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
March 8, 2018

DRAFT QUESTIONS

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1. **DISCUSSION:** The applicant has proposed an induction dosing regimen of 10 mg BID for a total for 16 Weeks in patients who have not achieved "adequate therapeutic benefit" by Week 8 based on exploratory analyses of trial data in patients who continued induction treatment when they had not achieved clinical response defined as a decrease from baseline in Mayo score of ≥3 points and ≥ 30%, with an accompanying decrease in the subscore of rectal bleeding of ≥ 1 point or absolute subscore for rectal bleeding of 0 or 1.

    a. Discuss the adequacy of the efficacy data to support the use of the 10 mg BID dosing for extended induction therapy for a total of 16 weeks <u>in patients who have not achieved "adequate therapeutic benefit" by Week 8.</u>

    b. Discuss the adequacy of the safety data to support the use of the 10 mg BID dosing for induction for a total of 16 weeks in patients who have not achieved "adequate therapeutic benefit" by Week 8.

    c. Do you recommend the inclusion of this dosing regimen for this population in the product label?

    d. If you recommend inclusion of this dosing regimen in the product label, discuss how inadequate therapeutic benefit that merits extension of induction treatment should be distinguished from inadequate therapeutic benefit that should prompt discontinuation of tofacitinib therapy.

2. **DISCUSSION:** For adult patients with moderately to severely active UC with an <u>inadequate response, loss of response, or intolerance to TNF blocker therapy</u>:

    a. Discuss the adequacy of the efficacy data to support the use of the 10 mg BID dosing as continuous maintenance treatment.

    b. Discuss the adequacy of the safety data to support the use of the 10 mg BID dosing as continuous maintenance treatment.

    c. Do you recommend inclusion of this dosing regimen for this population in the product label?

    d. Do you recommend that the Applicant conduct a post-marketing efficacy trial in this population comparing a 10 mg BID continuous dosing regimen vs a regimen of 10 mg induction and 5mg BID as maintenance?

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3. **DISCUSSION:** Discuss if additional post-marketing evaluation of safety is warranted, and the mechanism(s) you recommend (e.g., registry, observational study, etc.) for such evaluation.

4. **DISCUSSION:** Please discuss the following:

    a. Are there unique characteristics of the pediatric UC population that should be taken into account when planning the tofacitinib pediatric development program? In particular, consider the ontogeny of the immune system and the described mechanism of action of tofacitinib.

    b. Given the safety concerns (malignancy and serious infections) described with long term use of 10mg BID and the severity of UC in the pediatric population, please recommend the maximum dose that should be targeted for evaluation for long term treatment in pediatric UC.

    c. Discuss whether you recommend limiting enrollment in the pediatric trials (and subsequent pediatric indications) to patients who have failed other biologic therapies.