Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Gastrointestinal Drugs Advisory Committee Meeting

April 7, 2016

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland

Topic: The committee discussed new drug application (NDA) 207999, obeticholic acid oral tablets, submitted by Intercept Pharmaceuticals, Inc., proposed for the treatment of primary biliary cirrhosis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

These summary minutes for the April 7, 2016 meeting of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration were approved on April 21, 2016.

I certify that I attended the April 7, 2016 meeting of the Gastrointestinal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Cindy Hong, PharmD
Designated Federal Officer
Gastrointestinal Drugs
Advisory Committee (GIDAC)

_____/s/_____
Jean-Pierre Raufman, MD
Chairperson, GIDAC

Summary Minutes of the Gastrointestinal Drugs Advisory Committee Meeting
April 7, 2016

The following is the final report of the meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) held on April 7, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Division of Gastroenterology and Inborn Errors Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/ucm486125.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 7, 2016 at the FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and Intercept Pharmaceuticals Inc. The meeting was called to order by Jean-Pierre Raufman, MD (Chairperson). The conflict of interest statement was read into the record by Cindy Hong, PharmD (Designated Federal Officer). There were approximately 180 people in attendance. There were three Open Public Hearing speakers.

Issue: The committee discussed new drug application (NDA) 207999, obeticholic acid oral tablets, submitted by Intercept Pharmaceuticals, Inc., proposed for the treatment of primary biliary cirrhosis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

Attendance:
GIDAC Members Present (Voting): Elizabeth Bell-Perkins, MPH (Consumer Representative); Lin Chang, MD; Linda Feagins, MD; Sandeep Khurana, MBBS; Timothy Lipman, MD, Jean-Pierre Raufman, MD (Chairperson); Miriam Vos, MD, MSPH

GIDAC Members Not Present (Voting): Shrikant Bangdiwala, PhD; David Keljo, MD; Brennan Spiegel, MD

Temporary Members (Voting): David Assis, MD; Hari Conjeevaram, MD; Donna Cryer, JD (Patient Representative); Srinivasan Dasarathy, MD; Susan Ellenberg, PhD; Atul Kumar, MD; Patricia Lupole (Patient Representative); Michael Proschan, PhD; Marina Silveira, MD; Maria Sjogren, MD, MPH

Industry Representative to the Committee (Non-voting): Douglas Levine, MD, FACG

FDA Participants (Non-Voting): Yeh-Fong Chen, PhD; Lara Dimick-Santos, MD; Amy Egan, MD, MPH; Dhananjay Marathe, PhD; Ruby Mehta, MD; Dragos Roman, MD

Designated Federal Officer (Non-Voting): Cindy Hong, PharmD

Open Public Hearing Speakers: Deborah Sobel; Carol Roberts (PBCers); Thomas Nealon III (American Liver Foundation) (statement read by Jonathan Martin)

***The agenda proceeded as follows*:**

Call to Order and Introduction of Committee	**Jean-Pierre Raufman, MD** Chairperson, GIDAC
Conflict of Interest Statement	**Cindy Hong, PharmD** Designated Federal Officer, GIDAC
FDA Introductory Remarks	**Dragos Roman, MD** Associate Director Division of Gastroenterology and Inborn Errors Products (DGIEP) Office of Drug Evaluation III (ODE III) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Intercept Pharmaceuticals, Inc.**
Primary Biliary Cirrhosis (PBC): Diagnosis, Natural History and Role of Current Therapy	**Kris Kowdley, MD, FACP, FAASLD** Director of the Liver Care Network and Research Director of the Organ Care Program Swedish Medical Center Seattle, Washington
Introduction	**Linda Robertson, PhD** Vice President, Regulatory Affairs and Quality Assurance Intercept Pharmaceuticals, Inc.
Unmet Medical Need in Patients with PBC	**Dave Jones, MD** Professor of Liver Immunology University of Newcastle Institute of Cellular Medicine Director, UK-PBC Study Group Consortium
Program Rationale for OCA in Patients with PBC	**David Shapiro, MD, FRCP** Chief Medical Officer Intercept Pharmaceuticals, Inc.
Efficacy of OCA in Patients with PBC	**Leigh MacConell, PhD** Vice President, Clinical Development Intercept Pharmaceuticals, Inc.
Safety of OCA in Patients with PBC	**Roya Hooshmand-Rad, MD, PhD** Executive Director, Medical Safety and Pharmacovigilance Intercept Pharmaceuticals, Inc.

APPLICANT PRESENTATIONS (cont.)

Benefit-Risk of OCA in Patients with PBC: A Transplant Hepatologist's Perspective	**John M. Vierling, MD, FACP, FAASLD** Professor of Medicine and Surgery Chief of Hepatology Director of Advanced Liver Therapies Baylor College of Medicine

Clarifying Questions to the Presenters

BREAK

FDA PRESENTATIONS

Global PBC Study Group Data Analysis for the Clinical Trial Population	**Min Min, PhD** Mathematical Statistician Division of Biostatistics III Office of Biostatistics Office of Translational Sciences (OTS) CDER, FDA
OCA Safety and Efficacy	**Ruby Mehta, MD** Medical Reviewer DGIEP, ODE III, OND, CDER, FDA
Dosing Considerations for OCA for PBC	**Dhananjay Marathe, PhD** Senior Pharmacometrics Reviewer Division of Pharmacometrics Office of Clinical Pharmacology OTS, CDER, FDA
Regulatory Perspective	**Lara Dimick, MD** Cross Discipline Team Leader DGIEP, ODE III, OND, CDER, FDA

Clarifying Questions to the Presenters

LUNCH

Open Public Hearing

Questions to the Committee and Committee Discussion

BREAK

Questions to the Committee and Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

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.

   Committee Discussion: *There was a general consensus that the evidence from the Global PBC Study Group data presented 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). Some members commented that while ALP is the only surrogate endpoint in early stage of the disease, bilirubin should also be considered. A committee member commented that the evidence is persuasive in using stratified responder analysis from a statistical standpoint, but that the decision on accepting ALP as a surrogate reasonably likely to predict clinical benefit is both a clinical determination and a statistical determination. Please see the transcript for details of the committee discussion.*

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).

   Committee Discussion: *The majority of the committee agreed that the starting dose of 5mg with titration to 10 mg after 3 months is reasonable given the data presented. Members commented that the increased incidence of hepatic adverse events at the 10mg dose is concerning, but may be acceptable given the benefit provided by OCA, and that phase 4 trials should attempt to better characterize hepatic adverse events, as well as monitor HDL cholesterol levels. Please see the transcript for details of the committee discussion.*

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.

   Committee Discussion: *Committee members commented that the data supporting the use of OCA as monotherapy appear sufficient, but further study in patients who are non-responders to UDCA or intolerant of UDCA is warranted. Please see the transcript for details of the committee discussion.*

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.

Committee Discussion: *The majority of the committee agreed that the data are limited on the use of OCA in moderately advanced stage PBC patients, and absent in advanced stage PBC patients, to support the use of OCA in moderately advanced and advanced stages of PBC, while some members supported the use of OCA in moderately advanced PBC patients, but not advanced stage PBC patients. Please see the transcript for details of the committee discussion.*

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.

   Committee Discussion: *The majority of the committee commented on the insufficient data to support dosing of OCA in PBC patients with moderately advanced (Child-Pugh B) and advanced (Child-Pugh C) cirrhosis and called for additional studies. However, there were panel members who commented that there are sufficient data to justify treatment of patients with moderately advanced cirrhosis, but insufficient data to support treatment of patients with advanced cirrhosis. Please see the transcript for details of the committee discussion.*

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.

   Committee Discussion: *The majority of the committee agreed that it may be premature to discontinue therapy at 6 months despite no reduction in ALP. One member opined that therapy should be continued to 12 months, and if there is still no reduction in ALP, then treatment should be discontinued. Please see the transcript for details of the committee discussion.*

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?

   YES: 17 **NO: 0** **ABSTAIN: 0**

   Committee Discussion: *The committee unanimously agreed that there is substantial evidence to support accelerated approval of OCA for the proposed indication, based on its effect on alkaline phosphatase. Members commented on the efficacy of the drug when compared to placebo, favorable benefit to risk ratio, and the ability of the drug to address an unmet need. Please see the transcript for details of the committee discussion.*

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.

Committee Discussion: *The committee members suggested obtaining additional data including, but not limited, use of OCA as monotherapy in patients who do not respond to or are intolerant of UDCA;, pharmacokinetic profile of OCA in advanced stage PBC patients; long term cardiovascular/lipid profile effects of OCA; a broader spectrum of patients with PBC, i.e., patients with abnormal bilirubin levels, not just abnormal ALP levels; and safety and efficacy of OCA in compensated cirrhotic patients. Committee members also commented on the difficulty of getting patients to participate in a post-marketing placebo-controlled trial given that the drug will be commercially available. Some members expressed concern regarding the possible use of an historical control in the confirmatory trial. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:28 p.m.