Food and Drug Administration
Center for Drug Evaluation and Research
Final Summary Minutes of the Gastrointestinal Drugs Advisory Committee Meeting

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed new drug application (NDA) 212833, obeticholic acid (OCA) 25 mg oral tablets, submitted by Intercept Pharmaceuticals, Inc., for the treatment of pre-cirrhotic liver fibrosis due to nonalcoholic steatohepatitis.

These summary minutes for the May 19, 2023 meeting of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration were approved on ____6/16/2023___.

I certify that I attended the May 19, 2023 meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____	_____/s/_____
Jessica Seo, PharmD, MPH	Benjamin Lebwohl, MD, MS
Acting Designated Federal Officer, GIDAC	Chairperson, GIDAC

Summary Minutes of the Gastrointestinal Drugs Advisory Committee Meeting
May 19, 2023

The Gastrointestinal Drugs Advisory Committee (GIDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on May 19, 2023. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Intercept Pharmaceuticals, Inc. The meeting was called to order by Benjamin Lebwohl, MD, MS (Chairperson). The conflict of interest statement was read into the record by Jessica Seo, PharmD, MPH (Acting Designated Federal Officer). There were approximately 1358 people online. There were a total of 13 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:

The committee discussed new drug application (NDA) 212833, obeticholic acid (OCA) 25 mg oral tablets, submitted by Intercept Pharmaceuticals, Inc., for the treatment of pre-cirrhotic liver fibrosis due to nonalcoholic steatohepatitis.

Attendance:

Gastrointestinal Drugs Advisory Committee Members Present (Voting): David N. Assis, MD; Lin Chang, MD; Christopher S. Coffey, PhD, MS; Joy McVey Hugick, BA (*Consumer Representative)*; Benjamin Lebwohl, MD, MS (*Chairperson)*; Peter Mannon, MD, MPH; Steven F. Solga, MD

Gastrointestinal Drugs Advisory Committee Members Not Present (Voting): Sandeep Khurana, MBBS; Jennifer C. Lai, MD, MBA; Miguel Saps, MD; Sarah Streett, MD, AGAF

Gastrointestinal Drugs Advisory Committee Member (Non-Voting): Helmut H. Albrecht, MD, MS (*Industry Representative*)

Temporary Members (Voting): Mark J. Czaja, MD; James Floyd, MD, MS; Theo Heller, MD; Sally A. Hunsberger, PhD; Brian P. Lee, MD, MAS; Jacquelyn Maher, MD; Jorge Rakela, MD, MACP, FAASLD, FACG, AGAF; Jennifer Schwartzott, MS (*Patient Representative*); Peter W.F. Wilson, MD

FDA Participants (Non-Voting): Frank A. Anania, MD, FACP, AGAF, FAASLD; Ruby Mehta, MD; Paul H. Hayashi, MD, MPH, FAASLD; Charmaine Stewart, MD, FAASLD, AGAF, FACP; Rebecca Hager, PhD

Acting Designated Federal Officer (Non-Voting): Jessica Seo, PharmD, MPH

Open Public Hearing Speakers Present: Michael T. Abrams, MPH, PhD (Public Citizen); Wayne Eskridge (Fatty Liver Foundation); Michael Betel (Fatty Liver Alliance); Anthony J. Villiotti; Donna Cryer, JD (Global Liver Institute); Bruce D. Dimmig; Gina Villiotti Madison; Beth; Betsy Villiotti; David Frank (NASH Aware); Paul J. Pockros, MD; Manal F. Abdelmalek, MD, MPH; Kimberly Martinez

The agenda was as follows:

Call to Order	**Benjamin Lebwohl, MD, MS** Chairperson, GIDAC
Introduction of Committee and Conflict of Interest Statement	**Jessica Seo, PharmD, MPH** Acting Designated Federal Officer, GIDAC
FDA Introductory Remarks	**Ruby Mehta, MD** Medical Team Leader Division of Hepatology and Nutrition (DHN) Office of Immunology and Inflammation (OII) Office of New Drugs (OND) CDER, FDA
APPLICANT PRESENTATIONS	**Intercept Pharmaceuticals, Inc.**
Introduction	**M. Michelle Berrey, MD, MPH** President, Research & Development Chief Medical Office Intercept Pharmaceuticals
Medical Need	**Kris Kowdley, MD, AGAF, FAASLD, FACG, FACP, FASG** Director, Liver Institute Northwest Professor of Medicine Elson S. Floyd College of Medicine Washington State University
Non-Invasive Tests	**Rohit Loomba, MD, MHSc** Director, NAFLD Research Center Professor of Medicine Vice Chief, Gastroenterology Director, Hepatology University of California at San Diego
Efficacy Results	**Thomas Capozza, MD, FACP** Executive Director, Clinical Research Intercept Pharmaceuticals
OCA Safety	**Sangeeta Sawhney, MD** Vice President, Clinical Development Intercept Pharmaceuticals

Clinical Perspective	**Arun Sanyal, MD** Professor of Medicine, VCU School of Medicine Chair of NIDDK NASH Clinical Research Network Steering Committee
Clarifying Questions	
BREAK	
FDA PRESENTATIONS	
Regulatory Framework, Study Design, and Efficacy	**Rebecca Hager, PhD** Statistical Team Leader Division of Biometrics III (DBIII) Office of Biostatistics (OB) Office of Translational Sciences (OTS) CDER, FDA
Drug-Induced Liver Injury (DILI) Assessment	**Paul H. Hayashi, MD, MPH, FAASLD** DILI Team Leader DHN, OII, OND, CDER, FDA
Safety Assessment (non-DILI)	**Charmaine Stewart, MD, FAASLD, AGAF, FACP** Medical Officer DHN, OII, OND, CDER, FDA
Benefit:Risk	**Ruby Mehta, MD**
Clarifying Questions	
LUNCH	
OPEN PUBLIC HEARING	
Charge to the Committee	**Frank A. Anania, MD, FACP, AGAF, FAASLD** Director (Acting) DHN, OII, OND, CDER, FDA
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion (cont.)	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION:** Discuss the strength of the available efficacy data on the histopathologic endpoint, a surrogate endpoint that is reasonably likely to predict clinical benefit, in nonalcoholic steatohepatitis (NASH) patients with Stage 2 or 3 fibrosis treated with obeticholic acid (OCA) 25 mg.

   Committee Discussion*: Many Committee members acknowledged the Applicant met one of the prespecified surrogate histologic endpoints and agreed that modest efficacy of OCA 25mg was demonstrated. The Committee was broadly in agreement that there remains great uncertainty around the ability of available efficacy data on the surrogate histopathologic endpoint to translate into clinically important outcomes. Many members voiced concerns that the degree of the effect observed was likely not large enough to predict clinical benefit over a longer term in a real-world setting. One member opined that unlike Hepatitis C, where treatments are aimed at cure, in NASH the underlying disease is progressive. The significance of a one stage fibrosis reversal and its durability is unknown. However, many expressed difficulties weighing the evidence of efficacy without consideration of OCA's safety profile. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Based on the data presented concerning cholestatic drug-induced liver injury (DILI) in OCA 25 mg-treated patients, discuss:
   a. Whether periodic liver enzyme monitoring could adequately mitigate the risk of DILI
   b. The frequency of such monitoring
   c. What stopping criteria should be developed to aid clinicians' decisions to discontinue treatment

   Committee Discussion: *Most Committee members expressed concern about the data presented regarding cholestatic DILI in patients treated with OCA 25 mg. While one member acknowledged the periodic liver enzyme monitoring program established by the Applicant was associated with a reduction in events, the member was concerned that in the postmarket setting close monitoring every 3-4 weeks will be impractical, especially if patients are on OCA for a long duration. Most members were not convinced that periodic monitoring of enzymes could adequately mitigate the risk of DILI, citing the long latency, unpredictability of events, and variability of presentation. With respect to the frequency of such monitoring, there were concerns among panel members that what was suggested by the Applicant would either be very challenging in a real-world setting, or may not be adequate. Some members pointed out the potential public health implications of OCA's safety risks for a condition with a large disease burden such as NASH. Another member opined that if OCA was approved, then most patients who might receive OCA in the real world would have NAFLD rather than NASH with stage 2 or 3 fibrosis, which would expose patients with earlier stage of disease (who might not even progress to NASH) than were studied in the development program to the substantial safety risks of OCA. One panel member also expressed concern regarding uncertainty surrounding the adequacy of non-invasive tests (NITs) to identify patients who progress to cirrhosis, in whom there would be substantial safety concerns and no potential for efficacy. One member opined that if DILI were to occur in one patient in clinical practice, that will reduce the enthusiasm of treating any patient with this drug. Please see the transcript for details of the Committee's discussion.*

3. **VOTE:** Given the available efficacy and safety data, do the benefits of OCA 25 mg outweigh the risks in NASH patients with Stage 2 or 3 fibrosis?

   Vote Result: Yes: 2 No: 12 Abstain: 2

   Committee Discussion*: The majority of Committee members voted "No," and were in agreement that given the available efficacy and safety data, the benefits of OCA 25 mg did not outweigh its risks in NASH patients with Stage 2 or 3 fibrosis. While many acknowledged the Applicant met one of the primary surrogate histologic endpoints for efficacy and some found the efficacy data promising, the degree to which the surrogate histological endpoint would translate into clinical benefit remains uncertain. These panel members agreed that the potential for efficacy was outweighed by their concerns from clear evidence of safety risks associated with OCA treatment.*

   Those who voted "Yes" or abstained cited the seriousness of the disease and unmet need, and importance of empowering patients with a potential option for treatment. Please see the transcript for details of the Committee's discussion.

4. **VOTE:** Clinical outcome events in patients enrolled in Trial 747-303 will continue to be captured to evaluate clinical benefit in support of a future application for traditional approval. At present, which of the following would you recommend:
   A. Approval of OCA 25 mg at this time, under the accelerated (approval) pathway, based on efficacy data on a histopathologic surrogate and available clinical safety data;
   B. Defer approval until clinical outcome data from Trial 747-303 are submitted and reviewed, at which time the traditional approval pathway could be considered.

   Vote Result: A: 1 B: 15 Abstain: 0

   Committee Discussion: *The Committee members were nearly unanimous in voting to defer approval of OCA 25 mg until clinical outcome data from Trial 747-303 are submitted and reviewed, at which time the traditional approval pathway could be considered. Panel members encouraged the Applicant continue the clinical outcomes trial, given the unmet medical need. Many panel members acknowledged the great unmet need for treatment options among NASH patients with pre-cirrhotic liver fibrosis but were in agreement that additional data to address the uncertainty about clinical benefit would be needed to evaluate whether the benefits outweigh the substantial risks observed with OCA use.*

   The member who voted "A" acknowledged the benefit of further study but was swayed by consideration for the patients who are in need of treatment now. Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 4:45 p.m. ET.