreach to potential sites and contract research organizations and surveys of physician patient populations. Covis' initial survey of 400 ob/gyns and MFM specialists revealed that a large majority of physicians (78%) would likely recommend a pregnant patient to enroll in a controlled study comparing the efficacy of a product vs. placebo only when FDA has approved the product.[99] An even larger percentage of physicians (88%) stated that it is important for treatment options to be approved by FDA before recommending them to pregnant patients.[100] A follow-up survey conducted in a similar physician population (172 providers from the first survey as well as 150 new respondents) affirmed these results. Critically here, a significant majority of physicians (80%) stated that they would likely recommend a pregnant patient enroll in a placebo-controlled study when the product is FDA-approved.[101] In contrast, only 15% indicated interest in enrolling their patients if the product at

[99] *See* Covis Briefing Materials, Attachment A to the Appendix.

[100] *See id*.

[101] *See* Covis Briefing Materials, Attachment C to the Appendix; Oct. 19, 2022 Transcript at 40:09-19.

issue had its marketing authorization withdrawn, as would be the case here if Makena were withdrawn.[102] These findings suggest that knowledge that a clinical trial is being conducted for a drug that FDA has withdrawn from the market leads to the unsurprising result of greater hesitancy among potential participants and significant recruitment challenges. CDER relied on the recruitment challenges associated with PROLONG as evidence that it was not possible to complete a trial while the product remained on the market, but offered no new evidence to contradict Covis' survey results. For these reasons, as Covis fully detailed in prior briefing and at the hearing, Covis believes that it will not be feasible to enroll an RCT once the Makena NDA is withdrawn.

Covis explained at the hearing that it was confident of meeting enrollment targets based on these feasibility assessments. Covis also committed to voluntarily withdrawing Makena if three study conduct criteria were not met:

- Interim analysis for futility,
- Assessment of enrollment projections at Month 24 to evaluate feasibility of completing the trial in a 4- to 6- year time frame, or
- Outcome of study is negative.

Thus, at the hearing, Covis outlined a robust plan to confirm the clinical benefit of Makena and to address the outstanding questions raised by CDER, while at the same time preserving access to 17-OHPC for the highest risk group of patients.

c. Randomized Controlled Trials, Observational Studies, And Real-World Use For Over A Decade Demonstrate That Makena Has A Favorable Safety Profile For Pregnant Women And Their Offspring

Makena is among the most well-studied pharmacotherapies used in pregnancy, with multiple NICHD and MFMU trials conducted, numerous observational studies undertaken, and over a decade of postmarket surveillance, all aimed at establishing Makena's benefit-risk profile. Those studies, along with decades of real-world use, point to one inevitable conclusion: Makena has a favorable safety profile for pregnant women and their offspring.

For example, at the hearing (as detailed above), CDER agreed that "[w]e do not have significant concerns about the harms of this treatment," "this is not a high-risk drug by any means," and the safety risks associated with Makena "are not by any means substantial worrisome risks."[103]

Despite these acknowledgements, CDER and the Presiding Officer have pointed to a publication, Caitlyn Murphy et al., *In Utero Exposure to 17α-Hydroxyprogesterone Caproate and Risk of Cancer in Offspring*, AM. J. OBSTET. GYNECOL., 132e1 (2022) (the Murphy study), as raising "indeterminate"[104]

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[102] *See id*.

[103] Oct. 17, 2022 Transcript at 208:20-21 (*see supra* n.38 regarding the transcript error); *id.* at 211:21-212:06, answer by Dr. Stein.

[104] Division of Urology, Obstetrics and Gynecology (DUOG), Office of Rare Disease, Pediatrics, and Reproductive Medicine (ORPURM), Office of New Drugs, CDER, Newly Identified Safety Signal (NISS) Closure Memorandum

questions with respect to Makena. As discussed at the hearing, CDER's own evaluation of the publication makes clear that the study is deeply flawed and does not point to any identifiable safety issue regarding Makena.

As Covis previously has explained at length, the Murphy study is neither reliable nor relevant to considerations of the safety and efficacy of Makena.[105] First, the Murphy study is not relevant to Makena's safety profile because the article did not analyze data from use of Makena but of a different drug, Delalutin. Although Delalutin and Makena both contain 17-OHPC, the historical use of Delalutin was entirely distinct from modern clinical use with Makena. As the authors acknowledge, the two drugs differ in "the timing, frequency, and pregnancy-related indications."[106] Indeed, the authors' own analysis suggests that any increase in event rate associated with Delalutin is limited to exposure during the first trimester of pregnancy—a trimester in which Makena is not indicated for use. ACOG also recognized the inapplicability of Murphy to Makena and issued an announcement shortly after the article was published, pointing out its "limitations in the design," and stating, "the study's findings are not conclusive and should not influence practice."[107]

Critically, CDER's own internal documents acknowledge the numerous flaws in the study and conclude that the article did *not* identify a link between 17-OHPC and cancer. To this end, CDER's Division of Epidemiology II (DEPI II) Team Leader stated that the study's limitations "preclude this study from contributing definitively to this drug safety issue," as the study "provides insufficient evidence to support regulatory action regarding a long-term cancer risk in offspring who were exposed in utero to 17-OHPC."[108] The Murphy study therefore did not support any regulatory actions such as communication to the public or a labeling change, and CDER closed its Newly Identified Safety Signal (NISS) process, with the only recommended follow-up as "PubMed automated search emails."[109]

Notwithstanding these flaws and concessions, a number of public participants relied upon the Murphy study to raise questions about Makena's long-term safety.[110] Moreover, one of only two questions posed by the Presiding Officer to Covis after its affirmative presentation also focused on "some discussion yesterday from CDER, and also from members of the public, about longer term safety

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re: NDA 021945 (Jul. 14, 2022), https://www.regulations.gov/document/FDA-2020-N-2029-0335; Presiding Officer's Report at 18.

[105] For greater details on Covis' arguments that the Murphy study is neither reliable nor relevant to this proceeding, we refer you to Section VII.A.7 of our final briefing materials.

[106] The Murphy study at e8.

[107] ACOG, *ACOG Guidance on 17-OHPC Remains Unchanged*, ROUNDS (Nov. 12, 2021), https://www.magnetmail.net/actions/email_web_version.cfm?ep=ZXoixPhGZdQ3e6Q2dvjdZDwQFTvi0y3E8vmMV8yEYSCen1PqjHurjEQW5OcZEat1bek8Es8Fl1Bc-OK2WWEQeqpXXi6RJogR0lF-bOcAh12TWv9Ju9GGNuZlrp6THaS3.

[108] CDER, Division of Epidemiology II (DEPI II), Office of Surveillance and Epidemiology Review (OSE), Office of Pharmacovigilance and Epidemiology (OPE), Team Leader Review, Epidemiology: Review of published paper (Jun. 22, 2022), https://www.regulations.gov/document/FDA-2020-N-2029-0335.

[109] *See* NISS Closure Memorandum, *supra* n. 104.

[110] *See, e.g.*, Oct. 17, 2022 Transcript at 286:03-10, public participation by Adam Urato ("Cancers in the offspring are another major concern. . . . Caitlin Murphy and her group studied this issue with Delalutin, the same synthetic hormone as Makena, and they found increased rates of cancers in the group exposed in utero"); *id*. at 303:20-22, public participation by Suzanne Robotti ("a recent study showed increased risk for cancer in children who are exposed to this synthetic hormone in utero").

concerns."[111] Lastly, a few ORUDAC members also referred to the article during their discussion on the last day of the hearing, suggesting that "there should be a discussion to patients about the potential intergenerational risk" and encouraging Covis to work with FDA on a study to "investigate the risk of intergenerational outcome."[112] This focus was unwarranted, given the scientific limitations of this article, as conceded in large measure by CDER's internal documents.

d. The Advisory Committee Vote Was Influenced By The Ad Hoc Narrowing Of Question 3 Such That It Does Not Fully Reflect The Robust Discussion At The Hearing

The comments and subsequent discussion by the ORUDAC reflect that members of the Advisory Committee grasped the complexity of the issues at stake in the proposed withdrawal of Makena, and that they understood the significant public health impact that such a withdrawal would have. Issues including the ongoing unmet medical need, disproportionate impact of preterm birth, inconsistent study results, favorable safety profile, and feasibility of conducting further clinical study dominated the discussion. For much of the hearing, it appeared that collectively the ORUDAC members were endeavoring to find a path forward with respect to Makena in these difficult circumstances. It is possible that the outcome of these deliberations were altered, however, at the very end of the proceeding, when the Presiding Officer orally limited the scope of the third voting question, which had the effect of preventing the ORUDAC members from voting on Covis' proposal to narrow the indication while further study was conducted.

A simple comparison of the second and third voting questions shows that the second voting question was intended to elicit a conclusion about Makena's labeled indication, whereas the third was intended to allow the ORUDAC members to consider Covis' full set of proposals. Specifically, the second voting question asked, "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?"[113] In contrast, the third discussion and voting questions did not contain such a limitation; they simply asked:

> 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:

[111] Oct. 18, 2022 Transcript at 283:19-21.

[112] Oct. 19, 2022 Transcript at 111:15-21 and 129:16-20.

[113] October 17-19, 2022 Hearing of the Obstetrics Reproductive and Urologic Drugs Advisory Committee – Final Questions, https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-information-october-17-19-2022-hearing-announcement-involving-obstetrics-reproductive-and.

> 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?[114]

The difference in the phrasing of the second and third voting questions, which was the subject of extensive correspondence between the parties and the Presiding Officer long before the hearing,[115] reflects their distinct purposes: Question 2 was intended to address the status quo, i.e., whether there was substantial evidence of effectiveness to support Makena's current labeled indication, whereas Question 3 was intended to address Covis' proposal for a path forward—i.e., narrowing of the labeling to a higher-risk population while Covis conducted additional studies to verify Makena's benefit.

This is further evident from how *both parties* presented the questions to the ORUDAC members at the hearing. On the second day of the hearing, Covis' affirmative presentation ended with a section entitled "COVIS Position on Questions Presented," during which Dr. Raghav Chari showed each voting and discussion question on the screen and summarized Covis' position for each question in turn.[116] After showing slides containing the third discussion and voting questions,[117] Dr. Chari stated the following, clearly demonstrating that Covis was seeking ORUDAC's views regarding whether Makena could remain on the market with a narrowed indication:

> Next, the committee will be asked whether Makena should remain on the market, and importantly, whether or not FDA should allow Makena to remain on the market while an appropriate confirmatory study is designed and conducted. We urge this committee to recommend that Makena remain on the market for at least this subset of high-risk patients while we collect additional evidence to reaffirm its benefit. . . .[118]

Similarly, Dr. Chari's closing statement on the last day of the hearing walked ORUDAC through each of the three questions. When he arrived at the last question, Dr. Chari "urge[d] this committee to recommend that Makena remain on the market for at least this subset of higher risk patients while we collect additional evidence to confirm its benefit."[119]

CDER's discussion of the third voting question likewise noted that it was intended to address the sponsor's proposed path forward, including a narrowed indication limited to the higher risk subgroup. CDER structured its affirmative presentation at the hearing such that different presenters would cover each of the voting questions posed to the ORUDAC. Dr.

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[114] *Id.*

[115] *See* Letter from Rebecca Wood to Celia Witten, Ph.D., M.D., Dkt. No. FDA-2020-N-2029-0204 (Feb. 14, 2022), https://www.regulations.gov/document/FDA-2020-N-2029-0204; Letter from Christine Hunt to Celia Witten, Ph.D., M.D., Dkt. No. FDA-2020-N-2029-0202 (Feb. 14, 2022), https://www.regulations.gov/document/FDA-2020-N-2029-0202; Letter from Celia Witten, Ph.D., M.D. to Rebecca Wood and Christine Hunt, Dkt. No. FDA-2020-N-2029-0083 (Dec. 13, 2021), https://www.regulations.gov/document/FDA-2020-N-2029-0083.

[116] Covis' Affirmative Presentation Deck at 133.

[117] *Id.* at 143-44.

[118] Oct. 18, 2022 Transcript at 184:15-185:01.

[119] Oct. 19, 2022 Transcript at 48:11-14.

Christina Chang covered the first voting question and CDER's respective position;[120] Dr. Laura Lee Johnson then covered the second voting question;[121] and finally, Dr. Christine Nguyen covered the last discussion and voting question, which she referred to as Question 3 and 4, respectively. In her presentation, Dr. Nguyen read out loud the last voting question (or Question 4) and then answered the question by responding to Covis' proposal:

> Question 4 asks, should FDA allow Makena to remain on the market while an appropriate confirmatory study is designed and conducted? Our response here is no.
>
> . . .
>
> As I will discuss later, Covis proposes to narrow the indicated use or higher risk subgroup. Covis also proposes to conduct a 400-plus person RCT in the same narrow population, and anticipates it will take 4 to 6 years to complete. Aside from the significant challenges in recruitment I just discussed, we note this small sample size is the result of an underestimation of the standard deviation. . . .[122]

The hearing transcript shows that the ORUDAC members likewise understood Question 2 as tied to Makena's current indication and Question 3 as addressing Covis' proposal. Indeed, many of the "no" vote explanations for the second voting question demonstrate that the ORUDAC members were focused on the language of that question (specifically, its limit to the currently approved indication), under the assumption that the last voting question would address Covis' proposed path forward:

- Dr. Joseph Alukal voted "no" "based specifically on the fact that the question is asking us whether or not we believe there to be evidence of *this* effect."[123] He further stated that it was important to keep "questions of study design and enrollment" in mind "as we move on to the subsequent question of what are we to do next."[124]

- Dr. Aaron Caughey voted "no" regarding "the indication of prior spontaneous preterm birth" but noted that the "issue of subgroups might be something you might address going forward, but that's not in this question."[125]

- Dr. Lorie Harper voted "no" because the evidence "does not support effectiveness for the general population . . . ."[126]

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[120] Oct. 17, 2022 Transcript at 50:16-20 ("My presentation will address the first question posed by Dr. Witten. Do the findings from Trial 003 verify the clinical benefit of Makena? And as the evidence will show, CDER's response is no").

[121] *Id.* at 66:14-21 ("Moving on to question 2 posed to the advisory committee, does the available evidence demonstrate that Makena is effective for its approved indication? Considering the available evidence, Makena is not shown to be effective in reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth").

[122] *Id.* at 99:08-102:11.

[123] Oct. 19, 2022 Transcript at 69:09-11 (emphasis added).

[124] *Id.* at 69:17-70:05.

[125] *Id.* at 08-16.

[126] *Id.* at 74:19-20.

- Dr. Hudak voted "no" to "the question as written" because "the weight of the evidence did not support effectiveness for the indication, the labeling indication, which is the entire population."[127] He left open the "possibility that the drug may be effective in certain situations or certain populations."[128]

- Dr. Kaimal voted "no" "[g]iven the way the question is worded" to focus on "the approved indication" but was open to investigating "an additional population for that specific question."[129]

- Dr. Michael Lindsay voted "no" also based on "the way the question is worded."[130]

- Dr. Mary Munn's "no" vote also focused on the drug's "indication."[131]

- Dr. Kristine Shields voted "no", stating she "hope[d] that the sponsor will go on and do additional trials to more definitively answer this question in certain populations."[132]

These responses all reflect the ORUDAC members' expectation that the third voting question would give them an opportunity to address and vote on Covis' proposed path forward without being tied to Makena's current indication.

The Presiding Officer, however, preempted these discussions by reframing the last voting question immediately prior to the vote. After reading the third question, the Presiding Officer stated, "this question is asking about Makena with its labeled indication."[133] Although she stated that other populations could be raised during the discussion period, she stressed that "the vote should be on that specific question."[134]

The first ORUDAC member comment afterwards (by Dr. Eisenberg) was favorable towards Covis.[135] But then, Dr. Kaimal asked the following "clarifying question":

> Actually, it's a clarifying question. . . . My question, I guess maybe is for CDER; I'm not sure exactly. What's being proposed by Covis is to say they will narrow the indication to a higher risk population and simultaneously perform a study in that higher risk population. And my question is -- really just from a regulatory perspective -- is that a

[127] *Id.* at 75:04-07 and 75:16-17.

[128] *Id.* at 75:14-16.

[129] *Id.* at 76:03-09.

[130] *Id.* at 76:14-15.

[131] *Id.* at 77:01-04.

[132] *Id.* at 78:06-08.

[133] *Id.* at 80:04-05.

[134] *Id.* at 80:07-12 ("if you have additional comments about some of the populations that were discussed during either the meeting yesterday, you can make them during the discussion period, but the vote should be on that specific question").

[135] *Id.* at 81:04-82:21 ("I believe that the product should remain on the market in order to be able to do a study that could answer the question. . . .").

> possibility, which was sort of raised during the discussion but I think not really definitively answered?

In response, the Presiding Officer stated that the ORUDAC members needed "to provide scientific and clinical opinions and conclusions on the specific questions" posed. She then reiterated that the last voting question was tied to Makena's current indication:

> So I've already explained that for question 3, for the vote, we're asking specifically if we should allow Makena to remain on the market, meaning remain on the market *with its current indication*, while an appropriate confirmatory study is designed and conducted.
>
> So that's the question we're asking you to vote on. . . .[136]

Dr. Kaimal then again asked to confirm that "the question before us to vote on is Makena stays on the market *with the current labeled indication* while additional study is done; is that correct?," which the Presiding Officer affirmed.[137]

The net result is that due to the Presiding Officer's revised instruction at the hearing, there was no substantive difference between the second and third voting questions. The Presiding Officer's reframing of the question effectively shut down discussion of Covis' proposal to narrow the indication and meant that there was no longer an avenue for the ORUDAC to voice support for such a proposal. Thereafter, predictably, the ORUDAC's votes for the third voting question were predominantly negative.

III. Covis Requests Orderly Withdrawal Given Recent ORUDAC Recommendations

Covis stands by Makena's favorable benefit-risk profile, including its efficacy in women at highest risk of preterm birth. Covis remains concerned that the withdrawal of Makena will leave high-risk women with no FDA-approved therapy and will result in physicians resorting to higher-risk stop-gaps such as compounded 17-OHPC or cerclage. Nevertheless, Covis respects the recommendations of ORUDAC and the public process that culminated in these recommendations. In light of the recent ORUDAC vote, Covis has therefore made the very difficult decision to voluntarily withdraw the Makena NDA.

We note that shortly after the hearing, Covis provided a proposal to CDER to voluntarily withdraw the Makena NDA and obviate the need for further proceedings before the Presiding Officer or Office of the Commissioner. Specifically, on October 31, 2022, twelve days after the public hearing concluded, Covis reached out to CDER and the Presiding Officer regarding this proposal. Covis detailed its plan for an orderly winddown that would close enrollment in the Makena Care Connection program and ask that no new patients begin Makena treatment effective January 31, 2023. For patients who, in consultation with their healthcare provider, wished to finish their 21-week course of treatment, Covis offered to make Makena available through the end of that treatment cycle. Under this plan, Covis would have halted distribution of product as of May 31, 2023, and expected inventory to be available for completion of treatment through the end of June 2023. Covis offered to request that the Agency formally withdraw approval of the NDA for Makena after that time. In addition, Covis offered to reach out to the

[136] *Id.* at 84:21-85:06 (emphasis added).

[137] *Id.* at 86:01-05 (emphasis added).

relevant professional societies, as well as to the manufacturers of generic versions of Makena, to encourage all stakeholders to follow this wind-down plan. CDER declined this offer and indicated that it would abide by the post-hearing briefing schedule previously set by the Presiding Officer.[138]

Covis remains prepared to work cooperatively with the Agency to accomplish an orderly wind-down and withdrawal of Makena and its generics from the market. If a final order withdrawing the approval of Makena is issued, we respectfully request that the effective date of the order be set to allow for an orderly wind-down that would best serve the interests of the patients. There are numerous important public health reasons that support this approach. First, while there has been a significant decrease in the use of Makena since PROLONG, the 2019 BRUDAC meeting, and 2022 ORUDAC vote, Covis continues to see some new patient enrollment through Makena Care Connection. As demonstrated by the numerous written comments and oral presentations at the recent hearing, many professional societies, providers, patients, and patient organizations continue to rely on Makena's favorable benefit-risk profile and support its use for the reduction of subsequent preterm birth. As such, a sudden withdrawal of Makena from the market would be unprecedented and may have serious and wide-ranging implications.[139] In particular, for women who are in the middle of the indicated course of Makena treatment, sudden deprivation of the only FDA-approved drug for this indication may be distressing.[140]

Moreover, an appropriate wind-down period is especially warranted given CDER's acknowledgement that Makena does not raise significant safety concerns. Indeed, as detailed by Covis at the hearing and in its prior submissions, the withdrawal of Makena may itself raise public health safety concerns, as the withdrawal order may cause physicians and patients to resort to higher-risk options such as compounded 17-OHPC, off-label uses of other drugs including Delalutin,[141] and cerclage.

Accordingly, Covis respectfully requests that the Agency grant an orderly wind-down that would allow at least 21 weeks from the time of a withdrawal order for patients to complete their courses of treatment and for remaining in-channel inventory to be exhausted. Covis stands ready to work collaboratively with the Agency and would also welcome a chance to confer regarding an orderly wind-

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[138] Letter from Celia Witten, Ph.D., M.D., *supra* n.2.

[139] We note that FDA has permitted orderly wind-downs even in circumstances where—unlike here—the product presented severe public health safety risks. *See, e.g.*, 73 Fed. Reg. 7565 (Feb. 8, 2008) (granting intravenous colchicine manufacturers 30 days to stop manufacturing and 180 days to halt shipment); Robert Reinhold, "Califano, Citing 'Imminent Hazard,' Orders Drug for Diabetes Taken Off the Market," NY TIMES (Jul. 26, 1977), https://www.nytimes.com/1977/07/26/archives/califano-citing-imminent-hazard-orders-drug-for-diabetes-taken-off.html (granting 90-day orderly transition period to allow doctors to transition their patients from phenformin to other therapies).

[140] As mentioned above, the indicated length of Makena treatment can be as long as 21 weeks. Makena's labeling instructs providers and patients to "[b]egin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation" and "[c]ontinue . . . until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first." Makena Prescribing Information (Feb. 2018), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021945s013lbl.pdf.

[141] *See* Section VII.C.2 in Covis' Final Briefing Materials. For instance, because Delalutin is not approved for preterm birth, the Delalutin labeling lacks instructions for safe use for this therapeutic use and contains no warnings cautioning patients or providers about relevant risks. Generic Delalutin's labeling also uses an outdated, less accessible format and does not include any of the detailed patient information that is available on Makena's approved labeling. Additionally, since there is no currently marketed branded Delalutin, the drug's labeling will not be updated to reflect adverse event findings or any other emergent safety information.

down plan. Covis also commits to reaching out to professional societies, generic manufacturers, doctors, and patients and encouraging them to follow the wind-down plan.

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The issues raised by CDER's proposed withdrawal of Makena are complex and have profound implications for public health. The hearing, conducted pursuant to 21 § C.F.R. 314.530, ensured that there was meaningful opportunity for thoughtful discussion of issues raised by the withdrawal, including the unmet medical need, disproportionate impacts, conflicting clinical trial results, favorable safety profile, inconclusive secondary data, and continued physician and patient support for keeping the product on the market. We thank the Agency, CDER, ORUDAC members, as well as the public participants for engaging in this very important public health discussion.

Very truly yours,

/s/ Rebecca K. Wood

Rebecca K. Wood

cc: Celia Witten, Ph.D., M.D., Presiding Officer
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