Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
October 29, 2019

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland.

Topic: The committee discussed supplemental new drug application (sNDA 021945/S 023) for MAKENA (hydroxyprogesterone caproate injection, 250 milligrams per milliliter) manufactured by AMAG Pharmaceuticals. In 2011, MAKENA received approval under the accelerated approval pathway (21 CFR part 314, subpart H, and section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)) for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. MAKENA was shown in the preapproval clinical trial (Trial 002) to reduce the proportion of women who delivered at less than 37 weeks gestation, a surrogate endpoint that FDA determined was reasonably likely to predict a clinical benefit of preterm birth prevention, such as improved neonatal mortality and morbidity. As required under 21 CFR 314.510, the Applicant conducted a post approval confirmatory clinical trial (Trial 003) to verify and describe clinical benefit. AMAG Pharmaceuticals has disclosed that this completed confirmatory trial did not demonstrate a statistically significant difference between the treatment and placebo arms for the co-primary endpoints of reducing the risk of recurrent preterm birth at less than 35 weeks gestation or improving neonatal mortality and morbidity. The committee considered the trial's findings and the sNDA in the context of AMAG Pharmaceuticals' confirmatory study obligation.

These summary minutes for the Ocotber 29, 2019, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration were approved on November 22, 2019.

I certify that I attended the November 22, 2019, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/	**/S/**
Kalyani Bhatt, BS, MS *Designated Federal Officer, BRUDAC*	Vivian Lewis, MD *Chairperson, BRUDAC*

Summary Minutes of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
October 29, 2019

The Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on October 29, 2019, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and AMAG Pharmaceuticals. The meeting was called to order by Vivian Lewis, MD (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS (Designated Federal Officer). There were approximately 175 people in attendance. There were sixteen (16) Open Public Hearing (OPH) presentations.

A verbatim transcript will be available, in most instances, approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed supplemental new drug application (sNDA 021945/S-023) for MAKENA (hydroxyprogesterone caproate injection, 250 milligrams per milliliter) manufactured by AMAG Pharmaceuticals. In 2011, MAKENA received approval under the accelerated approval pathway (21 CFR part 314, subpart H, and section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)) for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. MAKENA was shown in the preapproval clinical trial (Trial 002) to reduce the proportion of women who delivered at less than 37 weeks gestation, a surrogate endpoint that FDA determined was reasonably likely to predict a clinical benefit of preterm birth prevention, such as improved neonatal mortality and morbidity. As required under 21 CFR 314.510, the Applicant conducted a post approval confirmatory clinical trial (Trial 003) to verify and describe clinical benefit. AMAG Pharmaceuticals has disclosed that this completed confirmatory trial did not demonstrate a statistically significant difference between the treatment and placebo arms for the co-primary endpoints of reducing the risk of recurrent preterm birth at less than 35 weeks gestation or improving neonatal mortality and morbidity. The committee considered the trial's findings and the sNDA in the context of AMAG Pharmaceuticals' confirmatory study obligation.

Attendance:
Bone, Reproductive and Urologic Drugs Advisory Committee Members Present (Voting): Douglas C. Bauer, MD; Matthew T. Drake, MD, PhD; Vivian Lewis, MD (Chairperson); Pamela Shaw, PhD

Bone, Reproductive and Urologic Drugs Advisory Committee Members Not Present (Voting): Toby Chai, MD; James Q. Clemens, MD, FACS, MSCI; ; Beatrice Edwards, MD, MPH, FACP; Margery Gass, MD; Christian P. Pavlovich, MD; Gloria Richard Davis, MD, MBA, NCMP, FACOG

Bone, Reproductive and Urologic Drugs Advisory Committee Member Not Present (Non-Voting): Gerard G. Nahum, MD, FACOG (Industry Representative)

Temporary Members (Voting): Jonathan M. Davis, MD; Ahizechukwu Eke, MD, MPH; Annie Ellis (Patient Representative); Daniel Gillen, PhD; Kimberly Hickey, MD; Sally Hunsberger, PhD; Michael K. Lindsay, MD, MPH; Michele Orza, ScD (Acting Consumer Representative); Uma M. Reddy, MD, MPH; Brian Smith MD, MPH, MHS; Kelly Wade, MD, PhD, MSCE; Deborah A. Wing, MD, MBA

Acting Industry Representative to the Committee (Non-voting): Venkateswar Jarugula, PhD (Acting Industry Representative)

FDA Participants (Non-Voting): Christine Nguyen, MD; Barbara Wesley, MD, MPH; Christina Chang, MD, MPH; Jia Guo, PhD

Open Public Hearing Speakers: Meena M. Aladdin, PhD (Public Citizen); Adam C. Urato, MD (MetroWest Medical Center); Stephanie Fox-Rawlings, PhD (National Center for Health Research); Washington Clark Hill, MD, FACOG (Florida Department of Health, Sarasota County); John R. Barton, MD, MS (Baptist Health Lexington); Danielle Boyce (statement read by Robin Osman); Mary Norton, MD (Society for Maternal-Fetal Medicine); Anabel Jimenez-Gomez (statement read by Amelia Chiaverini); Kelle Moley, MD (March of Dimes); Allison Johnson; Glory M. Joseph (statement read by Allison Johnson); Marc Jackson, MD, MBA (The American College of Obstetricians and Gynecologists); Amelia Chiaverini; Michael Randell, MD, MBA; Steven Caritis, MD (University of Pittsburgh School of Medicine); Elizabeth Thom, PhD (George Washington University)

The agenda was as follows:

Call to Order and Introduction of Committee	**Vivian Lewis, MD** Chairperson, BRUDAC
Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Designated Federal Officer, BRUDAC
FDA Opening Remarks	**Christine Nguyen, MD** Deputy Director for Safety Division of Bone, Reproductive and Urologic Products (DBRUP) Office of Drug Evaluation III (ODE III) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**AMAG Pharmaceuticals, Inc.**
Introduction	**Julie Krop, MD** Chief Medical Officer Executive Vice President, Development & Regulatory Affairs

	AMAG Pharmaceuticals, Inc.
Clinical Background and Unmet Need	**Michelle Owens, MD** Professor and Medical Director School of Medicine Department of Obstetrics and Gynecology The University of Mississippi Medical Center
Meis Study Design and Results	**Baha Sibai, MD** Professor Department of Obstetrics, Gynecology, and Reproductive Sciences Investigator, MFMU University of Texas Health Science Center of Houston MFMU[1] Network
PROLONG: Efficacy and Safety	**Laura Williams, MD, MPH** Sr. Vice President, Clinical Development & Biostatistics AMAG Pharmaceuticals, Inc.
Prevention of Preterm Birth: Clinical Perspective	**Sean Blackwell, MD** Professor and Chair Department of Obstetrics, Gynecology, and Reproductive Sciences Principal Investigator, MFMU University of Texas Health Science Center of Houston MFMU[1] Network
Conclusion	**Julie Krop, MD**
Clarifying Questions to Applicant	

BREAK

FDA PRESENTATIONS

Clinical Overview	**Barbara Wesley, MD, MPH** Medical Officer DBRUP, ODEIII, OND, CDER, FDA
Efficacy in Confirmatory Trial 003	**Jia Guo, PhD** Statistical Reviewer Division of Biometrics 3 (DB3) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA

Hydroxyprogesterone Caproate (HPC) Utilization in the United States	**Huei-Ting Tsai, PhD** Epidemiologist Division of Epidemiology II (DEPI-II) Office of Pharmacovigilance and Epidemiology (OPE) Office of Surveillance and Epidemiology (OSE) CDER, FDA
Summary Remarks	**Christina Chang, MD, MPH** Clinical Team Leader DBRUP, ODEIII, OND, CDER, FDA

Clarifying Questions to FDA

LUNCH

OPEN PUBLIC HEARING

Clarifying Questions to Applicant or FDA

BREAK

Questions to the Committee/Committee Discussion and Voting

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the effectiveness of Makena on recurrent preterm birth and neonatal morbidity and mortality.

   Committee Discussion: *There was general consensus among committee members that neither Trial 002 nor Trial 003 showed a treatment benefit of Makena on neonatal morbidity or mortality. The committee members further agreed that the data regarding preterm birth rates were conflicting, but there was a range of opinion as to which of the two trials better informed the efficacy of Makena for this outcome. Certain committee members opined that Trial 003 was large enough to show that there were no effect modifiers that could explain the differences in efficacy findings between 002 and 003. Further, the members could not identify a subgroup of patients where the efficacy results were consistent between Trials 002 and 003. Several members of the committee questioned the high rate of preterm birth in the placebo arm in Trial 002. Several commented on the smaller size of the US cohort in Trial 003 (23% of the total), making it difficult to interpret findings. Others were encouraged by the trend of positive treatment effect in the US subgroup in Trial 003, although the findings were not statistically significant. See the transcript for details of the committee discussion.*

2. **DISCUSSION:** If a new confirmatory 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.

   Committee Discussion: *The committee members agreed that, given the years to complete Trial 003, the number of sites used, and professional societies' guidelines, a new placebo-controlled trial would be extremely challenging and likely not feasible. Several committee members commented that pharmacokinetic studies should be performed to assess dosing, timing of drug administration and drug metabolism. Committee members also noted that studies should include an "enriched" population, such as pregnant women who are obese, with family histories of preterm birth, with substance abuse history, and recurrent preterm birth. Some committee members also recommended inclusion of other populations that might benefit, such as patients of different ages and racial groups. Some members recommended a study to look at "responders" vs "non-responders" and perhaps study pharmacogenetics. Other study design alternatives noted by committee members included comparing Makena to vaginal progesterone, a dose escalation study, a dose-response study, or creating a registry of women who used Makena. Some members noted that only a randomized control trial, and not observational studies, could provide the data needed. See the transcript for details of the committee discussion.*

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

   Committee Discussion: *Several members noted that Makena withdrawal from the US market would lead to resumption of use of compounded (hydroxyprogesterone caproate) HPC and use of other progesterone products. Some expressed concerns over unknown risks of compounded HPC from a safety perspective and quality perspective. Committee members also noted that the greatest burden could be felt by the most vulnerable groups (e.g., lower socioeconomic groups). Committee members also commented on the emotional burden for patients, and their providers, who are desperate for a treatment. On the other hand, some members commented on the potential positive consequences of Makena's withdrawal. These included the opportunity to bring the discussion of Makena's efficacy back to equipoise to allow the conduct of an adequate and well-controlled trial to inform Makena's efficacy in a defined population. See the transcript for details of the committee discussion.*

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

   Provide rationale for your vote.

   Vote Result: Yes: 0 No: 16 Abstain: 0

   Committee Discussion: *The committee unamiously agreed that the findings from Trial 003 do not verify the clinical benefit of Makena on neonatal outcomes. The committee*

members noted that there were no other data that supported the clinical benefit on the neonate. A neonatogist commented that significantly adverse neonatal outcomes in infants born after 32 – 34 weeks gestation are relatively rare. To detect treatment effect of Makena on these outcomes would likely require a trial larger than Trial 003. See the transcript for details of the committee discussion.

5. **VOTE**: 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?

   Vote Result: Yes: 3 No: 13 Abstain: 0

   Committee Discussion: *The majority of the committee members agreed that, based on the findings from Trial 002 and Trial 003, there is not substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth. The committee members who voted "No" based their vote on the statutory and scientific definition of "substantial evidence of effectiveness," because Trial 003 did not substantiate the positive findings on preterm birth seen in Trial 002. These members also noted there was no treatment effect seen in any of the Trial 003 subgroups analyzed, and that there was no evidence of an interaction between the treatment effect of Makena and risk factors for preterm birth to explain the differences in the efficacy findings between Trials 003 and 002. Because no subgroup could be identified to have benefitted from Makena in both Trials 002 and 003, the appropriate patient population could not be determined. Those who voted "Yes" stated that the findings from Trial 002 were compelling and the positive trend seen in the U.S. subgroup in Trial 003 was encouraging. Although there was no evidence of effectiveness of Makena in Trial 003, they opined that the study's population, a majority of whom were from Russia and Ukraine, was not relevant to the U.S. and that the population's low-risk of pre-term birth may have obscured the evidence of effectiveness in U.S. women. See the transcript for details of the committee discussion.*

6. **VOTE:** 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 post approval trial(s) to verify clinical benefit. If the Applicant fails to conduct such post approval 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 AND you believe 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.

Vote Result: **A: 9** **B: 7** **C: 0**

Committee Discussion: *The committee members who voted "A" noted that the totality of evidence did not provide substantial evidence of effectiveness of Makena in the reducing the risk of recurrent preterm birth. Furthermore, there is no evidence from Trials 002 and 003 that Makena benefits the neonate, which is the goal of treatment. These members stated that the only way to definitely determine whether Makena is effective would be to conduct a well-designed, prospective, randomized clinical trial. They expressed that the withdrawal of Makena would facilitate the conduct of such a trial in the US and that professional societies should take a leadership role in communicating the importance of gathering this information. Some of these committee members, however, expressed concerns over Makena's withdrawal, because of potential clinical and societal repurcussions.*

The committee members who voted "B" acknowledged the efficacy data for reducing the risk of recurrent preterm birth are conflicting and not particularly persuasive. They also

recognized the need for more data, especially to identify subpopulations that might benefit from Makena. However, these members did not believe another randomized, controlled trial would be feasible under any circumstance, including after withdrawal of Makena's approval. They were concerned that prescribers and patients would insist on receiving treatment, regardless of the evidence of efficacy, and would resort to compounded products or other progesterone products with even less evidence. Some members indicated that withdrawal of Makena would be warranted only if the drug was unsafe.

None of the committee members voted "C."

See the transcript for details of the committee discussion.

The meeting adjourned at approximately 4:30 p.m.