FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
October 29, 2019

DRAFT QUESTIONS

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

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

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

   Provide rationale for your vote.

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?

   Provide rationale for your vote.

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 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)

DRAFT QUESTIONS (cont.)

- 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.