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

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting
Tommy Douglas Conference Center
10000 New Hampshire Ave, Silver Spring, Maryland
May 10, 2018

QUESTIONS

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1. **DISCUSSION:** A reduction in fasting triglycerides (TG) has been accepted by FDA as an endpoint that can establish efficacy for several classes of drugs intended to treat patients with severe hypertriglyceridemia (TG >500 mg/dL), since lowering TG in this setting is expected to reduce the risk for acute pancreatitis. In trial CS6, patients with familial chylomicronemia syndrome (FCS) assigned to volanesorsen 300 mg weekly exhibited a 77% reduction in TG at month 3, on average, compared with an 18% increase among those assigned to placebo ($p<0.0001$).

   When efficacy is established via an effect on a surrogate endpoint, however, uncertainty generally remains regarding the magnitude of the drug's effect on clinical benefit (i.e., how patients feel, function, or survive). The expected type and magnitude of clinical benefit(s) are important to consider when making a benefit/risk assessment. Please discuss the efficacy/clinical benefits of volanesorsen in patients with FCS.
   a. Has the applicant adequately characterized the effect of volanesorsen on TG to inform labeling, despite the proposal of a dosing strategy that has not been studied in clinical trials?
   b. How does the extent of drug discontinuation after month 3 affect your assessment of the efficacy of volanesorsen, if at all?
   c. Discuss whether the available data provide evidence that volanesorsen reduces the risk of acute pancreatitis.
   d. Discuss whether the available data provide evidence that volanesorsen reduces abdominal pain in patients with FCS.
   e. Considering both the benefits that you expect based on the magnitude of TG lowering as well as what was observed in the development program, how would you characterize the overall magnitude of clinical benefit that results from treatment with volanesorsen?

2. **DISCUSSION:** Aside from thrombocytopenia, discuss the tolerability and safety of volanesorsen, such as injection site reactions, immunogenicity, hypersensitivity, liver-related safety, renal-related safety, and any other safety concerns you have identified.

3. **DISCUSSION:** Discuss the risk for thrombocytopenia and bleeding associated with volanesorsen.
   a. Discuss your level of concern for the risk of thrombocytopenia and bleeding with chronic treatment with volanesorsen.
   b. The applicant has proposed labeling that recommends intensive platelet monitoring (i.e., a minimum of every 2 weeks for the duration of treatment with this potentially lifelong therapy). Discuss whether the proposed frequency of monitoring adequately addresses the risk of thrombocytopenia and bleeding, as well as whether such monitoring would be feasible in clinical practice. If you disagree with the proposed monitoring scheme, discuss how patients treated with volanesorsen should be monitored for thrombocytopenia/bleeding, if approved.
   c. The applicant has proposed a dosing algorithm that recommends a dosing frequency based on platelet level and body weight. Discuss whether the available data in the clinical development program are adequate to inform dosing recommendations for labeling that would ensure the safe use of volanesorsen.

QUESTIONS (cont.)

4. **DISCUSSION:** Discuss whether "familial chylomicronemia syndrome," without further definition, sufficiently identifies a patient population for whom volanesorsen may have a favorable benefit/risk profile. If not, please discuss alternatives.

5. **DISCUSSION:** Discuss whether a risk evaluation and mitigation strategy (REMS) is necessary and would be able to ensure that the benefits of volanesorsen outweigh the potential risk of serious bleeding due to severe thrombocytopenia. If volanesorsen were to be approved with a REMS, discuss whether you would recommend any changes to the REMS presented by FDA.

6. **DISCUSSION:** Familial chylomicronemia syndrome can have the onset of symptoms in childhood, yet no pediatric patients have been studied in the volanesorsen development program. Discuss your level of concern with respect to the potential use of volanesorsen in this population if approved for adults and any recommendations you may have for future study in the pediatric population.

7. **VOTE:** Based on the information included in the briefing materials and presented today, has the applicant provided sufficient efficacy and safety data to support approval of volanesorsen?
    a. If yes, provide your rationale and any recommendations regarding the indicated patient population, dosing, clinical monitoring, risk management strategies, and/or post-marketing studies.
    b. If no, provide your rationale and comment on what additional data would be required to support approval.