FDA Briefing Document
NDA 021945
Hydroxyprogesterone Caproate Injection
(trade name Makena)

Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) Meeting
October 29, 2019
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Office of New Drugs

Division of Biometrics III
Division of Biometrics VII
Office of Biostatistics
Office of Translational Sciences

Division of Epidemiology II
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Center for Drug Evaluation and Research

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The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought new information from the new drug application for Makena (17-hydroxyprogesterone caproate) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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INTRODUCTORY MEMORANDUM

To: Bone, Reproductive and Urologic Drugs Advisory Committee

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Director

Division of Bone, Reproductive, and Urologic Products (DBRUP)

Subject: Makena (hydroxyprogesterone caproate injection)
New Drug Application 021945/Supplement 023
Overview of topics to be discussed at the October 29, 2019, advisory committee meeting

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The FDA is convening this Advisory Committee (AC) meeting to discuss the evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth and improving neonatal outcomes to inform FDA's regulatory decision-making for this product. In 2011, Makena received accelerated approval (a type of approval discussed in greater detail below) based on a reduced risk of recurrent preterm birth (PTB) prior to 37 weeks, a surrogate endpoint that FDA considered reasonably likely to predict clinical benefit to the neonate. Consistent with FDA's accelerated approval framework [21 CFR part 314, subpart H and section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)], FDA required the Applicant to conduct a post-approval confirmatory trial to verify and describe the clinical benefit. Completed at the end of 2018, this confirmatory trial did not verify Makena's efficacy on obstetrical or neonatal outcomes. In a supplemental new drug application (sNDA), the Applicant proposes to add findings from this trial to the drug label.

BACKGROUND:

Current clinical practice

Preterm birth, defined as birth prior to 37 weeks of gestation, currently affects approximately 10% of all births and 8% of singleton pregnancies.[1] Premature birth is a significant public health problem because these infants are at an increased risk of neonatal mortality and significant morbidity, as well as long-term physical and developmental impairment. To date, there are no drugs approved for reducing neonatal morbidity or mortality or long-term sequelae of preterm birth.

Progesterone, administered by intramuscular injection or intravaginally, has been used for certain conditions that may increase a pregnant woman's risk of PTB. Current professional practice

[1] https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm (accessed September 19, 2019)

guidelines recommend progesterone treatment starting in the second trimester of pregnancy to reduce the risk of recurrent preterm birth in women with a singleton pregnancy and a prior spontaneous preterm birth (sPTB). The guidelines also recommend vaginal progesterone to reduce the risk of PTB in women without a prior preterm birth and with a shortened cervix in the current pregnancy, although such use is not FDA-approved.[2] Makena is the only pharmacotherapy approved to reduce the risk of recurrent preterm birth. Based on its accelerated approval, Makena's indication states that it is approved to "reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity."

Regulatory History of Hydroxyprogesterone Caproate:
The drug substance of Makena, hydroxyprogesterone caproate (HPC), also referred to as 17-HPC, 17-OHPC, or 17P, was approved by FDA in 1956 for conditions generally responding to progestogens, under the tradename Delalutin (HPC) injection 125 mg/mL and 250 mg/ml (NDAs 010347, 016911). This approval was based on safety considerations because it occurred prior to the Kefauver-Harris Amendment of 1962 to the FD&C Act requiring that approved drugs be supported by substantial evidence of effectiveness, in addition to demonstrated safety. Delalutin remained approved for certain gynecologic indications after undergoing the Drug Efficacy Study Implementation review, which determined the efficacy of marketed drugs approved before 1962. At the Applicant's request, FDA withdrew approval of the NDAs for Delalutin in 2000 (not for efficacy or safety reasons) (65 Fed. Reg. 55264, Sept. 13, 2000). FDA has approved generic products of Delalutin that are currently marketed. Note that Delalutin and its generics are not approved for reducing the risk of preterm birth.

Published literature from the 1960s through the 1980s included several clinical studies evaluating the efficacy of HPC for obstetrical uses. Conflicting findings regarding the effectiveness of HPC for the prevention of PTB prompted the National Institute for Child Health and Human Development (NICHD), via the Maternal-Fetal Medicine Units (MFMU) Network, to conduct a multicenter, double-blind, placebo-controlled clinical trial in women with a history of spontaneous preterm singleton birth to assess the efficacy of HPC for preventing recurrent PTB (Study 17P-CT-002, or Trial 002 hereinafter). In June 2003, the trial's findings were published,[3] reporting that HPC 250 mg injection reduced the proportion of women who delivered at less than 37 weeks gestation.

[2] American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin: Prediction and Prevention of Preterm Birth (2012, reaffirmed 2018); Society for Maternal-Fetal Medicine Statement: "The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth" (March 2017). While the ACOG Practice Bulletin did not specify the formulation of progesterone for women with a prior sPTB, SMFM recommended treatment with hydroxyprogesterone caproate injection and not vaginal progesterone in this population.

[3] Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;348(24):2379-85.

Makena's accelerated approval

In 2006, an applicant submitted NDA 021945 seeking marketing approval of HPC injection for the prevention of recurrent PTB. The NDA relied on data from the MFMU Network Trial 002 for primary support of efficacy and safety. At that time, no drug was approved in the U.S. to reduce the risk of PTB. However, HPC was compounded and used widely for the prevention of PTB in women at high risk.

After three review cycles and one Advisory Committee meeting, in February 2011, the FDA granted Makena accelerated approval based on reduction in preterm birth prior to 37 weeks, a surrogate endpoint considered to be reasonably likely to predict the clinical benefit of reducing neonatal morbidity or mortality.

Initiated in 1999 and completed in 2002, Trial 002 enrolled 463 women with a singleton pregnancy and at least one prior sPTB from 19 university-based clinical centers in the United States in the MFMU Network. The primary efficacy endpoint was the proportion of pregnant women delivering prior to 37 weeks gestation, with those delivering prior to 35 or 32 weeks as secondary endpoints. The trial showed that Makena (HPC 250 mg) injection administered intramuscularly once weekly starting at 16 weeks 0 days (16^0) to 20 weeks 6 days (20^6) gestation and used through 36^6 weeks gestation or birth reduced the proportion of women who delivered <37 weeks gestation from 55% (placebo) to 37% (Makena). The treatment difference was -17.8% [95% confidence interval (CI): -28%, -7.4%]. This treatment benefit appeared independent of race, number of prior preterm deliveries, and gestational age of the prior preterm birth. The treatment effect was sufficiently persuasive to support drug approval based on the findings of a single adequate and well-controlled trial. The proportions of women delivering at <35 and <32 weeks gestation were also statistically lower among women treated with Makena compared to placebo. The treatment difference was -9.4% (95% CI: -19.0%, -0.4%) for delivery <35 weeks gestation and -7.7% (95% CI: -16.1%, -0.3%) for delivery <32 weeks gestation.

Issues regarding generalizability of Trial 002's findings to the broader U.S. population included (a) approximately 60% of the trial participants being self-identified Blacks, (b) subject recruitment from only academic centers, with 25% of subjects from a single academic center, and (c) the notably high rate of recurrent preterm birth in the placebo arm (55%).[4] As a condition of accelerated approval, the Applicant was required to submit data from a confirmatory efficacy and safety trial to verify the clinical benefits of Makena, and the trial was to be completed with due diligence.

CONFIRMATORY TRIAL (Trial 003)

Prior to approving Makena in 2011, the FDA recognized the challenges of the feasibility of conducting a confirmatory efficacy and safety trial in the United States, given the endorsement of professional practice guidelines and accepted clinical practice of using progesterone for preterm birth. Prior to approval, the FDA required that the Applicant provide evidence that it could successfully complete the confirmatory trial, which must be ongoing at the time of approval, and that at least 10% of subjects be enrolled from the U.S. and Canada. Initiated in 2009 and completed in 2018, this confirmatory trial (Trial 003) was a multicenter, international,

[4] Background recurrent preterm birth rate used to power Trial 002 was 36%, as this was the background rate from the MFMUN uterine monitoring trial in the 1990s.

randomized, double-blind, placebo-controlled study that enrolled women with eligibility criteria like those of Trial 002. The trial's coprimary efficacy endpoints were delivery prior to 35 weeks gestation and a neonatal morbidity/mortality composite index (neonatal composite index).[5] The inclusion of a clinical endpoint (the neonatal composite index) addressed the accelerated approval's regulations of verifying that initial findings based on a surrogate endpoint (gestational age at delivery) lead to direct clinical benefit. Trial 003 randomized a total of 1,708 women from nine countries, with Russia, Ukraine, and the United States enrolling 36%, 25%, and 23% of women, respectively. Data were available for 1651 liveborn neonates. The trial did not demonstrate a statistically significant treatment effect for the coprimary endpoints of proportion of women delivering prior to 35 weeks (11% Makena compared to 12% placebo, p=0.72) or neonatal composite index (5.4% Makena compared to 5.2% placebo, p=0.84). Also, no differences between Makena and placebo were seen in the secondary outcomes related to other gestational ages at delivery (<37 weeks [23% Makena vs. 22% placebo, p=0.57), <32 weeks gestation [4.8% Makena vs. 5.2% placebo, p=0.70]) or for the individual components of the neonatal index.

The Applicant raised concerns that the study populations of Trial 002 (U.S only) and Trial 003 (international, including U.S.) differed substantially and that this may have contributed to the discordant outcomes between the two trials. Therefore, exploratory subgroup analyses and comparisons of Trial 003's U.S. population (003-U.S. subgroup) and non-U.S. patients were undertaken. There were no relevant differences in the treatment effect when analyzed by region (U.S. vs. non-U.S.), even though the non-U.S. subgroup appeared to have a lower risk profile based on demographics, social, and behavioral factors compared to the U.S. subgroup. There was no evidence of interaction between treatment and U.S. vs. non-U.S. region for the coprimary endpoints. In the 003-U.S. subgroup:

- Makena did not improve the neonatal composite index. The treatment effect was -2.2% (95% CI: -8.3, 3.9) when analyzed using the stratified Cochran-Mantel-Haenszel (CMH) method and -0.2% (95% CI: -4.9, 2.8) using another approach known as shrinkage analysis.
- Makena did not reduce the risk of delivery <35 weeks (16% Makena vs. 18% placebo). The treatment difference was -2.2% (95% CI: -10.1, 5.7) using the stratified CMH analytical method; this difference was -0.8% (95% CI: -6.0, 3.5) with shrinkage estimation.
- Point estimates of the proportions of women with delivery occurring <37 weeks (33% Makena vs. 28% placebo, a treatment effect of 4.7% [95% CI: -5%, 14%] by the CMH method) or <32 weeks (5.5% Makena vs. 9.2% placebo, a treatment effect of -3.9% [95% CI: -9.6, 1.7] by the CMH method) showed contradictory trends in the treatment effect.

A comparison among Trial 003 overall, the 003-U.S. subgroup, and Trial 002 populations indicated that a greater proportion of subjects in Trial 002 had certain risk factors for PTB, such as being self-identified Blacks or having > 1 prior sPTB, than the 003-U.S. subgroup or Trial 003 overall. However, exploratory subgroup analyses did not show statistically significant

[5] The neonatal morbidity/mortality composite index includes neonatal death, Grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and proven sepsis.

interactions between these risk factors and treatment effect of Makena in Trial 002 or Trial 003. Although these risk factors may have an impact on the PTB rate, there was no evidence in Trial 003 that they impact the treatment effect nor was there consistent convincing evidence of treatment benefit within a specific subpopulation across the two trials.

Published literature on progesterone's effect on preterm birth in women with a prior sPTB
Because findings from Trial 003 were discordant with those of Trial 002, we evaluated published evidence from six randomized, placebo-controlled trials that assessed the effect of progesterone in preterm birth and that included pregnant women with a prior sPTB. These trials studied vaginal progesterone at different doses (90 – 200 mg) in women with various risks for PTB, including a history of sPTB, with different gestational ages at delivery as the primary outcome. The overall evidence based on subgroup analyses in pregnant women with a prior sPTB did not suggest a treatment benefit with progesterone over placebo in reducing the risk of recurrent PTB in these women. These trials and their findings, however, are not directly applicable to Makena; none evaluated injectable HPC in the same target population measuring the same efficacy endpoints as Makena. We also reviewed two recent large meta-analyses. These meta-analyses evaluated progesterone formulations, doses, patient populations, and endpoints dissimilar to those of the trials for Makena and did not reliably inform the treatment effect of Makena for its intended use.

Accelerated approval and evidentiary standards for drug approval
When appropriate, the accelerated approval pathway allows for earlier approval of a drug to treat a serious condition and fill an unmet medical need based on a surrogate endpoint that is reasonably likely to predict clinical benefit but is not itself a direct measure of clinical benefit. The Applicant is required to conduct trial(s) after receiving accelerated approval to confirm the expected clinical benefit. If the confirmatory trial(s) shows that the drug provides clinical benefit, then the conditions initially attached to accelerated approval are generally terminated. (See 21 CFR 314.560.) If the confirmatory trial(s) fail to demonstrate such benefit, FDA may withdraw approval of the drug in accordance with section 506(c)(3) of the FD&C Act and 21 CFR 314.530. With accelerated approval, there is less certainty at the time of approval that the drug will ultimately be shown to improve how patients feel, function or survive; however, this pathway provides earlier patient access than would otherwise be possible to an approved drug that is reasonably likely to confer clinical benefit for a serious condition with an unmet need. In the case of Makena, FDA granted accelerated approval based on the reduction in preterm birth seen in Trial 002; however, confirmatory Trial 003 did not verify clinical benefit on adverse neonatal outcomes to infants born prematurely.

For FDA approval, including accelerated approval, the drug must meet the regulatory standard of "substantial evidence" of effectiveness and the benefits must outweigh the risks. Generally, FDA interprets substantial evidence of effectiveness as evidence of effectiveness from two or more adequate and well-controlled trials. A single positive trial, even if well-designed and well-conducted, may have undetected systemic biases or may reflect a chance finding, increasing the risk of concluding that a drug is effective when in fact it is not. The requirement for at least two adequate and well-controlled trials ensures independent substantiation of experimental findings and strengthens a conclusion of effectiveness. Nonetheless, when appropriate, FDA has the authority and flexibility to conclude that there is substantial evidence of effectiveness based on a

single adequate and well-controlled trial. In the case of Makena, FDA determined that Trial 002 was adequate, well-controlled and very persuasive and concluded that this single trial provided substantial evidence of an effect on a surrogate endpoint (effectiveness for reduction in the risk of recurrent preterm birth). It is important to note, however, that at the time this determination was made in 2011, there were no other adequate and well-controlled trials with Makena, and that had there been such additional trial(s), FDA would have considered those data when deciding whether there was substantial evidence of effectiveness.

There are two important scientific and regulatory implications for Makena:

- Accelerated approval: A drug approved under the accelerated approval pathway based on a surrogate endpoint reasonably likely to predict clinical benefit must undergo a confirmatory trial postapproval to verify clinical benefit (i.e., an improvement in how patients feel, function or survive). In the case of Makena, confirmatory Trial 003 did not demonstrate a reduction in adverse neonatal outcomes from preterm birth; therefore, the clinical benefit of Makena remains unverified.

- Substantial evidence of effectiveness: Trial 003 also did not confirm an effect of Makena on gestational age of delivery, the surrogate endpoint used in Trial 002 to support accelerated approval. This raises the question as to whether Makena's accelerated approval is still supported by substantial evidence of effectiveness for the reduction in recurrent preterm birth.

AREAS OF FOCUS FOR ADVISORY COMMITTEE

Based on the above considerations, the key issues are whether there remains substantial evidence of effectiveness of Makena on preterm birth, the unconfirmed clinical benefit of Makena on neonatal outcomes, and implications for Makena's marketing status. Makena received accelerated approval based on findings from Trial 002, which showed a reduction in the proportion of women with preterm delivery <37 weeks compared to placebo, a surrogate endpoint considered reasonably likely to predict clinical benefit. However, Trial 003, an adequate and well-controlled, well-conducted and appropriately powered confirmatory trial, did not show a reduction in preterm birth with Makena compared to placebo, nor did it demonstrate a reduction in neonatal morbidity/mortality. Under accelerated approval regulations, FDA may withdraw the approval of Makena if the Applicant fails to provide confirmatory evidence of efficacy and safety. To place this discussion in the appropriate context, we ask that the Advisory Committee members consider:

- The applicability of the findings of Trial 003 to the U.S. population
- Factors, if any, that may account for the differences in outcomes between Trial 002 and Trial 003
- Whether there continues to be substantial evidence that Makena reduces the risk of recurrent preterm birth in the context of two adequate and well-controlled trials with discrepant efficacy findings on this surrogate endpoint
- If a new confirmatory trial is required, the design of such a trial, including the comparator arm, dose(s) of study medication, location (U.S./North America or international), efficacy endpoints and importantly, the feasibility and likelihood of successfully completing such a trial in a timely manner

- If Makena were to be withdrawn from the market because of lack of efficacy, the likely consequences and their potential impact on public health.

We look forward to a thorough and reasoned discussion of these complex, important matters. Thank you in advance for the vital public health contribution you are making through your participation in this meeting.

Draft Points to Consider:

1. Discuss the effectiveness of Makena, including:
    a. The effects of Makena on recurrent preterm birth in Trial 003, and your interpretation of the discrepant preterm birth results between Trial 002 and Trial 003;
    b. The effects of Makena on neonatal morbidity and mortality;
    c. Relevance of the findings in Trial 003 to the U.S. population and current clinical practice.

2. If a new efficacy trial were to be conducted, discuss the study design, including control, dose(s) of study medication, efficacy endpoints and the feasibility of completing such a trial.

3. Discuss the potential consequences of withdrawing Makena on patients and clinical practice.

4. Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal outcomes?

    Provide rationale for your vote.

5. Based on the findings from Trial 002 and Trial 003, is there substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth?

    Provide rationale for your vote.

6. FDA approval, including accelerated approval, of a drug requires substantial evidence of effectiveness, which is generally interpreted as clinically and statistically significant findings from two adequate and well-controlled trials, and sometimes from a single adequate and well-controlled trial. For drugs approved under the accelerated approval pathway based on a surrogate endpoint, the Applicant is required to conduct adequate and well-controlled postapproval trial(s) to verify clinical benefit. If the Applicant fails to conduct such postapproval trial(s) or if such trial(s) do not verify clinical benefit, FDA may, following an opportunity for a hearing, withdraw approval.

    Should FDA:

    A. Pursue withdrawal of approval for Makena
    B. Leave Makena on the market under accelerated approval and require a new confirmatory trial
    C. Leave Makena on the market without requiring a new confirmatory trial

    Provide rationale for your vote and discuss the following:

    - Vote (A) (withdraw approval) may be appropriate if you believe the totality of evidence does not support Makena's effectiveness for its intended use.

- Discuss the consequences of Makena removal (if not previously discussed in Discussion point 3)

- Vote (B) (require a new confirmatory trial) may be appropriate if you believe the totality of evidence supports Makena's effectiveness in reducing the risk of recurrent preterm birth, but that there is no substantial evidence of effectiveness on neonatal outcomes. Vote (B) would also reflect a belief that a new confirmatory trial is necessary and feasible.

    - Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth, based on the surrogate endpoint of gestational age at delivery.

    - Also discuss key study elements, including study population, control, dose(s), and efficacy endpoints of the new confirmatory trial (if not previously discussed in Discussion point 2) and approaches to ensure successful completion of such a trial.

- Vote (C) (leave Makena on the market without a new confirmatory trial) may be appropriate if you believe Makena is effective for reducing the risk of recurrent preterm birth and that it is not necessary to verify Makena's clinical benefit in neonates.

    - Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth and why it is not necessary to verify Makena's clinical benefits in neonates.

1. Background

1.1. The Condition and Treatment Options

1.1.1. Preterm Birth

Preterm birth (PTB), defined as delivery between 20 and 37 completed weeks of gestation, is a significant public health concern. Preterm birth may be spontaneous (birth following a spontaneous process, such as preterm labor or preterm premature rupture of membranes) or indicated (delivery initiated by the healthcare provider for maternal or fetal health). According to the Centers for Disease Control and Prevention, in 2017, the U.S. PTB rate was 9.9% overall and 8.1% in singleton pregnancies; the incidence was highest in black women (13.9%) compared to white or Hispanic women (9.1% and 9.6%, respectively).[6] The CDC reported that the rate of preterm birth in the U.S. declined from 2007 (10.4%) to 2014 (9.6%), mostly because of a decline in teenage pregnancy, but has increased from 2014 until 2017 (9.9%). The latter trend is mostly due to an increase in the rate of late preterm birth (delivery 34-36 weeks gestation), while rates for early preterm birth (less 34 weeks) have remained unchanged from 2015. The World Health Organization estimates the global PTB rate to be 10.6%, which is similar to the rate of 11.2% in North America, but there are differences across geographic regions, ranging from 8.7% in Europe to 13.4% in North Africa.[7] In 2015, PTB accounted for 17% of infant deaths [8] and surviving children often suffer developmental delay or long-term neurologic impairment. In 2016, complications of PTB were the leading cause of death globally in children younger than 5 years of age, accounting for approximately 16% of all deaths in this age group, and 35% of deaths among neonates.[9] In general, the risk of adverse outcomes in the preterm neonate decreases with increasing gestational age at delivery.

While the burden of PTB is clear, the causes of PTB are less so, and identifying women who will give birth preterm is challenging. Spontaneous PTB represents a syndrome and its causes are multifactorial. Risk factors for PTB include uterine distension (seen in multifetal pregnancies and polyhydramnios), dysfunction of the cervix (reduced mechanical competence, either resulting from genetic mutations in components of collagen that is required for integrity of the cervix or from repeated surgeries on the cervix), infection of the lower genital tract, and other factors (such as cigarette smoking, inadequate maternal weight, and illicit drug use). The contribution of these factors to PTB, however, is not well-characterized. However, an accepted major risk factor is short cervical length (typically defined as <25 mm observed prior to 24 weeks gestation). Regarding the risk of recurrent PTB, one of the strongest risk factors is a history of a preterm birth, which increases the risk of PTB by about 1.5 to 2-fold. Additionally, the number of prior PTBs and the gestational age of the prior PTBs impact the recurrence risk.

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[6] National Vital Statistics Reports, Vol 67, No. 8, November 7, 2018. https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_08-508.pdf

[7] Chawanpaiboon S, Vogel JP, Moller A-B, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systemic review and modelling analysis. Lancet Glob Health 2019;7(1): e37-46.

[8] CDC – Division of Reproductive Health, National center for Chronic Disease Prevention and Health Promotion. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm

[9] UN Inter-Agency Group for Child Mortality Estimation. Levels and trends in child mortality: Report 2017. New York: United Nations Children's Fund, 2017.

Nonetheless, two-thirds of PTBs occur among women with no identifiable risk factors, causality of PTB has been difficult to determine, and the pathogenesis remains poorly understood.[10]

1.1.2. Treatment to Reduce the Risk of Recurrent Preterm Birth

In January 2003, Trial 002 was presented by the NICHD as the first abstract at the Society for Maternal-Fetal Medicine Meeting. The positive findings from this trial immediately gained extensive media attention, leading to the wide use of compounded HPC to reduce the risk of recurrent PTB. Following the June 2003 publication of Trial 002 in the New England Journal of Medicine, the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice endorsed the use of progesterone only in women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation. In its most recent Practice Bulletin (published 2012, reaffirmed 2018), ACOG recommends progesterone (without specifying the formulation of progesterone) starting in the second trimester in women with a singleton pregnancy and a prior sPTB. ACOG also recommends vaginal progesterone in women with a singleton pregnancy with a shortened cervix and without a prior sPTB. In 2003, the Society for Maternal-Fetal Medicine (SMFM) recommended treatment with either HPC injection or vaginal progesterone for women with a prior spontaneous PTB to prevent the recurrence of PTB; this recommendation was reaffirmed in 2008.[11] Based on published findings of several clinical trials, the SMFM in 2012 revised the guideline to recommend that HPC 250 mg IM weekly be given, starting at 16 to 20 weeks of gestation until 36 weeks or birth, to women with a singleton gestation whose prior sPTB occurred between 20-$36^{6/7}$ weeks gestation.[12] In 2017, SMFM reaffirmed its 2012 recommendation and added that vaginal progesterone should not be considered a substitute for HPC in these patients.[13] As noted previously, Makena is the only FDA-approved treatment for PTB.

1.2. Regulatory Background

1.2.1. Regulatory Standards of Drug Approval

1.2.1.1. Accelerated Approval

Under the accelerated approval pathway [21 CFR part 314, subpart H, and 506(c) of the FD&C Act], FDA may grant marketing approval for a new drug based on adequate and well-controlled clinical trials establishing that the drug has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict

[10] PRETERM BIRTH CAUSES, CONSEQUENCES, AND PREVENTION. Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Board on Health Sciences Policy. Richard E. Behrman and Adrienne Stith Butler, Editors. INSTITUTE OF MEDICINE OF THE ACADEMIES. THE NATIONAL ACADEMIES PRESS. Washington, D.C. Copyright 2007 by the National Academy of Sciences.

[11] Society for Maternal-Fetal Medicine Publications Committee: Use of progesterone to reduce preterm birth. ACOG Committee opinion number 419, October 2008 (replaces no. 291, November 2003) Obstet Gynecol, 112 (2008), pp. 963-965.

[12] Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. Am J Obstet Gynecol, 206 (2012), pp. 376-386.

[13] The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth Society for Maternal-Fetal Medicine (SMFM) Publications Committee, 2017

clinical benefit. A measurement of clinical benefit directly assesses how a patient feels, functions, or survives. Because gestational age at delivery does not directly measure how a neonate feels, functions, or survives, it is considered a surrogate endpoint, but one that we determined to be a reasonably reliable predictor of the clinical benefit for the neonate. In general, two major concerns with surrogate endpoints are (1) it may not be a true predictor of the clinical benefit and (2) it may not provide a quantitative measure of benefit. Thus, approval under this regulation requires that the Applicant study the drug further to verify and describe its clinical benefit. The confirmatory trials must be adequate and well-controlled and be conducted with due diligence. These trials are usually already ongoing at the time of accelerated approval to ensure their timely completion.

For drugs approved under the accelerated approval pathway, the regulations also outline the conditions that may prompt FDA to withdraw approval:

(1) A postmarketing clinical study fails to verify clinical benefit;
(2) The Applicant fails to perform the required postmarketing study with due diligence;
(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;
(4) The Applicant fails to adhere to the postmarketing restrictions agreed upon;
(5) The promotional materials are false or misleading; or
(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.
(See 21 CFR 314.530)

1.2.1.2. Substantial Evidence of Effectiveness

For FDA approval, including accelerated approval, a drug must meet the regulatory standard of "substantial evidence" of effectiveness for the intended use and the benefits must outweigh the risks.[14] Traditionally, FDA has interpreted substantial evidence of effectiveness as clinically and statistically significant findings from at least two adequate and well-controlled trials. A single positive trial, even if well-conducted, may have biases or may reflect a chance finding, increasing the risk of concluding that a drug is effective when in fact it is not. The requirement for at least two adequate and well-controlled trials ensures independent substantiation of experimental findings and strengthens a conclusion of effectiveness. Nonetheless, when appropriate, FDA has the authority and flexibility to conclude that there is substantial evidence of effectiveness based on a single adequate and well-controlled trial. Conclusions based on two high-quality trials will generally be more secure than those based on a single comparably persuasive study. Therefore, reliance on a single trial is generally limited to situations where a second trial is not feasible (e.g., rare diseases) or ethical (e.g., when one trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a serious disease). Characteristics of a single trial that could support a conclusion of substantial evidence of effectiveness include a large multicenter trial with consistency across study subsets, multiple studies within a single study, multiple endpoints involving different events, and statistically very persuasive findings.

[14] FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998.

1.3. Trial 002 and Approval of Makena

1.3.1. Trial 002

In 1999, the National Institute of Child Health and Human Development initiated a multicenter, double-blind, randomized, placebo-controlled clinical trial through its Maternal-Fetal Medicine Units Network to evaluate the efficacy and safety of HPC injection. The study randomized pregnant women with at least one documented prior sPTB of a singleton fetus to either HPC or placebo in a 2:1 ratio. Eligible subjects were at a gestational age between 16^0 weeks and 20^6 weeks at randomization. Pregnancies with multifetal gestation and known major fetal anomaly (as documented by an ultrasound examination after 14 weeks gestation) were excluded. Women who had progesterone treatment prior to randomization were also excluded, as were women experiencing maternal medical complications (e.g., hypertension requiring medication, seizure disorder) or obstetrical complications. The subjects received HPC 250 mg weekly injections or placebo vehicle beginning on the day of randomization through 36^6 weeks gestation or delivery, whichever occurred first. The primary efficacy endpoint was the proportion of delivery prior to 37^0 weeks gestation in the intent-to-treat (ITT) population.

A total of 463 women were randomized to receive either HPC (N=310) or placebo (N= 153). The two study groups were similar with respect to age, race or ethnicity, body mass index prior to pregnancy, marital status, education, and substance use during pregnancy; 59% of the subjects were African American. Of the 463 women randomized, 418 (90.3%) completed dosing through 36^6 weeks or birth, including 279 (90.0%) in the HPC group and 139 (90.8%) in the placebo group. The efficacy results for gestational age at delivery are shown in Table 1.

Table 1: Proportion of Subjects in Each Treatment Arm Who Delivered at <37 Weeks, <35 Weeks, and <32 Weeks Gestational Age (Trial 002)

Delivery outcome	HPC* %	Placebo %	Treatment Difference and 95% Confidence Interval**
<37 weeks	37.1	54.9	-17.8% [-28.0%. -7.4%]
<35 weeks	21.3	30.7	-9.4% [-19.0%, -0.4%]
<32 weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]

*Four HPC-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact (184, 220, 343, and 364 weeks).
**Adjusted for interim analysis.
Source: FDA-approved Makena prescribing information

Pregnancy after the time of randomization was maintained for an average of six days longer in the HPC group (131 vs. 125 days), with the mean gestational age at delivery being one week greater (36.2 vs. 35.2 weeks for HPC and placebo subjects, respectively).

Makena's effect on reducing recurrent preterm birth appeared independent of race, number of previous preterm deliveries, and gestational age of previous preterm birth. The proportion of women who delivered at <37 weeks in the placebo group appeared notably high (55%). See Table 2.

Table 2: Percentages of Subjects With Delivery <37 Weeks by Gestational Age of Previous Birth, Race, and Number of Previous Preterm Deliveries (Trial 002)

Characteristics	HPC n/N (%)	Placebo n/N (%)
Previous sPTB by gestational age		
20^0 - <28^0 weeks	32/82 (40.2%)	19/29 (65.5%)
28^0 - <32^0 weeks	21/66 (31.8%)	17/30 (56.7%)
32^0 - <35^0 weeks	30/84 (35.7%)	27/55 (49.1%)
35^0 - <37^0 weeks	31/78 (39.7%)	21/39 (53.8%)
Race		
Black	66/183 (36.1%)	47/90 (52.2%)
Non-black	49/127 (38.6%)	37/63 (58.7%)
Number of previous PTB		
1 prior PTB	74/224 (33.0%)	40/90 (44.4%)
2 prior PTB	27/56 (48.2%)	31/46 (67.4%)
≥3 prior PTB	14/30 (46.7%)	13/17 (76.5%)

Data based on ITT Population (all randomized subjects). The 4 subjects with missing outcome data were classified as having a preterm birth <37^0 weeks (i.e., treatment failure).
Abbreviations: n = number of subjects in a specific category who delivered study pregnancy at <37^0 weeks gestation; N = total number of subjects overall in a specific category
Source: Table 11-4, Final Report for Study 17-CT-002

This trial was terminated by the Data and Safety Monitoring Board prior to enrolling the planned 500 subjects because the pre-specified stopping criteria for the primary efficacy endpoint of delivery < 37 weeks gestation were attained at an interim analysis.

Data on the individual components that subsequently constituted the neonatal composite index were prospectively collected. The analysis of a composite index, developed by the Applicant at the request of the FDA, was conducted post-hoc, after the initial submission of the NDA in 2006, to evaluate adverse outcomes in live births and as supportive evidence of Makena's benefit on reducing the risk of recurrent preterm delivery. The neonatal composite index was based on the number of neonates who died or experienced respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis, or necrotizing enterocolitis (NEC). Although the proportion of neonates who experienced one or more events was numerically lower in the Makena arm than placebo (12% vs. 17%, P=0.7), the number of adverse outcomes was limited and the difference between arms was not statistically significant. The same neonatal composite index was prospectively evaluated as a coprimary endpoint for Trial 003.

1.3.2. Approval of Makena

Following the publication of results from Trial 002 in 2003, Adeza Biomedical[15] obtained access to the NICHD data and began discussion with the FDA regarding submission of a new drug application (NDA) based on Trial 002.

[15] The NDA ownership was subsequently transferred to several entities, including Hologics, KV Pharmaceutical, Lumara Health, Inc., and AMAG. Hereafter, all are referred to as "the Applicant."

During the first review cycle of the NDA, FDA brought Makena to the Advisory Committee on Reproductive Health Drugs (the Committee) for discussion in August 2006. As noted previously, the primary endpoint of Trial 002 was the rate of PTB prior to 37 weeks gestation; however, 16 of 21 Committee members found that PTB <37 weeks was not an adequate surrogate for reduction in fetal/neonatal mortality and neonatal morbidity. Thirteen of the 21 Committee members voted that PTB <35 weeks was an adequate surrogate, and 12 members voted that the data submitted provided substantial evidence that Makena prevents PTB at <35 weeks. However, the Committee overwhelmingly voted (19 no, 2 yes) that the submitted data did not provide substantial evidence of benefit on neonatal mortality or morbidity, based on the results of the neonatal morbidity/mortality composite index.[16]

FDA did not approve the application in 2006.[17] The primary deficiency was that efficacy based on a single trial that relied on a surrogate endpoint (deemed by most Committee members to be an inadequate surrogate of neonatal morbidity and mortality) was not sufficiently robust to support approval. 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. To address this deficiency, the FDA recommended that the Applicant submit a draft protocol and evidence of the feasibility of conducting an additional adequate and well-controlled trial to verify and describe further the clinical benefit of preventing recurrent PTB, as stated under the accelerated approval regulations.

In the second review cycle that began in 2008, the Applicant provided a protocol for a postapproval confirmatory trial for an accelerated approval, and another protocol for an infant follow-up study. During the review, the American College of Obstetricians and Gynecologists (ACOG) issued a revised Committee Opinion on Use of Progesterone to Reduce Preterm Birth.[18] In contrast to the 2003 Committee Opinion,[19] which stated:

> *"When progesterone is used, it is important to restrict its use to only women with a documented history of previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug."*

The 2008 Committee Opinion stated:

> *"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."*

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[16] Cross-Discipline Team Leader Review dated February 3, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000CrossR.pdf

[17] Approvable Letter, dated October 20, 2006.

[18] ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 419, October 2008.

[19] ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 291, November 2003.

FDA interpreted this new Opinion as establishing a *de facto* standard of care for women with a previous spontaneous PTB. FDA was concerned that this opinion could adversely impact recruitment of subjects into a placebo-controlled trial. Although the trial protocol (including study design, planned sample size, primary and secondary objectives, and proposed analysis plan) was deemed satisfactory, FDA declined to approve the application again in 2009, requesting that the Applicant provide adequate documentation that it would be feasible to conduct and successfully complete the confirmatory trial. FDA stated that "adequate assurance of feasibility of [the confirmatory trial] can only be addressed by actual initiation of the trial." Further, noting that one clinical site (University of Alabama at Birmingham) contributed 27% of the total number of subjects in Trial 002, FDA requested that the confirmatory trial include at least 15 investigational sites (US and non-US), with no single site enrolling more than 15% of the total number of subjects. Also, at least 10% of the total randomized subjects would need to be from US and Canadian sites.[20]

By the time of the third review cycle for Makena, multiple clinical studies evaluating the consequences of "late preterm birth" (births between 34^0 to 36^6 weeks gestation) had emerged to show that late-preterm infants are less physiologically and metabolically mature than term infants and are thus at higher risk of morbidity and mortality than term infants.[21,22,23,24] This new evidence led the FDA to determine that PTB < 37 weeks was an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit. This determination also led the FDA to reconsider data from Trial 002. For the endpoint of delivery at < 37 weeks, the results were deemed compelling (with a sizeable treatment difference between groups and a p value of 0.0004) and not driven by data obtained from the University of Alabama at Birmingham alone. FDA concluded that evidence in Trial 002 was sufficient to support Makena improving the proportion of PTB occurring at < 37 weeks under accelerated approval.[16] Furthermore, the Applicant initiated the confirmatory trial in 2009 and provided documentation supporting that this trial could be conducted and completed.

1.4. Hydroxyprogesterone and Progesterone Usage

1.4.1. Use During Pregnancy

FDA conducted a Sentinel query to assess the use of HPC or progesterone during the second or third trimester among pregnancies with live-birth deliveries and their potential reasons for use to characterize the context of real-world use of HPC, the drug substance in Makena. The query captured all pregnancies ending in live birth in the Sentinel Distributed Database, including

[20] Cross-Discipline Team Leader Review dated January 23, 2009 and Complete Response letter dated January 23, 2009.

[21] Engle WA, et al. Committee on Fetus and Newborn, American Academy of Pediatrics. Pediatrics 2007;120(6):1390-401.

[22] McIntire DD, et al. Neonatal mortality and morbidity rates in late preterm births compared with births at term. Obstet Gynecol 2008;111(1):35-41.

[23] Martin JA, et al. Born a bit too early: recent trends in late preterm birth. NCHS Data Brief 2009;Nov(4):1-8.

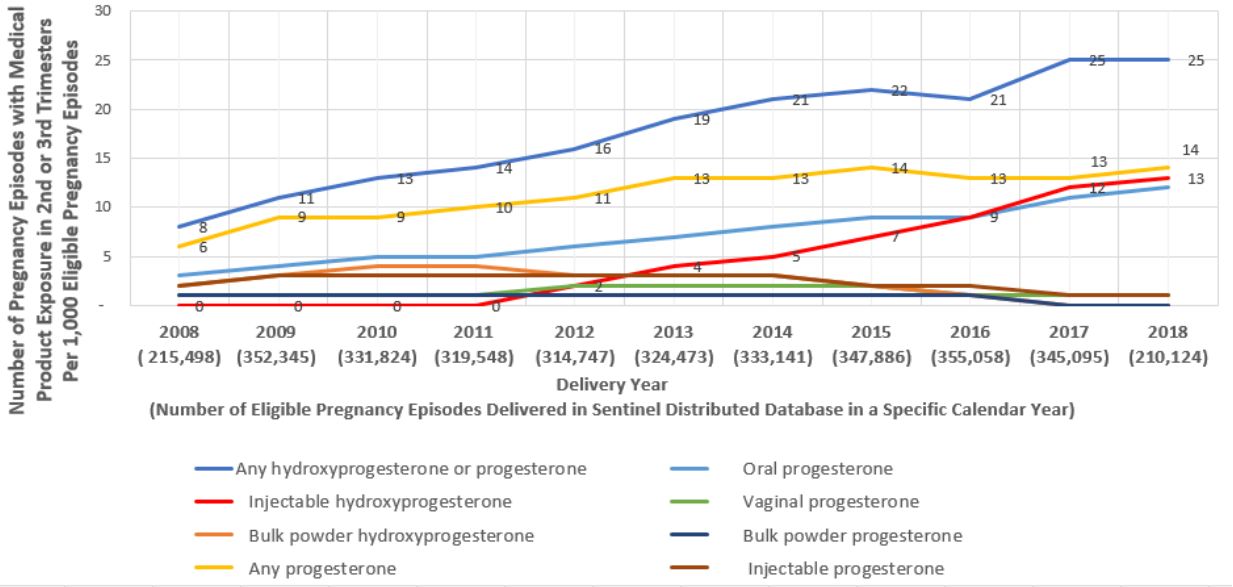
[24] Consortium on Safe Labor, Hibbard JU et al. Respiratory morbidity in late preterm birth. JAMA 2010;304(4):419-25.

singleton and multiple gestations. Progesterone use was included in this analysis because clinical guidelines recommend progesterone treatment for women at risk for preterm delivery.

Methods: This query was conducted in FDA's Sentinel Distributed Database (SDD) using electronic health care data from a distributed network of 15 data partners. The data were primarily comprised of patients with employer-based health care benefits and a small proportion of Medicaid recipients. The study population included women with a live-birth pregnancy (from the current pregnancy) between January 2008 and April 2019 (study period). The exposures of interest were HPC (injectable or bulk powder forms) and progesterone (injectable, oral, vaginal and bulk powder forms). Medical conditions related to potential reasons for HPC or progesterone use were identified by narrow and broad definitions using ICD-9 and ICD-10 diagnosis codes. Included under the narrow definition were diagnosis codes for: (1) history of preterm delivery recorded anytime until one day prior to the start of the current pregnancy, and (2) preterm labor or cervical shortening recorded during the current pregnancy. The broad definition expanded the narrow definition to add the diagnosis for (1) history of preterm labor or cervical shortening recorded anytime until one day prior to the start of the current pregnancy, and (2) preterm delivery recorded during the current pregnancy. Using the diagnostic codes, we could not determine whether the history of preterm delivery was spontaneous or indicated, or whether multiple gestations or other risk factors were present around the time of current pregnancy.

Results: We identified a total of 3,451,121 live-birth pregnancies (from 2,912,911 women) between 2008 and 2019 in FDA's SDD. Note that this number is not a total or annual number of live births in the U.S. Of these, 16,535 pregnancies (5 per 1,000 pregnancies) used injectable HPC during their second or third trimesters and 7,917 used bulk powder HPC (2 per 1,000 pregnancies). In addition, 40,144 (11 per 1,000 pregnancies) pregnancies were exposed to progesterone during the second or third trimesters. In total, approximately 18 per 1,000 pregnancies were exposed to HPC or progesterone during their second or third trimester. The number of exposed pregnancies in each year increased over the study period; the overall the number of exposed pregnancies is modest compared to total pregnancies. The use of HPC or progesterone remains low among pregnancies having a related medical condition, including history of preterm delivery (15%) (Table 3).

Figure 1: Hydroxyprogesterone or Progesterone Use in 2nd or 3rd Trimesters Among 3,449,739, Live-Birth Pregnancy Episodes With Live-Birth Deliveries in the Sentinel Distributed Database Between January 1, 2008, and December 31, 2018, by Delivery Year[1]



[1] Data from 2019 was incomplete and excluded from the figure

Table 3: Proportion of Total Pregnancy Episodes With Related Conditions and With Any Prevalent Hydroxyprogesterone or Progesterone Use During 2nd or 3rd Trimesters Among Women With Live-Birth Deliveries in Sentinel Distributed Database Between January 1, 2008, and April 30, 2019

Related Conditions	Total Number of Pregnancy Episodes with the Related Condition of Interest	Pregnancy Episodes (%) with the Related Conditions of Interest and Any Hydroxyprogesterone or Progesterone Use in the 2nd or 3rd Trimesters
	N	N (%)
Narrow Definition of Related Conditions		
History of preterm delivery[1]	82,255	12,416 (15%)
Preterm labor during the current pregnancy[2]	509,832	29,252 (6%)
Cervical shortening during the current pregnancy[2]	64,557	16,448 (26%)
Any of the narrowly defined conditions above	591,908	40,185 (7%)
Broad Definition of Related Conditions		
History of preterm labor or delivery[1] OR recorded personal history of preterm labor[2]	307,269	34,337 (11%)
Preterm labor or delivery during the current pregnancy[2]	657,719	34,809 (5%)
History of cervical shortening or cervical shortening during the current pregnancy[3]	73,899	17,857 (24%)
Any of the broadly defined conditions above[3]	860,043	51,152 (6%)

[1]Evaluated throughout available enrollment history until the day before pregnancy start date.
[2]Evaluated the day after pregnancy start date until 301 days after pregnancy start date.
[3]Evaluated throughout available enrollment history until 301 days after pregnancy start date.

Among pregnancies exposed to HPC or progesterone, 65% and 83% had at least one related medical condition by narrow and broad definitions, respectively (Table 4), most commonly preterm labor recorded during the current pregnancy. For the pregnancies exposed to injectable HPC, 73% and 98% had at least one narrowly or broadly defined medical condition, respectively.

Table 4: Proportion of Pregnancy Episodes with Related Conditions and Use of Hydroxyprogesterone or Progesterone During 2nd or 3rd Trimesters Among Women With Live-Birth Deliveries in Sentinel Distributed Database Between January 1, 2008, and April 30, 2019

	Any hydroxyprogesterone or progesterone		Hydroxyprogesterone				Progesterone							
			Injectable		Bulk powder		Any		Injectable		Oral		Vaginal	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Number of Pregnancy Episodes with Medical Product Exposure[1]	61,615		16,535		7,917		40,144		8,561		25,471		5,234	
Narrow Definition of Related Conditions														
History of preterm delivery[2]	12,416	20%	6,443	39%	2,568	32%	4,449	11%	1,646	19%	2,365	9%	318	6%
Preterm labor during the current pregnancy[3]	29,252	47%	8,137	49%	5,050	64%	17,969	45%	4,734	55%	10,337	41%	2,515	48%
Cervical shortening during the current pregnancy[3]	16,448	27%	3,228	20%	1,603	20%	12,650	32%	1,694	20%	8,404	33%	2,349	45%
Any of the narrowly defined conditions above[3]	40,185	65%	12,060	73%	6,240	79%	24,351	61%	5,717	67%	14,638	57%	3,499	67%
Broad Definition of Related Conditions														
History of preterm labor or delivery[2] OR recorded personal history of preterm labor during the current pregnancy[3]	34,337	56%	15,696	95%	6,387	81%	14,875	37%	5,381	63%	7,902	31%	1,285	25%
Preterm labor or delivery during the current pregnancy[3]	34,809	56%	8,861	54%	5,811	73%	22,256	55%	5,710	67%	12,875	51%	3,226	62%
History of cervical shortening or cervical shortening during the current pregnancy[4]	17,857	29%	3,982	24%	1,816	23%	13,199	33%	1,840	21%	8,745	34%	2,396	46%
Any of the broadly defined conditions above[4]	51,152	83%	16,240	98%	7,576	96%	30,268	75%	7,344	86%	18,109	71%	4,155	79%

[1] Numbers on the top row are not exclusive because a pregancy could use more than one medicaton of interest
[2] Evaluated throughout available enrollment history until the day before pregnancy start date.
[3] Evaluated the day after pregnancy start date until 301 days after pregnancy start date.
[4] Evaluated throughout available enrollment history until 301 days after pregnancy start date.

We note several study limitations. First, this analysis did not examine the timing of the related medical conditions relative to the use of HPC or progesterone. Therefore, we interpret the presence of the related medical conditions as possible reasons for use. It should be noted that this analysis captured all live-birth pregnancies in the Sentinel Distributed Database. However, we could not determine whether the recorded diagnosis for a history of preterm delivery was spontaneous or indicated, nor did we examine whether the current pregnancy was singleton or multiple gestation. Therefore, HPC exposed pregnancies may not entirely reflect the approved obstetrical indication of HPC. Second, given that women in the SDD were covered primarily by commercial insurance health plans, our findings may have limited generalizability to women without commercial health insurance. Third, we only examined HPC or progesterone use among pregnancies ending with live births. Lastly, the exposure could be under-estimated owing to the capture of pharmacy dispensing data and medication claims only (no capture of out of pocket payments). Some pharmacies create their own National Drug Codes (NDCs) for compounded HPC which would not have been captured in the analysis.

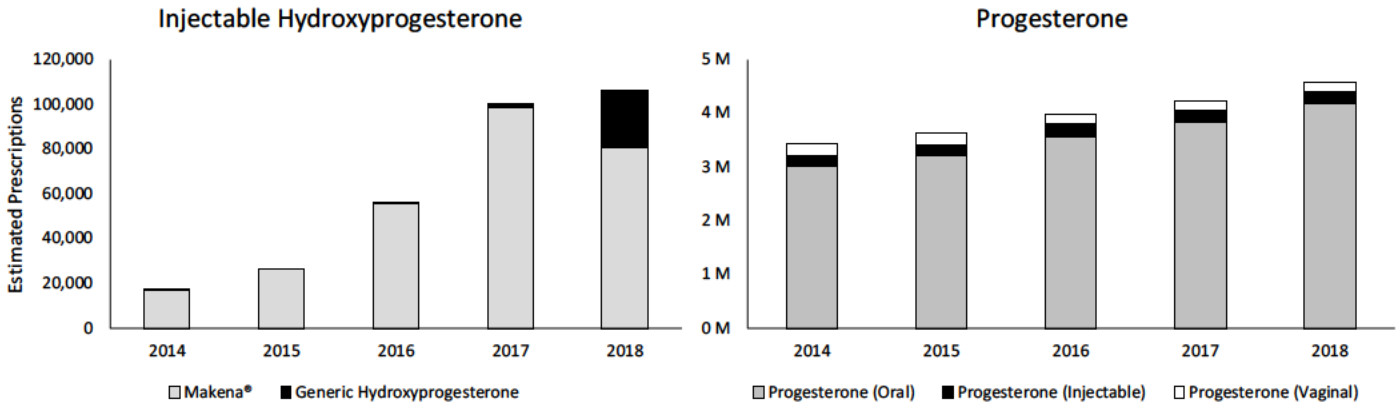
In summary, this analysis found modest use of HPC and progesterone during the second or third trimesters, even among pregnancies with a diagnostic code of a history of preterm delivery (15%). A high percentage (65% and 83% by narrow and broad definitions, respectively) of

pregnancies exposed to HPC or progesterone during their second or third trimester had at least one related medical condition recorded before or during the current pregnancy.

1.4.2. Estimated Use in U.S. Outpatient Settings

FDA analyzed use patterns of injectable HPC and oral, vaginal, or injectable dosage forms of progesterone. Prescriptions for bulk powder forms were excluded due to the inability to determine the final product form and the likelihood that these are underrepresented in the data. We used the Symphony Health PHAST™ Prescription monthly database to estimate the number of prescriptions for injectable HPC and oral, vaginal, or injectable progesterone products dispensed to patients of any age from U.S. outpatient retail or mail order/specialty pharmacies, stratified by molecule and form, annually from 2014 through 2018 (Figure 2). Total prescriptions dispensed for HPC or progesterone products (products with a non-proprietary name of 'hydroxyprogesterone' or 'progesterone') increased 35% from an estimated 3.5 million prescriptions in 2014 to 4.7 million prescriptions in 2018. During this time there was an increase in HPC dispensed prescriptions from an estimated 16,600 prescriptions in 2014 to 106,000 prescriptions in 2018. In 2018, 4.6 million prescriptions (98%) dispensed were for progesterone products.

Figure 2: Estimated Annual Number of Prescriptions Dispensed for Hydroxyprogesterone or Progesterone Products*, Stratified by Molecule and Form, From U.S. Retail or Mail Order/Specialty Pharmacies, Years 2014 to 2018



Prescriptions for bulk powder forms of hydroxyprogesterone and progesterone were not included.
* Products with a non-proprietary name of 'hydroxyprogesterone' or 'progesterone'
Source: Symphony Health PHAST™ Prescription Monthly. Years 2014-2018. Extracted July 2019. File: SH Progesterone and Hydroxyprogesterone Rx 07-29-2019.xlsx

The Symphony Health IDV® Integrated Dataverse was used to obtain the estimated number of 15- to 44-year-old patients who were dispensed prescriptions for injectable HPC and oral, vaginal, or injectable progesterone products from U.S. outpatient retail and mail order/specialty pharmacies, stratified by molecule and form, annually from 2014 through 2018. The total number of patients who were dispensed HPC or progesterone increased by 17% from an estimated 479,000 patients in 2014 to 560,000 patients in 2018 (Table 17 in the Appendix). In 2018, an estimated 42,000 patients (8%) were dispensed prescriptions for HPC, and an estimated 521,000 patients (93%) were dispensed prescriptions for progesterone products. The number of

patients who received a prescription for HPC increased from approximately 8,000 patients in 2014 to 25,500 patients in 2016 and 42,000 patients in 2018.

Table 18 in the Appendix provides the estimated number of drug use mentions of progesterone or HPC products among 15- to 44-year-old women, stratified by molecule and form, associated with a diagnosis as reported on U.S. office-based physician surveys from 2013 through 2018, aggregated. An estimated 50% of HPC use mentions were associated with a diagnosis of supervision of high-risk pregnancy (ICD-10 code O09), of which 78% were associated specifically with supervision of a pregnancy with a history of preterm labor (O09.21, data not shown) and 10% were associated specifically with supervision of elderly primigravida and multigravida (O09.5, data not shown). Twenty percent of HPC use mentions were associated with personal history of preterm labor (Z87.51, data not shown), 13% were associated with encounter for supervision of a normal pregnancy (Z34), and 10% were associated with preterm labor (in the current pregnancy, O60). Among progesterone products, an estimated 42% of progesterone injectable use mentions were associated with supervision of high-risk pregnancy and 41% were associated with female infertility (N97). An estimated 59% of progesterone vaginal use mentions were associated with female infertility.

Table 19 in the Appendix provides the estimated number of drug use mentions among women 15 to 44 years old associated with selected diagnoses as reported on U.S. office-based physician surveys from 2013 through 2018, aggregated. An estimated 42% of office visits with any drug use mentions that were associated with a diagnosis of history of preterm labor (O09.21 or Z87.51) mentioned Makena, and an additional 32% mentioned generic HPC products. Of office visits with drug use mentions that were associated with preterm labor in the current pregnancy, physicians mentioned Makena in 14% of visits. Of office visits associated with cervical shortening, physicians mentioned the use of progesterone products but no other products.

In summary, HPC use increased from 2014 to 2018 with the number of patients treated increasing over the same time period. However, HPC use represents a small proportion of the total use of progesterone in FDA's assessment. The primary use of HPC appeared related to obstetrical diagnoses whereas progesterone was used for both obstetrical and infertility related conditions.

2. Confirmatory Trial—Trial 003

2.1. Development of Trial 003

Please refer to Section 1.3 for a detailed discussion regarding the regulatory history of Makena. After the first non-approval of the NDA in 2006, FDA and the Applicant engaged in discussion regarding a clinical protocol to provide evidence verifying clinical benefit. In 2009, Trial 003 was initiated; the study design mirrored that of Trial 002, except that Trial 003 had coprimary endpoints of delivery prior to 35 weeks and the neonatal morbidity/mortality composite index. When Makena was approved under accelerated approval in 2011, the completion of Trial 003 became a requirement post-approval to verify and describe the clinical benefit of Makena.

Trial 003 was initiated in the United States to ensure at least 10% of subjects would be from the United States and Canada before expanding to Europe. However, after Makena's approval in

2011, enrolling U.S. subjects became increasingly difficult. Additional study sites were subsequently opened in Ukraine and Russia.

2.2. Trial Design

Trial 003 was a multicenter, randomized, double-blind, placebo-controlled clinical trial in women, aged 18 years or older, with a singleton pregnancy, and with a history of a previous singleton spontaneous preterm delivery.

2.2.1. Study Objectives

Primary objectives:

- Determine if treatment with Makena reduces the rate of preterm birth prior to 35^0 weeks of gestation.
- Determine if Makena reduces the rate of neonatal mortality or morbidity.

Secondary objectives:

- Exclude a doubling of the risk of fetal/early infant death, defined as spontaneous abortion/miscarriage (delivery from 16^0 through 19^6 weeks of gestation), early infant death (from minutes after birth until 28 days of life) occurring in livebirths prior to 24 weeks gestation, or stillbirth (antepartum or intrapartum death from 20 weeks gestation through term), in the Makena group compared to the placebo group.
- Determine if Makena reduces the rate of preterm birth prior to 32^0 and 37^0 weeks of gestation, respectively.
- Determine if Makena reduces the rate of stillbirth defined as all stillbirths/fetal deaths/in-utero fetal losses occurring from 20 weeks gestation until term.
- Determine if Makena reduces the rate of neonatal death (from minutes after birth until 28 days life) occurring in livebirths born at 24 weeks gestation or greater.

2.2.2. Trial Design and Conduct

Trial 003 was conducted in the United States, Canada, Russia, Ukraine, Hungary, Spain, Bulgaria, the Czech Republic, and Italy. Eligible subjects were randomized in a 2:1 ratio to receive either Makena or placebo and received weekly injections of study drug from randomization (16^0 through 20^6 weeks of gestation) until 36^6 weeks of gestation or delivery, whichever occurred first.

2.2.3. Eligibility Criteria

Major inclusion criteria:

1. Women aged 18 years or older.
2. Singleton gestation.
3. Estimated gestational age between 16^0 weeks and 20^6 weeks, inclusive, at the time of randomization.
4. Documented history of a previous singleton spontaneous preterm delivery. Spontaneous preterm birth was defined as delivery from 20^0 to 36^6 weeks of gestation following spontaneous preterm labor or preterm premature rupture of membranes (pPROM).

Major exclusion criteria:

1. Multifetal gestation.
2. Known major fetal anomaly or fetal demise;
3. Presence of a uterine anomaly (uterine didelphys or bicornuate uterus)
4. Maternal medical/obstetrical complications or had any significant medical disorder
5. Subjects who received a progestin during the current pregnancy AND met one of the following criteria:
    a. Progestin was administered in the 4 weeks preceding the first dose of study medication.
    b. Subjects received HPC
    c. Progestin was administered by a route other than oral or intra-vaginal.
6. Participation in an antenatal study in which the clinical status or intervention may have influenced gestational age at delivery.
7. Participation in this trial in a previous pregnancy.

2.2.4. Analysis Populations

The Applicant defined the following analysis populations:

- Intent-to-treat (ITT) population: all randomized subjects. Subjects were analyzed by the treatment group to which they were randomized, regardless of the blinded study medication (active or placebo) the subject received.
- Safety population: all subjects who received at least one dose of blinded study medication. Subjects were analyzed by the treatment that they received.
- Liveborn neonatal population: all babies of randomized women in the ITT Population who were liveborn and for whom morbidity/mortality data were available.

2.2.5. Efficacy Endpoints

There were two coprimary endpoints:

- Surrogate endpoint: PTB prior to 35^0 weeks of gestation
    - Scored as a 1 if any of the following events occurred: a delivery occurring from randomization up through 34^6 weeks of gestation, including a miscarriage occurring from 16^0 through 19^6 weeks of gestation, and an elective abortion.
    - Otherwise, scored as a 0.

- Clinical endpoint: Composite neonatal morbidity and mortality index
    - Scored as a 1 if the liveborn neonate had any of the following events occur at any time during the birth hospitalization up through discharge from the neonatal intensive care unit (NICU): neonatal death, grade 3 or 4 intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), or proven sepsis.
    - Otherwise, scored as a 0.

Key secondary endpoints:

- Neonatal death (from minutes after birth until 28 days of life) occurring in livebirths born at 24 weeks or older gestation
- Preterm birth prior to 32^0 weeks of gestation.

- Preterm birth prior to 37^0 weeks of gestation

Preterm birth endpoints were analyzed using the ITT population and neonatal endpoints were analyzed using the liveborn neonatal population.

The study was designed to detect a 30% reduction in PTB $<35^0$ weeks (from 30% to 21%) and 35% reduction (17% to 11%) in the neonatal composite index, based on the findings from Trial 002. An estimated sample size of 1707 provided at least 90% power to detect the hypothesized difference at alpha level 0.05, and approximately 83% power to rule out a doubling of risk of fetal/early infant death (upper bound of the 95% confidence interval of relative risk <2).

2.2.6. Statistical Analysis Methods

2.2.6.1. Primary Analyses

For each of the coprimary efficacy endpoints, the number and percentage of subjects for the event were presented by treatment groups. Statistical significance between Makena and placebo treatments for each endpoint was determined using a Cochran–Mantel–Haenszel test (CMH) stratified by gestational age at randomization (16^0 to 17^6 weeks and 18^0 to 20^6 weeks).

The interaction between treatment and gestational age at the time of randomization was assessed by a logistic regression model of preterm delivery prior to 35^0 weeks of gestation with terms for treatment, gestational age at randomization stratum, and treatment-by-gestational age at randomization stratum interaction. A similar analysis was performed for the neonatal composite index.

2.2.6.2. Exploratory Analyses

After Trial 003 failed to demonstrate efficacy with the coprimary endpoints, the Applicant conducted a series of exploratory subgroup analyses to understand the potential reasons for the negative findings in Trial 003. The Applicant analyzed the coprimary efficacy endpoints by subgroups defined in Table 5 for the overall study population in Trial 003 and its U.S. subgroup.

Table 5: Trial 003 Subgroup Categories

Subgroup	Categories
Geographic region	U.S., Non-U.S.
Gestational age at randomization	16^0-17^6 weeks, 18^0-20^6 weeks
Gestational age at qualifying delivery*	20^0-<28^0 weeks, 28^0-<32^0 weeks, 32^0-<35^0 weeks, 35^0-<37^0 Weeks
Gestational age at earliest prior PTBs	0-<20^0, 20^0-<28^0, 28^0-<32^0, 32^0-<35^0, 35^0-<37^0
Number of previous PTBs	1, 2, ≥3
Cervical length at randomization	<25 mm ≥25 mm
BMI before pregnancy (kg/m^2)	<18.5, 18.5 - <25, 25-<30, ≥30
Any substance use during pregnancy	Yes, No
Smoking	Yes, No
Alcohol	Yes, No
Illicit drugs	Yes, No
Race	Non-Hispanic black, non-Hispanic non-black
Ethnicity	Hispanic, non-Hispanic
Years of education	≤12, >12

* Qualifying delivery is the most recent preterm delivery.

Generally, FDA does not support unplanned exploratory subgroups analyses, especially when the overall result does not demonstrate efficacy. There are multiple reasons to not consider exploratory subgroup analyses to support establishing efficacy when treatment benefit in the overall population is not significant (FDA draft guidance on multiple endpoints in clinical trials,[25] E17 General Principles for Planning and Design of Multi-Regional Clinical Trials,[26] and E9 Statistical Principles for Clinical Trials[27]). The major statistical reason is inflation of type I error, that is, the heightened probability of incorrectly concluding treatment benefit. When such post-hoc subgroup analyses are used to search for evidence of benefit, there is a high probability that any observed favorable subgroup results are due to chance alone. Therefore, FDA considers exploratory analyses hypothesis-generating.

2.3. Trial Results

2.3.1. Subject Disposition

A total of 1708 subjects were randomized to either Makena (n=1130) or placebo (n=578). Almost all (99%) subjects completed the study and completed treatment (93%). Russia, Ukraine and the U.S. were the three highest enrolling countries, randomizing 621 (36%), 420 (25%) and 391 (23%) subjects, respectively, followed by Hungary, Spain, Bulgaria, Canada, the Czech Republic, and Italy, which each had less than 100 subjects (16% of all subjects).

[25] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf

[26] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM519603.pdf

[27] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf

Table 6: Trial 003 Subject Disposition

	Makena, N(%)	Placebo, N(%)
Subjects randomized (ITT population)	1130	578
Subjects who received at least one dose of study drug (safety population)	1128 (99.8)	578 (100)
Liveborn infant with morbidity data available (liveborn neonatal population)	1091 (96.5)	560 (96.9)
Subjects withdrawing from study	18 (1.6)	6 (1.0)
Subjects discontinuing study drug	80 (7.1)	43 (7.4)

Source: Applicant's study report

2.3.2. Demographics and Baseline Characteristics

The Makena and placebo groups were comparable across all demographic and baseline characteristics. The mean age was 30 years and pre-pregnancy BMI was 24.4 kg/m^2. Of the randomized subjects, 88% were white, 7% were black, and the rest included Native Hawaiian/Pacific Islanders, Asian and American Indian or Alaska native, mixed race and other. Almost all black subjects were from the United States. Approximately 10% of women were never married or divorced/widowed/separated, approximately 8% smoked, approximately 3% consumed alcohol, and 1.3% used illicit drugs.

The treatment groups were also well balanced with respect to obstetrical characteristics in the current and previous pregnancies. Slightly more subjects initiated study drug between 18^0 to 20^6 weeks of gestation (56% Makena, 58% placebo) than between 16^0 to17^6 weeks (44% Makena, 41% placebo). Overall, the median estimated gestational age at randomization was 18.1 weeks for the Makena group and 18.4 weeks for the placebo group.

2.3.3. Primary Efficacy Results

The neonatal composite index was scored as positive (value of 1) in 5.4% and 5.2% of liveborn infants in the Makena and placebo groups, respectively, with a difference of 0.2% (95% CI: -2.0%, 2.5%) as shown in Table 7. The rate of preterm births prior to 35^0 weeks gestation was 11.0% and 11.5% in the Makena and placebo groups, respectively, with a difference of -0.6% (95% CI: -3.8%, 2.6%). The treatment effect of Makena compared to placebo was not statistically significant for both coprimary endpoints.

The rates of preterm birth prior to 32 weeks gestation and prior to 37 weeks gestation were also not different between the Makena and placebo groups.

Table 7: Trial 003 Efficacy Results

Efficacy Endpoints	Makena (N=1130)	Placebo (N=578)	Difference (95% CI)*	P-value*
Neonatal composite index	5.4% (59/1091)	5.2% (29/560)	0.2% (-2.0, 2.5)	0.84
PTB <35^0 weeks (%)	11.0% (122/1113)	11.5% (66/574)	-0.6% (-3.8, 2.6)	0.72
PTB <32^0 weeks (%)	4.8% (54/1116)	5.2% (30/574)	-0.4% (-2.8, 1.7)	
PTB <37^0 weeks (%)	23.1% (257/1112)	21.9% (125/572)	1.3% (-3.0, 5.4)	

Abbreviations: N: number of randomized subjects, CI: confidence interval, PTB: preterm birth
*Difference, 95% CI and P-value were from CMH method stratified by gestational age at randomization
Source: FDA analysis

2.3.4. Exploratory Analyses Results

Applicant's subgroup analysis results: The Applicant's results for the subgroup analyses of the coprimary efficacy endpoints are presented in Table 21 and Table 22 in the Appendix.

FDA's subgroup analysis results:
FDA reviewed all results and conducted subgroup analyses by region and race because these subgroups are evaluated by FDA routinely. Also, they are important subgroups that differentiate the study populations between Trial 003 and Trial 002.

1. By geographic region (U.S. versus non-U.S.)

The Applicant asserts that the overall lower than expected rate of study outcomes substantially limited the ability of Trial 003 to assess the effects of Makena on these outcomes. The Applicant also believes that the lower rate of PTB in Trial 003 could be accounted for by significant geographic differences in PTB rates, where Russia and Ukraine enrolled more subjects but had much lower rates than the United States.

Generally, FDA does not support unplanned subgroup analyses but performed exploratory analysis by region (U.S. versus non-U.S.) to examine whether there were potentially important differences in treatment benefit between U.S. and non-U.S. patients in Trial 003.

For Trial 003, FDA calculated the rate difference between the Makena and placebo groups for each coprimary endpoint, and also the secondary endpoints of birth prior to 32 and 37 weeks gestation, using two methodologies, a stratified CMH method and shrinkage estimation through Bayesian modeling. Traditional subgroup analysis evaluates a particular subgroup category independently from other subgroup categories and relies only on the data from the subjects in that particular category, whereas the Bayesian shrinkage estimation analysis evaluates all subgroup categories jointly. In any trial, some subgroups will perform well, and others will perform poorly. The traditional subgroup analysis is likely to have an increase in the overall error of the estimates compared with the shrinkage analysis, which borrows strength across subgroups.

In the U.S. subgroup of Trial 003, both the neonatal composite index and preterm birth prior to 35 weeks endpoints showed no evidence of a treatment effect using stratified CMH and shrinkage estimation. Although the point estimates of -2.2%, based on the CMH analytic method, for the coprimary endpoints in the U.S. subgroup are in the direction of a beneficial treatment effect, the 95% confidence intervals around these point estimates include 0, indicating

no evidence of effect even in these exploratory subgroup analyses. Similarly, no evidence of a treatment effect was seen for the endpoints of delivery < 37 weeks or < 32 weeks. In addition, the interaction between treatment and region for each coprimary endpoint was assessed by a logistic regression model with treatment, region and treatment-by-region interaction; no significant interaction effect was noted. This Trial 003 subgroup analysis did not show that Makena had a favorable treatment effect compared to placebo for either coprimary endpoints in either the U.S. or non-U.S. region (see Table 8). The lack of evidence of an interaction between region and treatment and the lack of evidence of a treatment effect within the U.S. subgroup in Trial 003 does not provide support for regional differences explaining the differences in results between Trial 002 and 003.

Table 8: Trial 003 Results of Efficacy Endpoints by Region (U.S. vs. non-U.S.)

			Difference (95%CI) Makena vs. Placebo	
	Makena (N=1130)	**Placebo (N = 578)**	**Stratified CMH**	**Shrinkage Estimation**
Neonatal composite index	(N=1091)	(N=560)		
U.S.	7.1% (18/252)	9.5% (12/126)	-2.2% (-8.3, 3.9)	-0.2% (-4.9, 2.8)
Non-U.S.	4.9% (41/839)	3.9% (17/434)	1.0% (-1.4, 3.3)	0.6% (-1.6, 2.8)
Preterm birth <35^0 weeks gestation	(N=1113)	(N=574)		
U.S.	15.6% (40/256)	17.6% (23/131)	-2.2% (-10.1, 5.7)	-0.8% (-6.0, 3.5)
Non-U.S.	9.6% (82/857)	9.7% (43/443)	-0.2% (-3.6, 3.2)	0.4% (-3.6, 2.8)
Preterm birth <32^0 weeks gestation	(N=1116)	(N=574)		
U.S.	5.5% (14/256)	9.2% (12/131)	-3.9% (-9.6, 1.7)	-0.6% (-8.4, 3.8)
Non-U.S.	4.7% (40/860)	4.1% (18/443)	0.6% (-1.7, 2.9)	0.5% (-1.8, 2.8)
Preterm birth <37^0 weeks gestation	(N=1112)	(N=572)		
U.S.	33.2% (85/256)	28.2% (37/131)	4.7% (-5.0, 14.3)	1.8% (-3.6, 9.0)
Non-U.S.	20.1% (172/856)	20.0 % (88/441)	0.2% (-4.4, 4.8)	0.9% (-3.5, 5.2)

Source: FDA analysis

2. By race (black/African American vs. non-black/African American)

FDA conducted a subgroup analysis by race (black and non-black) for Trial 003. This race subgroup analysis did not provide evidence that Makena had a treatment effect on either coprimary efficacy endpoints in the black or non-black subgroups.

Table 9: Trial 003 Results of Coprimary Efficacy Endpoints by Race*

	Makena (N=1130)	Placebo (N=578)	Difference (95%CI)
Neonatal composite index			
Black/African American	8.7% (6/69)	7.5% (3/40)	0.8% (-9.9,11.5)
Non-black/African American	5.2% (53/1022)	5.0% (26/520)	0.2% (-2.1, 2.5)
PTB <35^0 weeks gestation			
Black/African American	23.6% (17/72)	19.5% (8/41)	3.0% (-12.5, 18.5)
Non-black/African American	10.1% (105/1041)	10.9% (58/533)	-0.8% (-4.1, 2.4)

*This is based on the entire Trial 003 study population
Source: FDA analysis

Considering the Applicant's and FDA's subgroup analyses results, Makena did not demonstrate any favorable effect (positive finding with nominal statistical significance) over placebo in the key efficacy endpoints in any of the evaluated subgroups.

2.4. Comparisons Between Trial 003 and Trial 002

FDA does not generally support cross-study comparisons to draw efficacy conclusions. Both Trials 003 and 002 were well-controlled and well-conducted, such that each should provide evidence of efficacy on its own merit. Nevertheless, we explored the potential for significant differences in key aspects between Trials 003 and 002 that might clarify their divergent results.

Study design:
Trials 002 and 003 were nearly identical in design. However, trial 002 was conducted entirely in the United States between 1999 to 2002 with preterm birth <37 weeks as the primary efficacy endpoint. Trial 003 was a multinational trial conducted between 2009 to 2018 with coprimary endpoints of a neonatal composite index and preterm birth <35 weeks and was approximately 3.5 times larger than Trial 002. Trial 003 was powered to detect the treatment difference in the coprimary endpoints based on the effect size observed in Trial 002.

Study populations and trial outcomes:
Trial 003 had the following notable differences compared to Trial 002:

Table 10: Comparisons of Selected Characteristics Between Trial 003 and Trial 002

	Trial 003 Overall (N=1708)	Trial 003 U.S. Subgroup (N=391)	Trial 002 (N=463)
Demographics			
Black race	7%	29%	59%
Single or without a partner	10%	31%	50%
Risk factors			
Use of substance* during pregnancy	10%	28%	26%**
Gestational age of qualifying delivery (weeks)	32	33	31
History of more than one previous PTB	15%	27%	28%/41%***
Rate PTB <35 weeks in placebo group+	12%	18%	30%
Rate PTB <37 weeks in placebo group+	22%	28%	55%

*Including tobacco, alcohol, illicit drugs
**Trial 002 collected information on substance use prior to the study pregnancy and not during the pregnancy; 26% is expected to be the higher end of the estimate because it assumes that all women who used substance prior to the pregnancy continued substance use after becoming pregnant.
***HPC – 28%; Placebo – 41%
+It is assumed that the rate in the placebo group approximates that of the contemporaneous intended population

The overall study population of Trial 003 appeared to be at lower risk for factors that might affect the risk of PTB. The 003-U.S. subgroup, however, was more similar to the Trial 002 study population (see Table 10). Yet, unlike Trial 002, there was no consistent evidence of benefit of Makena over placebo in the U.S. subgroup of Trial 003 (see Table 8). As noted above, no statistically significant interaction was seen between treatment and region in Trial 003.

In its briefing document, the Applicant presented post-hoc efficacy analyses exploring a potential relationship between efficacy and the proportion of subjects in a trial with more than one of 5 selective risk factors (history of > 1 prior PTB, black race, substance use in pregnancy, ≤ 12 years of education, unmarried with no partner). The Applicant concluded that Trial 002 had the "highest" risk population (based on the observation that this trial had the highest proportion of study subjects with more than one of these 5 factors), followed by the Trial 003-U.S. subgroup, and then the overall Trial 003 population as being the relatively lowest risk population. The Applicant's analysis showed a trend toward decreasing efficacy in subpopulations the Applicant considered as lower risk. As described earlier, subgroup analyses, especially when conducted post-hoc when the study findings are known, are exploratory and cannot be relied upon for inferences of efficacy.

In addition, it is challenging to identify specific patient subpopulations that may be more responsive to treatment based on the totality of the data. FDA conducted exploratory analyses of Trial 003 using logistic regression models for each coprimary efficacy endpoint with treatment, region, each of the aforementioned 5 risk factors, and its interaction with treatment. These analyses do not provide convincing evidence of efficacy over placebo in any subpopulation and there is no statistically significant interaction between Makena and any of these risk factors. Analogous analyses in the Trial 003-U.S. subgroup produced similar results. In summary, although these risk factors may have an impact on the overall PTB or neonatal composite index rate, there was no evidence in Trial 003 that they impact the treatment effect nor was there consistent convincing evidence of an effect within a specific subpopulation across the two trials. For example, while black women in the U.S. have a higher rate of PTB compared to non-black

women, there was no interaction between race (blacks vs. non-blacks) and treatment effect in Trial 002 or Trial 003, nor was there evidence of an effect in the U.S. subgroup in Trial 003. Similarly, women with > 1 prior PTB are considered at higher risk of having recurrent PTB. However, there was no consistent trend in treatment benefit in this population (see Table 22). In Trial 002, these women had a treatment benefit compared to placebo in reduced rate of delivery < 35 weeks (30% Makena vs. 44% placebo). This benefit was not observed in Trial 003, where women with > 1 PTB randomized to Makena had higher rates of birth < 35 weeks compared to placebo (Trial 003 overall: 26% Makena vs. 19% placebo; Trial 003 US subgroup: 25% Makena vs. 17% placebo). Importantly, Makena is approved in women with a singleton pregnancy and a prior sPTB, and evidence of efficacy must be based on that intended population.

In summary, Trial 003 did not demonstrate a treatment benefit of Makena on reducing the neonatal composite index or the rate of spontaneous preterm birth prior to 35 weeks gestation, nor was there evidence of a treatment benefit on the rate of spontaneous preterm birth prior to 37 weeks or 32 weeks gestation. The significant statistical limitations with exploratory subgroup analyses preclude reliable inference of efficacy based on findings from these analyses.

3. Other Evidence of Effects of Progesterone on Preterm Birth

There are published data on other progesterone formulations that have been investigated for the treatment of PTB. To explore the consistency of results, FDA evaluated pertinent published literature on the effect of progesterone on the risk of PTB from randomized, placebo-controlled trials and recent, larger meta-analyses. In its briefing document, the Applicant references several studies that evaluated 17-HPC.[28,29,30,31,32,33] However, most of these publications are not applicable to Makena's approved use because the studies assessed different clinical outcomes (early recurrent pregnancy losses or the prevention of preterm labor). There are additional publications that evaluated the effect of hydroxyprogesterone caproate intramuscular injections on pregnancy outcomes (with dosing regimens ranging from 500 mg weekly or twice weekly to

[28] Levine L. Habitual abortion. A controlled study of progestational therapy. West J Surg Obstet Gynecol. 1964;72:30-36.

[29] Papiernik-Berkhauser E. Double blind study of an agent to prevent pre-term delivery among women at increased risk. Edition Schering. 1970;Serie IV(fiche 3):65-68.

[30] Johnson JWC, et al. Efficacy of 17α-hydroxyprogesterone caproate in the prevention of premature labor. New Engl J Med. 1975;293:675-680.

[31] Yemini M, et al. Prevention of premature labor by 17 alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 1985:151(5):574-577.

[32] Suvonnakote T. Prevention of pre-term labour with progesterone. J Med Assoc Thailand. 1986;69(10):537-542.

[33] Saghafi N, et al. Efficacy of 17α-hydroxyprogesterone caproate in the prevention of preterm delivery. J Obstet Gynaecol Res. 2011;37(10):1342-1345.

1000 mg weekly); however, they are not discussed further here because of the smaller sample size (80 subjects)[34] or the absence of a concurrent control group.[35,36,37,38]

3.1. Randomized, Placebo-Controlled Clinical Trials

The following six placebo-controlled trials evaluated the treatment effect of progesterone on preterm birth and included pregnant women with a history of a prior sPTB. Note that all these trials evaluated vaginal progesterone.

- The 2003 da Fonseca et al. publication reported findings from a single center trial in Brazil that randomized 142 women with a current singleton pregnancy and a history of previous PTB, cerclage, or uterine malformation in a 1:1 ratio to daily vaginal progesterone insert (100 mg) or placebo.[39] Study drug was applied from 24 to 34 weeks of gestation. The majority (>90%) of women enrolled had previous PTB (mean gestational age at delivery 33 weeks). The rate of PTB <37 weeks was 14% in the progesterone group compared to 29% with placebo (p=0.03).
- The 2007 O'Brien et al. publication reported findings from an international trial that randomized 659 women with a singleton pregnancy and a prior singleton sPTB (delivery between 20^0 and 35^0 weeks of gestation) in a 1:1 ratio to daily vaginal progesterone (8% gel, 90 mg) or placebo starting at 18 to 22^6 weeks until 37 weeks or delivery.[40] Both treatment groups had normal cervical length at randomization (3.7 cm). The primary endpoint, the rate of PTB ≤32 weeks, was not statistically different between the two study groups (10% progesterone vs. 11% placebo, odds ratio: 0.9). Similar results were seen for rate of PTB <37 weeks (42% progesterone vs. 41% placebo, odds ratio: 1.08) and ≤35 weeks (23% progesterone vs. 27% placebo., odds ratio: 0.9). No differences were seen in neonatal outcome (Apgar score, birth weight, NICU admission, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and death).

[34] Hauth JC, et al. The effect of 17 alpha- hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. Am J Obstet Gynecol. 1983;146(2):187-190.

[35] Katz Z, et al. Teratogenicity of progestogens given during the first trimester of pregnancy. Obstet Gynecol. 1985;65(6):775-780.

[36] Rozenberg P, Chauveaud A, Deruelle P, et al. Prevention of preterm delivery after successful tocolysis in preterm labor by 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Am J Obstet Gynecol. 2012;206(3):206 e1-9.

[37] Senat MV, Porcher R, Winer N, et al. Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. Am J Obstet Gynecol. 2013;208(3):194 e1-8.

[38] Winer N, Bretelle F, Senat MV, et al. 17 alpha-hydroxyprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: a randomized controlled trial. Am J Obstet Gynecol. 2015;212(4):485 e481-485 e410.

[39] Da Fonseca EB, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2003 Feb;188(2):419-24

[40] O'Brien JM, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007;30: 687 – 696

- The 2007 Fonseca et al. publication reported findings from an international trial that randomized, in a 1:1 ratio, 250 women with a singleton (N=226) or twin (N=24) pregnancy and a short cervix to daily 200 mg micronized progesterone capsule or placebo.[41] The qualifying risk factor was a cervical length ≤15 mm identified incidentally on routine anatomy ultrasound performed at 20 to 24 weeks of gestation, irrespective of history of PTB; the majority of women (>50%) were nulliparous, approximately a third had no prior PTBs, and 15% had a history of one or more PTB. The study medication was used from 24 to 33^6 weeks of gestation. The primary endpoint was spontaneous delivery <34 weeks. The rate of PTB <34 weeks was 19% in the progesterone group compared to 34% in the placebo group, and this difference was statistically significant (relative risk: 0.56; p=0.007). There was no between-group difference for birthweight, fetal/neonatal death, admission to the NICU or major adverse neonatal outcomes before discharge. Among women with a history of PTB (N=38), progesterone administration did not reduce the incidence of PTB before 34 weeks (95% confidence for relative risk included 1).
- In 2011, Hassan et al. reported results of an international (23 U.S. and 21 non-U.S. sites) trial that randomized 465 asymptomatic women with a singleton pregnancy and a shortened cervix (cervical length between 10 to 20 mm) to daily vaginal progesterone (8% gel, 90 mg) or placebo in a 1:1 ratio.[42] Enrollment was stratified by presence/absence of a history of PTB. Women received study drug from 20 to 23^6 weeks until 36^6 weeks or delivery. The primary endpoint was delivery <33 weeks of gestation. The progesterone group had a significantly lower rate of delivery <33 weeks of gestation compared with the placebo (9% vs. 16%, respectively, p=0.02). In women with a history of PTB (13% of the study population) <35 weeks gestation, vaginal progesterone gel administration was not associated with a reduction in the rate of delivery <33 weeks compared to placebo (relative risk: 0.77, 95% CI 0.29-2.06).
- Published in 2016, the OPPTINUM trial was conducted primarily in the United Kingdom and randomized 1228 women with a singleton pregnancy and at risk for PTB in a 1:1 ratio to daily vaginal progesterone (200 mg) or placebo from 22-24 weeks to 34 weeks of gestation.[43] Eligible women had the following risk factors: previous sPTB at ≤34 weeks gestation, a cervical length ≤25 mm, or a positive fetal fibronectin test combined with other clinical risk factors for preterm birth. Three primary outcomes were defined: fetal death or birth <34 weeks (obstetric), a composite of death, brain injury, or bronchopulmonary dysplasia (neonatal), and a standardized cognitive score at 2 years of age (childhood). After adjusting for multiplicity (i.e. overall type I error for multiple outcomes) progesterone was not found to have a significant benefit on the three primary outcomes. In the subgroup of women with a history of sPTB (N=903), there were no

[41] Fonseca EB, et al. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462-9.

[42] Hassan SS, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2011; 38: 18–31.

[43] Norman JE, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet 2016; 387: 2106–16.

significant differences in the rate of sPTB prior to 34 weeks gestation between the progesterone and placebo groups (odds ratio: 0.82, 95% confidence interval 0.58 to 1.16).

- The 2017 Crowther et al. publication reported findings of the PROGRESS trial, an international trial that randomized 787 women with a singleton or twin pregnancy and a history of sPTB <37 weeks gestation in a 1:1 ratio to vaginal progesterone pessary (100 mg) or placebo.[44] Women were asked to self-administer a vaginal pessary (equivalent to 100 mg vaginal progesterone as active substance) daily from 20 weeks gestation until 34 weeks or delivery. Progesterone treatment had no benefit on the primary outcome of neonatal respiratory distress syndrome (RDS) or other neonatal and maternal morbidities related to preterm birth. Progesterone treatment also had no effect on the incidence of PTB at <37 weeks gestation, a secondary outcome (37% in both treatment groups).

These randomized, placebo-controlled clinical trials enrolled women with varying risk factors for PTB, evaluated different vaginal progesterone doses and formulations, and assessed different outcome measures. Overall, the evidence from these publications does not suggest that vaginal progesterone is beneficial in reducing the risk of preterm birth in women with a history of PTB. Note that FDA has not approved vaginal progesterone for indications related to preterm birth.

3.2. Meta-Analyses

Two published meta-analyses of clinical trials studied the efficacy of progesterone on reducing the risk of PTB: Romero et al. (2018)[45] and Dodd et al. (2013)[46] (Table 11). This section summarizes the meta-analyses, discusses the limitations of each meta-analysis and the regulatory utility of these meta-analyses in supporting the efficacy of Makena. To be consistent with the coprimary endpoint used in Trial 003, we focus on PTB <35 weeks and neonatal composite index.[47]

[44] Crowther et al. Vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS study): A multicentre, randomised, placebo-controlled trial. PLoS Med 2017 Sep 26;14(9):e1002390.

[45] Romero R, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. Am J Obstet Gynecol 2018;218(2): 161-180.

[46] Dodd, Jodie M., et al. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database of Systematic Reviews*7 (2013).

[47] The components of neonatal composite index include neonatal death prior to discharge, grade 3/4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and proven sepsis.

Table 11: Comparison of Study Designs

	Trial 003	Romero et al.	Dodd et al.
Number of subjects (Number of studies)	HPC (Makena): 1,130 Vehicle: 578 (1 RCT)	Progesterone: 498 Placebo: 476 (5 RCTs)	Progesterone: 1,029 Placebo: 869 (11 RCTs)
Study population	Women with singleton birth and history of spontaneous PTB	Women with singleton birth and short cervix	Women with singleton birth and history of spontaneous PTB
Dose	250 mg weekly	90-100 or 200 mg daily	<500 mg weekly or ≥500 mg weekly
Administration	Intramuscular	Intravaginal	Intramuscular, intravaginal, oral, intravenous
Number of subjects from the United States	HPC (Makena): 258 Placebo: 133	Progesterone: 115 Placebo: 117	No U.S. subjects

Source: Reviewer's table

Romero et al. (2018) assessed whether vaginal progesterone prevents PTB and improves perinatal outcomes in women with a singleton gestation and a mid-second trimester, sonographic short cervix (cervical length ≤25 mm). The authors defined a composite neonatal morbidity and mortality[48] outcome. The doses were either 90-100 mg/day or 200 mg/day by intravaginal administration. The authors performed a meta-analysis and estimated the pooled relative risk (RR) with an associated 95% confidence interval (CI). An additional post-hoc subgroup analysis was conducted using an interaction test to examine whether intervention effects differ between the country of enrollment (United States versus other countries). When the heterogeneity of treatment effect was substantial (I^2 >30%), the results were pooled using a random-effect model. Otherwise, a fixed-effect model was used.

The authors' meta-analysis included 5 studies (498 progesterone subjects versus 476 placebo subjects). The meta-analysis showed that vaginal progesterone significantly reduced the risk of PTB <35 weeks (RR [95% CI] = 0.72 [0.58–0.89]) and the risk of composite neonatal morbidity and mortality (RR [95% CI] = 0.59 [0.38–0.91]). A subgroup analysis compared the risk of PTB <33 weeks (PTB <35 weeks and composite neonatal morbidity and mortality not available) between women enrolled from the United States (RR [95% CI] = 0.73 [0.42–1.27]) and women from other countries (RR [95% CI] = 0.59 [0.43–0.80]). The interaction test for subgroup difference did not show significant difference (p = 0.51). Romero et al. included similar proportions of Caucasian subjects (37.2% vs. 39.7%, progesterone and placebo, respectively) and black subjects (36.3% vs. 37.0%, progesterone and placebo, respectively). The subgroup analysis for reduction of PTB among black subjects had a 95% confidence interval that crossed 1 (RR [95% CI] = 0.86 [0.58–1.26]), whereas that of Caucasian subjects had a 95% confidence interval that excluded 1 (RR [95% CI] = 0.45 [0.28–0.73]).

This meta-analysis included subjects with various dose levels (90-100 or 200 mg per day) and the analysis was mainly driven by 3 large studies. In addition, the meta-analysis was underpowered to evaluate interactions. Although both Trial 003 and Romero et al. included

[48] The only difference between neonatal composite index and composite neonatal morbidity and mortality is whether the intraventricular hemorrhages are restricted to grade 3/4 or all grades, respectively.

women with a singleton pregnancy, subjects of Trial 003 had a high prevalence of spontaneous PTB history (100%) with a low prevalence of short cervix (1.6%), while 30% of subjects in the Romero et al. meta-analysis had a history of sPTB history with a high prevalence of short cervix (100%). Romero et al. does not provide information for the approved dose of 250 mg per week administered by intramuscular injection. Because of the difference in study population, formulation, dose levels, and route of administration in Romero et al., the characteristics of the trials in this meta-analysis are not comparable to Trial 003 and the meta-analysis findings do not inform the efficacy of Makena.

Dodd et al. (2013) assessed the benefits and risks of progesterone for the prevention of PTB for women considered to be at increased risk of PTB. This article did not provide a composite neonatal outcome. However, components of the neonatal composite index, except bronchopulmonary dysplasia, were available. The authors performed a meta-analysis and estimated the pooled RR with an associated 95% CI. A random-effect model was employed when the heterogeneity of treatment effect was substantial (I^2 >30%). Otherwise, a fixed-effect model was used.

We focused on the results from the indicated population, women with a singleton pregnancy and history of spontaneous PTB. The authors dichotomized the weekly cumulative dose to either <500 mg or ≥500 mg per week, and the drug was administered through multiple routes: intramuscular, intravaginal, oral, and intravenous. The authors used a total of 11 clinical studies (1,029 progesterone subjects versus 869 placebo subjects) to conduct a meta-analysis in the indicated population. Not all 11 studies were used to analyze the outcomes. Because the result using an outcome of PTB <35 weeks of gestation was not available, we used the authors' outcome of PTB <34 weeks, which concluded that progesterone significantly reduced the risk of PTB (5 studies; RR [95% CI] = 0.31 [0.14–0.69]). The authors reported that neonatal death (6 studies; RR [95% CI] = 0.45 [0.27–0.76]) and necrotizing enterocolitis (3 studies; RR [95% CI] = 0.30 [0.10–0.89]) showed significant risk reduction.

The analysis using 5 studies to estimate the risk of PTB <34 weeks included subjects treated with multiple dose levels and routes of administration. Therefore, the treatment effect of the indicated dose (250 mg) and administration route is unclear. The I^2 from the five studies indicated substantial heterogeneity (I^2 = 56%), raising concerns of whether the trials were too different to be incorporate into the meta-analysis.

Compared to Trial 003, Dodd et al. neither studied the approved dose (250 mg weekly) nor used the intramuscular injection only for administration. Therefore, this meta-analysis is not directly comparable to Trial 003, providing limited inference from the pooled estimate of the treatment effect. None of the five pooled studies that estimated PTB<34 weeks were conducted in the United States; study sites were Iran, Turkey, Brazil, and India.

The two meta-analyses combined different patient populations, formulations, doses and routes of administration. Thus, these studies did not investigate Makena's indicated population, dose, and route of administration and are not comparable to Trial 003. In addition, we do not have access to the patient-level data, individual study protocols and study reports. Because of issues with the

relevancy and the unknown quality of these meta-analyses, the utility of these meta-analyses is limited in addressing the efficacy of Makena.

4. Safety

In Trial 002, total fetal/neonatal deaths included miscarriages (delivery from 16^0 up through 19^6 weeks, stillbirths ([antepartum or intrapartum death] from 20 weeks gestation through term) and neonatal deaths (death of a liveborn born from 20 weeks gestation through term). Of concern was the numerically higher rate of miscarriages and stillbirths in Trial 002. The number of these events were small, and no clear conclusions about the effect of HPC on this safety concern could be made. Trial 003 was powered to exclude a doubling of the risk of fetal/early infant deaths, the primary safety outcome. Fetal/early infant deaths were comprised of the following:

- Spontaneous abortion/miscarriage (delivery from 16^0 up through 19^6 weeks), and
- Stillbirth (antepartum or intrapartum death) from 20 weeks gestation through term, and
- Early fetal death (from minutes after birth until 28 days of life) occurring in livebirths born at < 24 weeks gestation

Fetal and early infant death data from Trial 002 and Trial 003 are juxtaposed in Table 12 and pooled results from both trials are shown in Table 13. Note that the "early fetal death," as defined in 003, was not analyzed as such in Trial 002. The results for "early fetal death" for Trial 002 in Table 12 and Table 13 were analyzed post-hoc for this efficacy supplement. As shown in Table 12, Trial 003 excluded a doubling of the risk of fetal/early infant deaths for Makena (upper bound of 95% was 1.81). When the data from Trial 002 and 003 were pooled, there was no difference in the overall incidence of fetal/early infant deaths with Makena compared to placebo in either trial. There appeared to be a trend toward an increase in stillbirths in both trials; however, the numbers are small, precluding reliable determination of risk. The pooled data from Trials 002 and 003 showed similar results.

Table 12: Fetal and Early Infant Deaths in Trial 002 and Trial 003 (Safety Population)

	Trial 002			Trial 003		
Safety Outcomes N[a], n[b] (%)	**Makena N=310**	**Placebo N=153**	**RR[c] (95% CI)**	**Makena N=1130**	**Placebo N=578**	**RR 95% CI**
Total fetal/early infant deaths[e]	15 (4.8%)	6 (3.9%)	1.22 (0.48, 3.1)	19 (1.7%)	11 (1.9%)	0.87 (0.42, 1.81)
Miscarriages (<20 weeks)	5 (2.4%)	0	N/A	4 (0.5%)	6 (1.3%)	0.32 (0.09, 1.14)
Stillbirths (≥20 weeks)	6 (2.0%)	2 (1.3%)	1.52 (0.31, 7.52)	12 (1.1%)	3 (0.5%)	2.07 (0.59, 7.29)
Early infant deaths	4 (1.3%)	4 (2.6%)	0.49 (0.13, 1.92)	3 (0.3%)	2 (0.4%)	0.73 (0.12, 4.48)

Abbreviations: RR = relative risk, calculated for 17-HPC relative to placebo; CI = confidence interval

[a]N = number of subjects in the Intent to Treat Population in the specified treatment group. The safety population consists of all subjects who received any amount of study medication.

[b]n = number of subjects within a specific category. Percentages are calculated as 100x (n/N)

[c]Relative risk of fetal/early infant death for Makena relative to placebo and is for the Cochran-Mantel-Haenszel test adjusted for gestational age at randomization

[e] Defined as spontaneous abortion/miscarriage, stillbirth, and early fetal death (from minutes after birth until 28 days of life) occurring in livebirths born at <24 weeks gestation

Source: Applicant's analysis (submitted September 25, 2019)

Table 13: Fetal and Early Infant Deaths in Trial 002 and Trial 003 Subjects Combined (Safety Population)

Safety outcomes Na, nb (%)	Trials 002 and 003 Combined		
	Makena N = 1438	Placebo N = 731	RR (95% CI)
Total fetal/neonatal deaths[e]	34 (2.4%)	17 (2.3%)	1.01 (0.57, 1.79)
Miscarriages (<20 weeks)	n = 1075 9 (0.8%)	n = 555 6 (1.1%)	0.73 (0.26, 2.04)
Stillbirths (≥20 weeks)	n = 1429 18 (1.3%)	n = 724 5 (0.7%)	1.86 (0.69, 4.99)
Early infant deaths	n = 1411 7 (0.5%)	n = 720 6 (0.8%)	0.58 (0.20, 1.73)

Source: Applicant's analysis (submitted September 25, 2019)

Birth at 24 weeks is traditionally considered to be the threshold for viability for a preterm neonate, and the Applicant counted only deaths in livebirths born < 24 weeks (early infant death) in the primary safety outcome. FDA, however, considers deaths occurring from minutes after birth until 28 days of life in livebirths born ≥ 20 weeks gestation (neonatal deaths) to be an important safety measurement. These results on fetal and neonatal deaths from Trial 002 and Trial 003 are juxtaposed in Table 14 and pooled results from both trials are shown in Table 15. Overall, these findings are consistent with those above.

Table 14: Fetal and Neonatal Deaths in Trial 002 and Trial 003 (Safety Population)

	Trial 002			Trial 003		
Safety Outcomes Na, nb (%)	Makena N=310	Placebo N=153	RR[c] (95% CI)	Makena N=1130	Placebo N=578	RR 95% CI
Total fetal/neonatal deaths[c]	19 (6.1%)	11 (7.2%)	0.83 (0.41, 1.70)	22 (2.0%)	13 (2.2%)	0.85 (0.43, 1.67)
Miscarriages (<20 weeks)	5 (2.4%)	0	N/A	4 (0.5%)	6 (1.3%)	0.32 (0.09, 1.14)
Stillbirths (≥20 weeks)	6 (2.0%)	2 (1.3%)	1.52 (0.31, 7.52)	12 (1.1%)	3 (0.5%)	2.07 (0.59, 7.29)
Neonatal deaths	8 (2.7%)	9 (6.0%)	0.44 (0.18, 1.12)	6 (0.5%)	4 (0.7%)	0.73 (0.21, 2.58)

[a]N = number of subjects in the Intent to Treat Population in the specified treatment group. The safety population consists of all subjects who received any amount of study medication.

[b]n = number of subjects within a specific category. Percentages are calculated as 100x (n/N)

[c] Defined as spontaneous abortion/miscarriage, stillbirth, and neonatal death (from minutes after birth until 28 days of life) occurring in livebirths born ≥ 20 weeks gestation

Source: Applicant's analysis (submitted September 27, 2019)

Table 15: Fetal and Neonatal Deaths in Trial 002 and Trial 003 Subjects Combined (Safety Population)

Safety outcomes N[a], n[b] (%)	Trials 002 and 003 Combined		
	Makena N = 1438	Placebo N = 731	RR (95% CI)
Total fetal/neonatal deaths[c]	41 (2.9%)	24 (3.3%)	0.85 (0.52, 1.40)
Miscarriages (<20 weeks)	n = 1075 9 (0.8%)	n = 555 6 (1.1%)	0.73 (0.26, 2.04)
Stillbirths (≥20 weeks)	n = 1429 18 (1.3%)	n = 724 5 (0.7%)	1.86 (0.69, 4.99)
Neonatal deaths	n = 1411 14 (1.0%)	n = 720 13 (1.8%)	0.54 (0.25, 1.31)

[a]N = number of subjects in the Intent to Treat Population in the specified treatment group. The safety population consists of all subjects who received any amount of study medication.

[b]n = number of subjects within a specific category. Percentages are calculated as 100x (n/N)

[c] Defined as spontaneous abortion/miscarriage, stillbirth, and neonatal death (from minutes after birth until 28 days of life) occurring in livebirths born ≥ 20 weeks gestation

Source: Applicant's analysis (submitted September 27, 2019)

In Trial 003, the same proportion of subjects in each treatment group (3%) experienced serious treatment-emergent adverse event (TEAE) or maternal pregnancy complications (MPC). The most frequently reported serious TEAE or MPC for subjects treated with Makena were premature separation of placenta (5 subjects, 0.4%), placental insufficiency (4 subjects, 0.4%), and pneumonia (3 subjects, 0.3%). The most frequently reported serious TEAE or MPC for subjects treated with placebo were cholestasis (3 subjects, 0.5%) and premature separation of placenta (2 subjects, 0.3%).

Table 16: Most Common (≥ 2 subjects Overall) Serious TEAE and MPC by Preferred Term in Trial 003 (Safety Population)

Preferred Term	Makena N = 1128 N (%)	Placebo N = 578 N (%)
Subjects with at least one serious TEAE/MPC	**34 (3%)**	**18 (3%)**
Cholestasis	0 (0)	3 (0.5)
Endometritis	1 (0.1)	1 (0.2)
Escherichia sepsis	2 (0.2)	0 (0)
Migraine	1 (0.1)	1 (0.2)
Placental insufficiency	4 (0.4)	1 (0.2)
Pneumonia	3 (0.3)	0 (0)
Premature separation of placenta	5 (0.4)	2 (0.3)
Pyelonephritis	2 (0.2)	1 (0.2)
Wound infection	2 (0.2)	0 (0)

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. Otherwise, the safety profile of Makena remains unchanged.

5. Appendix

Table 17: Estimated Annual Number of 15- to 44-Year-Old Patients With Dispensed Prescriptions for Hydroxyprogesterone or Progesterone Products, Stratified by Molecule and Form, From U.S. Retail or Mail Order/Specialty Pharmacies 2014-2018

	2014		2015		2016		2017		2018	
	Patients (N)	**%**	**Patients (N)**	**%**	**Patients (N)**	**%**	**Patients (N)**	**%**	**Patients (N)**	**%**
Total Patients (Hydroxyprogesterone and Progesterone)*	478,567	100%	492,992	100%	513,900	100%	546,499	100%	559,985	100%
All Hydroxyprogesterone	8,039	2%	12,581	3%	25,477	5%	38,744	7%	42,320	8%
Makena®	8,035	100%	12,581	100%	25,126	99%	37,581	97%	31,684	75%
Generic Hydroxyprogesterone Caproate	0	0%	0	0%	117	<1%	769	2%	12,325	29%
All Progesterone Products	471,252	98%	481,858	98%	491,869	96%	510,955	93%	520,992	93%
Progesterone (Oral)	341,067	72%	358,172	74%	377,479	77%	403,335	79%	427,085	82%
Progesterone (Injectable)	94,578	20%	96,532	20%	100,647	20%	102,199	20%	113,736	22%
Progesterone (Vaginal)	117,579	25%	107,735	22%	96,986	20%	89,305	17%	77,378	15%

* Prescriptions for bulk powder forms of hydroxyprogesterone and progesterone were not included.
Source: Symphony Health IDV® Integrated Dataverse. Data years 2014-2018. Extracted August 2019. File: SH UPC Progesterone and Hydroxyprogesterone Pt 08-07-2019.xlsx.
Unique patient counts should not be added across time periods or drug categories due to the possibility of double counting those patients who received multiple products within the same calendar year or over multiple periods in the study. Generic hydroxyprogesterone caproate use in 2016 and 2017 were generic Delalutin products.

Table 18: Diagnoses Associated With the Estimated Number of Progesterone or Hydroxyprogesterone Use Mentions Among 15- to 44-Year-Old Women From U.S. Office-Based Physician Surveys, 2013 Through 2018, Aggregated

January 2013 - December 2018

	Uses (000)	95% CI (000)	% Share
Total Progesterone and Hydroxyprogesterone	**3,786**	**3,401-4,172**	**100%**
Hydroxyprogesterone Inj	**1,592**	**1,342-1,842**	**42%**
O09 Supervision of high-risk pregnancy	797	620-973	50%
Z87.51 Personal history of preterm labor	324	211-437	20%
Z34 Encounter for supervision of normal pregnancy	211	120-302	13%
O60 Preterm labor in current pregnancy	158	79-237	10%
O34 Maternal care for abnormality of pelvic organs	28	<0.5-61	2%
All Others	75	21-130	5%
Progesterone (all forms)	**2,194**	**1,901-2,488**	**58%**
Progesterone oral	**677**	**514-840**	**31%**
O20 Hemorrhage in early pregnancy	80	24-136	12%
N97 Female infertility	79	23-134	12%
Z34 Encounter for supervision of normal pregnancy	68	17-120	10%
N91 Absent, scanty and rare menstruation	68	16-119	10%
O26 Maternal care for pregnancy-related conditions	64	14-114	9%
All Others	318	206-430	47%
Progesterone injectable	**416**	**288-543**	**19%**
O09 Supervision of high-risk pregnancy	173	91-256	42%
N97 Female infertility	169	87-250	41%
O20 Hemorrhage in early pregnancy	41	1-81	10%
O60 Preterm labor in current pregnancy	17	<0.5-43	4%
O34 Maternal care for abnormality of pelvic organs	9	<0.5-28	2%
All Others	7	<0.5-23	2%
Progesterone vaginal	**1,054**	**851-1,258**	**48%**
N97 Female infertility	622	466-779	59%
O09 Supervision of high-risk pregnancy	125	55-195	12%
O20 Hemorrhage in early pregnancy	121	52-190	11%
O26 Maternal care for pregnancy-related conditions	105	41-170	10%
N96 Recurrent pregnancy loss	45	3-87	4%
All Others	36	<0.5-73	3%

Source: Syneos Health Research and Insights, TreatmentAnswers™ with Pain Panel. Data years 2013-2018. Extracted July 2019. File: Progesterone and Hydroxyprogesterone products by diagnosis 07-22-2019.xlsx. Diagnosis data are not directly linked to dispensed prescriptions but obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity one day a month. Drug use mentions below 100,000 may not represent reliable estimates of use and should be interpreted with caution because the sample size may be very small with corresponding large confidence intervals.

Table 19: Estimated Drug Use Mentions Among 15- to 44-Year-Old Women Associated With Selected Diagnoses From U.S. Office-Based Physician Surveys, 2013-2018, Aggregated

January 2013 through December 2018

	Uses (000)	95% CI Uses (000)	Share %
Current/history preterm labor or cervical shortening	**2,364**	**2,059-2,668**	**100%**
History of preterm labor (O09.21X, Z87.51)	1,277	1,054-1,501	54%
Makena	539	394-685	42%
17-Alpha Hydroxyprogesterone	290	184-397	23%
Hydroxyprogesterone	112	46-178	9%
Prenatal OTC	88	29-146	7%
Prenatal Rx	73	19-126	6%
All Others	175	92-258	14%
Preterm labor in current pregnancy (O60.XXX)	936	744-1,127	40%
Nifedipine	172	90-254	18%
Makena	135	62-207	14%
Procardia	132	60-203	14%
Terbutaline Inj	85	27-143	9%
Betamethasone Inj	75	21-129	8%
All Others	338	223-453	36%
Cervical shortening (O26.87X)	151	74-228	6%
Progesterone vaginal	73	20-127	48%
Prometrium	60	11-109	40%
Prochieve	11	<0.5-32	7%
Crinone	7	<0.5-23	5%

Source: Syneos Health Research and Insights, TreatmentAnswers™ with Pain Panel. Data years 2013-2018. Extracted July 2019. File: Progesterone and Hydroxyprogesterone products by diagnosis 07-22-2019.xlsx. Diagnosis data are not directly linked to dispensed prescriptions but obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity one day a month. Drug use mentions below 100,000 may not represent reliable estimates of use and should be interpreted with caution because the sample size may be very small with corresponding large confidence intervals.

Table 20: Comparison of Demographics and Baseline Characteristics: Studies 002 and 003

	Trial 003		Trial 003 U.S. subset		Trial 002	
Variable	**Makena (N=1130)**	**Placebo (N=578)**	**Makena (N=258)**	**Placebo (N=133)**	**Makena (N=310)**	**Placebo (N=153)**
Gestational age of qualifying delivery, weeks	31.3 ± 4.4	31.6 ± 4.2	32.5 ± 3.9	32.5 ± 3.9	30.6 ± 4.6	31.3 ± 4.2
Number of previous preterm deliveries						
1 previous PTB, N (%)	964 (85)	494 (86)	187 (72)	97 (73)	224 (72)	90 (59)
>1 previous PTB, N (%)	166 (15)	82 (14)	71 (28)	36 (27)	86 (28)	63 (41)
Number with cervical length <25 mm at randomization, N (%)	18 (2)	9 (2)	13 (5)	3 (2)	NA	NA
Age, years	30 ± 5	30 ± 5	28 ± 5	27 ± 5	26 ± 6	27 ± 5
Race, N (%)						
Black or African American/African Heritage	73 (6)	41 (7)	72 (28)	41 (31)	183 (59)	90 (59)
White	1004 (89)	504 (87)	170 (66)	84 (63)	79 (25)	34 (22)
Asian	23 (2)	22 (4)	4 (2)	2 (2)	2 (1)	1 (1)
Other	30 (3)	11 (2)	12 (5)	6 (5)	3 (1)	2 (1)
Ethnicity, N (%)						
Hispanic or Latino	101 (9)	54 (9)	31 (12)	23 (17)	43 (14)**	26 (17)**
Non-Hispanic or Latino	1029 (91)	524 (91)	227 (88)	110 (83)	267 (86)	127 (83)
Marital Status, N (%)						
Married or living with partner	1013 (90)	522 (90)	180 (70)	91 (68)	159 (51)	71 (46)
Never married	86 (8)	40 (7)	61 (24)	33(25)	119 (38)	64 (42)
Divorced, widowed or separated	31 (3)	16 (3)	17 (7)	9 (7)	32 (10)	18 (12)
BMI before pregnancy	24.3 ± 7.1	24.7 ± 8.7	27.4 ± 11.8	29.3 ± 15.3	26.9 ± 7.9	26.0 ± 7.0
Years of education	13 ± 2	13 ± 2	13 ± 2	13 ± 2	12 ± 2	12 ± 2
Any substance use during pregnancy, N (%)	105 (9)	51 (9)	69 (27)	40 (30)	85 (27)	36 (24)
Smoking	92 (8)	40 (7)	58 (22)	31 (23)	70 (23)	30 (20)
Alcohol	23 (2)	18 (3)	20 (8)	16 (12)	27 (9)	10 (7)
Illicit drugs	15 (1)	8 (1)	15 (6)	8 (6)	11 (4)	4 (3)

**Hispanic or Latino included in both race and ethnicity category for Study 002

Table 21: Summary of Neonatal Composite Index by Subgroups

Neonatal Composite Index, Subgroup	Trial 003		Trial 003 U.S. subset		Trial 002	
	Makena (N=1091)	Placebo (N=560)	Makena (n=252)	Placebo (n=126)	Makena (N=295)	Placebo (N=151)
GA at randomization (weeks)						
16^0-17^6	25/481 (5.2)	12/230 (5.2)	4/93 (4.3)	4/36 (11.1)	12/97 (12.4)	11/47 (23.4)
18^0-20^6	34/610 (5.6)	17/330 (5.2)	14/159 (8.8)	8/90 (8.9)	23/198 (11.6)	15/104 (14.4)
Overall	59/1091 (5.4)	29/560 (5.2)	18/252 (7.1)	12 /126 (9.5)	35/295 (11.9)	26/151 (17.2)
GA of qualifying delivery* (weeks)						
20^0 - $<28^0$	17/221 (7.7)	3/97 (3.1)	3/30 (10.0)	2/17 (11.8)	11/74 (14.9)	9/29 (31.0)
28^0 - $<32^0$	14/198 (7.1)	13/102 (12.7)	3/37 (8.1)	4/18 (22.2)	5/65 (7.7)	5/30 (16.7)
32^0 - $<35^0$	15/339 (4.4)	9/182 (4.9)	3/73 (4.1)	5/39 (12.8)	11/79 (13.9)	9/54 (16.7)
35^0 - $<37^0$	13/330 (3.9)	4/176 (2.3)	9/110 (8.2)	1/51 (2.0)	8/77 (10.4)	3/38 (7.9)
GA of earliest prior PTB** (weeks)						
0 - $<20^0$	24/445 (5.4)	11/228 (4.8)	5/75 (6.7)	3/35 (8.6)	6/46 (13.0)	1/16 (6.3)
20^0 - $<28^0$	13/153 (8.5)	2/71 (2.8)	4/27 (14.8)	1/18 (5.6)	10/47 (21.3)	9/23 (39.1)
28^0 - $<32^0$	9/112 (8.0)	7/59 (11.9)	2/29 (6.9)	3/13 (23.1)	4/39 (10.3)	4/20 (20.0)
32^0 - $<35^0$	7/198 (3.5)	6/99 (6.1)	2/59 (3.4)	4/29 (13.8)	8/55 (14.5)	6/34 (17.6)
35^0 - $<37^0$	6/183 (3.3)	3/102 (2.9)	5/62 (8.1)	1/31 (3.2)	5/40 (12.5)	2/26 (7.7)
Previous PTB, N (%)						
1	43/933 (4.6)	22/478 (4.6)	11/184 (6.0)	8/92 (8.7)	18/210 (8.6)	10/89 (11.2)
>1‡	16/158 (10.1)	7/80 (8.8)	7/78 (9.0)	4/34 (11.8)	17/85 (10.0)	16/62 (25.8)
2	14/125 (11.2)	5/66 (7.6)	6/52 (11.5)	4/28 (14.3)	12/55 (21.8)	8/45 (17.8)
≥3	2/33 (6.1)	2/14 (14.3)	1/16 (6.3)	0/6 (0.0)	5/30 (16.7)	8/17 (47.1)
Cervical length at randomization***, N (%)						
<25 mm	2/17 (11.8)	2/9 (22.2)	1/13 (7.7)	1/3 (33.3)	NA	NA
≥25 mm	44/890 (4.9)	23/444 (5.2)	11/110 (10.0)	10/63 (15.9)	NA	NA
BMI before pregnancy (kg/m^2)						
Underweight (<18.5)	4/80 (5.0)	3/37 (8.1)	0/11 (0)	0/2 (0)	4/25 (16.0)	2/10 (20.0)
Normal (18.5 - <25)	34/629 (5.4)	12/328 (3.7)	7/112 (6.3)	2/49 (4.1)	13/116 (11.2)	14/73 (19.2)
Overweight (25 - <30)	10/249 (4.0)	9/125 (7.2)	6/63 (9.5)	6/34 (17.6)	6/56 (10.7)	5/30 (16.7)
Obese (≥30)	11/133 (8.3)	5/69 (7.2)	5/66 (7.6)	4/41 (9.8)	10/86 (11.6)	5/34 (14.7)

Neonatal Composite Index, Subgroup	Trial 003		Trial 003 U.S. subset		Trial 002	
	Makena (N=1091)	Placebo (N=560)	Makena (n=252)	Placebo (n=126)	Makena (N=295)	Placebo (N=151)
Any substance use during pregnancy, N (%)						
Yes	8/101 (7.9)	5/49 (10.2)	5/67 (7.5)	4/38 (10.5)	12/82 (14.6)	6/35 (17.1)
No	51/990 (5.2)	24/511 (4.7)	13/185 (7.0)	8/88 (9.1)	23/213 (10.8)	20/116 (17.2)
Smoking						
Yes	8/89 (9.0)	4/39 (10.3)	5/57 (8.8)	3/29 (10.3)	10/67 (14.9)	6/29 (20.7)
No	51/1002 (5.1)	25/521 (4.8)	13/195 (6.7)	9/97 (9.3)	25/228 (11.0)	20/122 (16.4)
Alcohol						
Yes	0/23 (0)	4/17 (23.5)	0/19 (0)	3/15 (20.0)	3/26 (11.5)	0/10 (0)
No	59/1068 (5.5)	25/543 (4.6)	18/233 (7.7)	9/111 (8.1)	32/269 (11.9)	26/141 (18.4)
Illicit drugs						
Yes	1/14 (7.1)	1/7 (14.3)	1/13 (7.7)	1/7 (14.3)	2/10 (20.0)	0/4 (0)
No	58/1077 (5.4)	28/553 (5.1)	17/239 (7.1)	11/119 (9.2)	33/285 (11.6)	26/147 (17.7)
Race						
Non-Hispanic black	6/69 (8.7)	3/39 (7.7)	5/68 (7.4)	3/39 (7.7)	22/176 (12.5)	20/89 (22.5)
Non-Hispanic non-black	50/923 (5.4)	23/468 (4.9)	13/153 (8.5)	7/64 (10.9)	8/81 (9.9)	6/36 (16.7)
Ethnicity						
Hispanic	3/99 (3.0)	3/53 (5.7)	0/31 (0)	2/23 (8.7)	5/38 (13.2)	0/26 (0)
Non-Hispanic	56/992 (5.6)	26/507 (5.1)	18/221 (8.1)	10/103 (9.7)	30/257 (11.7)	26/125 (20.8)
Years of education						
≤12	28/458 (6.1)	18/249 (7.2)	9/116 (7.8)	9/69 (13.0)	29/213 (13.6)	18/101 (17.8)
>12	31/632 (4.9)	11/311 (3.5)	9/135 (6.7)	3/57 (5.3)	6/82 (7.3)	8/50 (16.0)

* 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.

Table 22: Summary of PTB <35^0 Weeks by Subgroups

	Trial 003		Trial 003 U.S. Subset		Trial 02	
Stratification Groups, n/N (%)	**Makena (N=1130)**	**Placebo (N=578)**	**Makena (N=258)**	**Placebo (N=133)**	**Makena (N=310)**	**Placebo (N=153)**
GA at randomization (weeks)						
16^0-17^6	61/493 (12.4)	31/238 (13.0)	16/96 (16.7)	9/40 (22.5)	22/103 (21.4)	21/47 (44.7)
18^0-20^6	61/620 (9.8)	35/336 (10.4)	24/160 (15.0)	14/91 (15.4)	41/203 (20.2)	26/106 (24.5)
Overall	122/1113 (11.0)	66/574 (11.5)	40/256 (15.6)	23/131 (17.6)	63/306 (20.6)	47/153 (30.7)
GA of qualifying delivery* (weeks)						
20^0 - <28^0	29/229 (12.7)	9/101 (8.9)	7/31 (22.6)	3/18 (16.7)	21/82 (25.6)	13/29 (44.8)
28^0 - <32^0	24/201 (11.9)	20/104 (19.2)	9/37 (24.3)	4/18 (22.2)	12/65 (18.5)	6/30 (20.0)
32^0 - <35^0	36/344 (10.5)	24/186 (12.9)	9/75 (12.0)	10/40 (25.0)	12/81 (14.8)	18/55 (32.7)
35^0 - <37^0	32/336 (9.5)	13/180 (7.2)	14/111 (12.6)	6/54 (11.1)	18/78 (23.1)	10/39 (25.6)
GA of earliest prior PTB** (weeks)						
0 - <20^0	53/459 (11.5)	26/234 (11.1)	13/78 (16.7)	5/36 (13.9)	9/46 (19.6)	3/16 (18.8)
20^0 - <28^0	21/156 (13.5)	7/73 (9.6)	7/27 (25.9)	3/19 (15.8)	21/55 (38.2)	11/23 (47.8)
28^0 - <32^0	15/113 (13.3)	12/60 (20.0)	8/30 (26.7)	3/13 (23.1)	7/39 (17.9)	5/20 (25.0)
32^0 - <35^0	18/201 (9.0)	12/100 (12.0)	5/59 (8.5)	6/29 (20.7)	9/56 (16.1)	13/35 (37.1)
35^0 - <37^0	15/184 (8.2)	9/106 (8.5)	7/62 (11.3)	6/34 (17.6)	10/40 (25.0)	5/26 (19.2)
Previous PTD, N (%)						
1	80/949 (8.4)	51/491 (10.4)	22/185 (11.9)	17/96 (17.7)	37/220 (16.8)	19/90 (21.1)
>1‡	42/164 (25.6)	15/81 (18.5)	18/71 (25.3)	6/35 (17.1)	26/86 (30.2)	28/63 (44.4)
2	29/127 (22.8)	10/67 (14.9)	13/52 (25.0)	4/29 (13.8)	18/56 (32.1)	17/46 (37.0)
≥3	13/37 (35.1)	5/14 (35.7)	5/19 (16.3)	2/6 (33.3)	8/30 (26.7)	11/17 (64.7)
Cervical length at randomization***, N (%)						
<25 mm	4/18 (22.2)	4/9 (44.4)	2/13 (15.4)	1/3 (33.3)	NA	NA
≥25 mm	92/907 (10.1)	45/455 (9.9)	21/112 (18.8)	13/66 (19.7)	NA	NA
BMI before pregnancy						
Underweight (<18.5)	13/83 (15.7)	4/38 (10.5)	0/11 (0)	0/3 (0)	5/25 (20.0)	6/10 (60.0)
Normal (18.5 - <25)	59/637 (9.3)	33/335 (9.9)	20/112 (17.9)	10/51 (19.6)	23/131 (17.6)	26/77 (33.8)
Overweight (25 - <30)	29/255 (11.4)	16/127 (12.6)	9/66 (13.6)	6/34 (17.6)	14/60 (23.3)	10/32 (31.3)
Obese (≥30)	21/138 (15.2)	13/74 (17.6)	11/67 (16.4)	7/43 (16.3)	21/90 (23.3)	5/34 (14.7)

Stratification Groups, n/N (%)	Trial 003		Trial 003 U.S. Subset		Trial 02	
	Makena (N=1130)	Placebo (N=578)	Makena (N=258)	Placebo (N=133)	Makena (N=310)	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)	16/36 (44.4)
No	103/1008 (10.2)	53/523 (10.1)	29/187 (15.5)	13/91 (14.3)	47/221 (21.3)	31/117 (26.5)
Smoking						
Yes	18/92 (19.6)	11/40 (27.5)	10/58 (17.2)	8/30 (26.7)	13/70 (18.6)	15/30 (50.0)
No	104/1021 (10.2)	55/534 (10.3)	30/198 (15.2)	15/101 (14.9)	50/236 (21.2)	32/123 (26.0)
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)

* 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. ǂFDA Analysis.