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

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
April 7, 2016

QUESTIONS

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1. **DISCUSSION:** Discuss whether the evidence from the Global PBC Study Group data presented today on the reduction in alkaline phosphatase (ALP) supports the use of alkaline phosphatase as a surrogate endpoint reasonably likely to predict clinical benefit in the treatment of early stage Primary Biliary Cirrhosis (PBC). Comment on the strength of evidence that supports the stratified responder criteria that were developed by the FDA statistical team's review of the Global PBC Study Group data.

2. **DISCUSSION:** Discuss the appropriateness of the Applicant's proposed dosage schema, i.e., a starting dose of 5 mg of obeticholic acid (OCA) with up titration to 10 mg after 3 months. Include in your discussion and dosing recommendation the safety and tolerability of obeticholic acid in addition to the biochemical response (alkaline phosphatase reduction).

3. **DISCUSSION:** Discuss the adequacy of the data to support the use of OCA as monotherapy for patients intolerant to ursodeoxycholic acid (UDCA). Include in your discussion whether the applicant should be required to further study the use of OCA as monotherapy.

4. **DISCUSSION:** Discuss the adequacy of the data to support the use of OCA in moderately advanced and advanced stages of PBC. Include in your discussion whether the applicant should be required to further study the use of OCA in moderately advanced and advanced stages of PBC.

5. **DISCUSSION:** Discuss whether the available evidence (i.e., PK modeling, dose response) supports the FDA's proposed dosing of OCA in PBC patients with moderately advanced (Child-Pugh B) and advanced (Child-Pugh C) cirrhosis.

6. **DISCUSSION:** Discuss the pros and cons of continuing OCA treatment in patients who do not demonstrate reduction in alkaline phosphatase after 6 months of treatment on a maximally tolerated dose. Take into consideration the risk of alterations in lipid profile vs. the potential for benefit.

7. **VOTE:** Taking into account the risks and benefit of OCA in the population studied, is there substantial evidence to support accelerated approval of OCA for the proposed indication, based on its effect on alkaline phosphatase?

8. **DISCUSSION:** Discuss what if any changes in the enrollment criteria or design of the postmarketing confirmatory trial would be necessary to obtain any additional information that you think is necessary for full/regular approval of OCA for the treatment of PBC.

   Alternatively, discuss what additional post-marketing studies you think would be necessary to obtain any data or information that has not been provided.