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

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform.

Topic: The Committee discussed supplemental new drug application (sNDA) 207999 S-011, for OCALIVA (obeticholic acid) 5 mg titrated to 10 mg oral tablets, administered once a day, submitted by Intercept Pharmaceuticals, Inc., to fulfill the accelerated approval postmarketing requirements specified in the OCALIVA approval letter dated May 27, 2016. The sNDA included data proposed to describe and verify clinical benefit for the indication of reducing the risk of death, liver transplant, and hepatic decompensation in adult patients with primary biliary cholangitis without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension, either in combination with ursodeoxycholic acid (UDCA) with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA.

These summary minutes for the September 13, 2024 meeting of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration were approved on October 10, 2024.

I certify that I attended the September 13, 2024 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
Designated Federal Officer, GIDAC	Chairperson, GIDAC

Summary Minutes of the Gastrointestinal Drugs Advisory Committee Meeting
September 13, 2024

The Gastrointestinal Drugs Advisory Committee (GIDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on September 13, 2024, at FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing 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 (Designated Federal Officer). There were approximately 75 people in attendance in-person and approximately 697 people online. There was a total of 19 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 supplemental new drug application (sNDA) 207999 S-011, for OCALIVA (obeticholic acid) 5 mg titrated to 10 mg oral tablets, administered once a day, submitted by Intercept Pharmaceuticals, Inc., to fulfill the accelerated approval postmarketing requirements specified in the OCALIVA approval letter dated May 27, 2016. The sNDA included data proposed to describe and verify clinical benefit for the indication of reducing the risk of death, liver transplant, and hepatic decompensation in adult patients with primary biliary cholangitis without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension, either in combination with ursodeoxycholic acid (UDCA) with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA.

Attendance:

Gastrointestinal Drugs Advisory Committee Members Present (Voting): Christopher S. Coffey, PhD, MS; Theo Heller, MD; Benjamin Lebwohl, MD, MS (*Chairperson*); Brian P. Lee, MD, MAS; Joy M. McVey (*Consumer Representative*)

Gastrointestinal Drugs Advisory Committee Members Not Present (Voting): David N. Assis, MD; Lin Chang, MD

Gastrointestinal Drugs Advisory Committee Member Not Present (Non-Voting): Wallace V. Crandall, M.D., M.M.M. (*Industry Representative*)

Acting Industry Representative to the Committee (Non-Voting): Marek J. Honczarenko, MD, PhD (*Acting Industry Representative*)

Temporary Members (Voting): Danielle Alstat, BAHM, RRT, CPFT (*Patient Representative*); Therese Bittermann, MD, MSCE; Daniel L. Gillen, PhD; David Goldberg, MD, MSCE; Patrick S. Kamath, MD *(via video conferencing platform);* Vincent Lo Re, MD, MSCE; Pamela Shaw, PhD, MS; Til Stürmer, MD, MPH, PhD *(via video conferencing platform);* Almut G. Winterstein, RPh, PhD, FISPE *(via video conferencing platform)*

FDA Participants (Non-Voting): Frank A. Anania, MD, FACP, AGAF, FAASLD; Ruby Mehta, MD; Tram Tran, MD, FAASLD, FACG; Yura Kim, PhD; Eugenio Andraca-Carrera, PhD; Joel L. Weissfeld, MD, MPH

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

Open Public Hearing Speakers Present: Susan Popfinger; Jane Gisselquist; LaToya Marie Jones-Asad; Robert Mitchell-Thain (PBC Foundation); Lance Stein, MD, FAASLD, AGAF, FACP; Tracy J. Mayne, PhD; Abigail (Abby) Hunt-Metzbower (PBCers Organization); Suzanne M. Krol; Diana Zuckerman, PhD (National Center for Health Research); Deborah F. Sobel; Leslie Stratta; Cecilia Dueñas (Fryckman), PsyD; Kris V. Kowdley, MD; Julio Gutierrez, MD; Ziad Younes, MD; Steven Flamm, MD; Robert Tyler; Robert Gish; Mitchell L. Shiffman

The agenda was as follows:

8:30 a.m.	Call to Order and Introduction of Committee	**Benjamin Lebwohl, MD** Chairperson, GIDAC
8:35 a.m.	Conflict of Interest Statement	**Jessica Seo, PharmD, MPH** Designated Federal Officer, GIDAC
8:45 a.m.	FDA Introductory Remarks	**Ruby Mehta, MD** Cross-Discipline Team Leader Division of Hepatology and Nutrition (DHN) Office of Inflammation and Immunology (OII) Office of New Drugs (OND) CDER, FDA
8:55 a.m.	**APPLICANT PRESENTATIONS**	**Intercept Pharmaceuticals, Inc.**
	Introduction	**Sangeeta Sawhney, MD** Senior Vice President, Head of US Research and Development Intercept Pharmaceuticals, Inc.
	Disease Background	**Robert S. Brown, Jr, MD, MPH** Vincent Astor Distinguished Professor of Medicine Chief, Division of Gastroenterology and Hepatology Editor-in-Chief, Liver Transplantation Weill Cornell Medical College

	Methods Used to Estimate Clinical Benefit	**Andrew Damokosh, PhD** Senior Vice President, Biostatistics Intercept Pharmaceuticals, Inc.
	Study 302 Efficacy and Safety	**Thomas Capozza, MD FACP** Vice President, Clinical Research Intercept Pharmaceuticals, Inc.
	Drug-Induced Liver Injury	**Lily Dara, MD** Assistant Professor of Medicine Department of Medicine, Division of GI/Liver USC Research Center for Liver Disease Keck School of Medicine University of Southern California
	Study 405 and Other Real-World Evidence (RWE)	**Leona Bessonova, PhD** Executive Director, Medical Affairs Research Intercept Pharmaceuticals, Inc.
	Clinical Perspective	**David Jones, OBE** Director, Newcastle Health Innovation Partners Academy Director, Newcastle Center for Rare Disease Professor of Liver Immunology, Newcastle University Honorary Consultant Hepatologist, Newcastle upon Tyne Hospitals
	Conclusions	**Sangeeta Sawhney, MD**
10:10 a.m.	Clarifying Questions to the Applicant	
10:40 a.m.	**BREAK**	
10:55 a.m.	**FDA PRESENTATIONS**	
	Clinical Pharmacology	**Tao Liu, PhD** Clinical Pharmacology Reviewer Division of Inflammation and Immune Pharmacology (DIIP) Office of Clinical Pharmacology (OCP) Office of Translational Sciences (OTS) CDER, FDA
	Study 747-302	**Tram Tran, MD, FAASLD, FACG** Medical Officer DHN, OII, OND, CDER, FDA
	Study 747-405	**Joel L. Weissfeld, MD, MPH**

		Senior Medical Officer Division of Epidemiology (DEPI) Office of Surveillance and Epidemiology (OSE) CDER, FDA
		Eugenio Andraca-Carrera, PhD Division of Biometrics-VII (DB-VII) Office of Biostatistics (OB) OTS, CDER, FDA
12:10 p.m.	Clarifying Questions to FDA	
12:40 p.m.	**LUNCH**	
1:30 p.m.	**OPEN PUBLIC HEARING**	
2:30 p.m.	Charge to the Committee	**Frank A. Anania, MD, FACP, AGAF, FAASLD** Acting Director DHN, OII, OND, CDER, FDA
2:40 p.m.	Questions to the Committee/Committee Discussion	
3:40 p.m.	**BREAK**	
4:00 p.m.	Questions to the Committee/Committee Discussion (cont.)	
5:00 p.m.	**ADJOURNMENT**	

Questions to the Committee:

1. **DISCUSSION:** Discuss whether the evidence generated post-approval verify the benefit of obeticholic acid (OCA, Ocaliva®) on clinical outcomes (hepatic decompensation, liver transplant, and death) in adults with PBC? Specifically, discuss the evidence generated in the:
    - Post-marketing required Study 302, and
    - Observational Study 405

    Committee Discussion*: In evaluating the data presented, the panel members noted concerns regarding the reliability of the evidence from both studies. There was an acknowledgement in general of the challenges in conducting Study 302 after the drug was available commercially. Some panel members were in agreement that more than treating a lab value, a drug should be treating the disease, i.e., there should be a clinical benefit. However, many panel members felt Study 302 did not verify clinical benefit (liver transplant, death, liver decompensation). There was acknowledgement that the two labeling changes that occurred while the randomized controlled trial (RCT) was ongoing, limited the ability of Study 302 to verify*

benefit. It was noted that alkaline phosphatase (ALP) normalization correlates with outcomes was based on published data from prior studies; however, the degree of correlation between the biomarker and clinical outcomes may be changing in recent times and we cannot expect clinical benefit even the drug showed effect on ALP. Regarding Study 302, some panel members acknowledged the data showed potential subgroup benefit, but the study was underpowered to conclusively verify clinical benefit in this subgroup, with one member noting the subgroup analysis was considered hypothesis-generating rather than definitive.

Panel members were also in overall agreement that the data generated by observational Study 405 were not interpretable due to uncertainties in the data validity, concerns about methodology, missing data, imbalance in index dates between the two groups, and potential differential misclassification. Concerns were expressed for reliance on codes from administrative claims and International Classification of Diseases (ICD) codes which were not cross-referenced or verified by clinical chart review to confirm whether patients in the control group actually had a clinical diagnosis of PBC. The panel questioned whether Kaplan-Meier curves that showed separation between the OCA and control cohorts within a relatively short time (as early as six months) could represent a true treatment effect, or, whether these data were more likely to be indicative of differences between the study cohorts; also whether these data demonstrated an inadequate analysis strategy. Another challenge identified was that while the Agency and the Applicant reviewed the same observational data each arrived at different conclusions. These discrepancies added to the complexity and challenges of interpreting the observational study.

While several members acknowledged the challenges of conducting a randomized controlled clinical trial under the circumstances following commercial availability of OCA all but one committee member agreed that Study 405 as an observational study did not verify clinical benefit. There was a general consensus that neither study verified a definitive benefit of OCA on clinical outcomes.

Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION:** Discuss the safety of OCA, including the incidence of liver transplant and all-cause death in the United States Prescribing Information (USPI)-labeled and the overall study population.

Committee Discussion: *In discussing the safety of OCA in the USPI-labeled and overall study populations there was overall agreement among members that the safety of OCA remains a significant concern. Several panelists pointed to the high rate of liver transplants among OCA users, including seven out of eight transplant cases in which Study 302 subjects were being treated with OCA. This led to questions and discussion about hepatotoxicity. Duration of Latency for hepatotoxicity was discussed., The Committee noted that liver transplantation might occur months or years after OCA was stopped and the Model for End-Stage Liver Disease (MELD) score might decrease just prior to liver transplant. Hence the long interval from OCA exposure to transplantation could have been the result of the long waiting time on a (liver) transplant and does not rule out the possibility that OCA was responsible for decompensation. OCA is hepatotoxic in higher doses, and the Committee was*

concerned about hepatoxicity at the lower doses used for the treatment indication. One member opined about the lessons learned from our experience with the glitazones about long latent period prior to observation of hepatotoxicity. One member stated that the hazard ratio and confidence interval for liver transplant and death as assessed by FDA analyses is not an outlier to other analyses, as asserted by the Applicant, as the point estimates for other analyses presented by the Applicant were included in the confidence interval. The imbalance in numbers of liver transplant and death on the OCA arm compared to the placebo arm was cited by several panel members and noted to be concerning.

It was noted that these clinical benefit trials do not have to prove harm and are not designed to demonstrate harm on rare events such as death and liver transplants; however, there has to be a reasonable doubt for harm. Individual practitioners might not discern these rare events. Many deaths that occurred could have been due to hepatotoxicity or underlying liver disease. Multiple panelists stressed the importance of further studies with rigorous design to clarify the risk, as the existing safety data were deemed inadequate. Please see the transcript for details of the Committee's discussion.

3. **VOTE:** Does the available evidence verify the benefit of OCA on clinical outcomes (hepatic decompensation, liver transplant, and death) in the USPI-labeled population?
    - Provide a rationale for your vote.

    Vote Result: Yes: 1 No: 13 Abstain: 0

    Committee Discussion*: The Committee members were in near unanimous agreement that the available evidence does not verify the benefit of OCA on clinical outcomes in the USPI-labeled population. In providing support for their vote, members who voted "No" cited inconclusive results from Study 302, noting the trial did not meet its primary endpoint and the numerous challenges faced by this study including crossovers due to OCA's commercial availability discussed in Question 1. In addition, panel members reiterated the unreliability of Study 405's results due to the methodological limitations detailed during discussion of Question 1 and the study was difficult to interpret. The panel member who voted "Yes" also acknowledged the inconclusive results of Study 302 but noted the real-world evidence from Study 405 suggested a benefit of OCA if given at the right dose for the right patient with appropriate follow-up. Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Is the benefit-risk profile of OCA favorable in the USPI-labeled population?
    - Provide a rationale for your vote.

    Vote Result: Yes: 1 No: 10 Abstain: 3

    Committee Discussion*: The majority of Committee members agreed that OCA's benefit-risk profile is not favorable in the USPI-labeled population. Members who voted "No" cited the unproven benefit and significant safety concerns of OCA in providing the rationale for their vote. Without clear evidence of benefit from the clinical trials, many panel members found it difficult to balance the risk of serious adverse events such as liver transplant and death. Several panel members also pointed to safety signals, particularly related to hepatotoxicity*

and decompensation, as concerning. Some panel members acknowledged challenges to discern disease progression from drug-induced hepatotoxicity. Many panelists mentioned the need for more rigorous studies to clarify the benefit-risk ratio. The unmet need for treatment options in PBC was acknowledged from all panel members, but the lack of proven benefit, as well as the presence of serious risks persuaded the majority of panelist to vote against a favorable benefit-risk profile. Those who voted "Abstain" also cited the uncertainty of the evidence for benefit and the need for more data. In addition to the panel member who voted "Yes", those who abstained also expressed empathy for patients who may have few treatment options. In terms of developing drugs for PBC, there is difficulty in the road ahead for developing second line therapies given the course of OCA and challenges in conducting such trials in the current landscape (i.e., when drug is available commercially). One panelist commented that the Agency and the industry needs to do a better job in communicating with patients the difference between surrogate endpoints versus clinical endpoints, and what it means when a drug has an accelerated approval. Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 4:18pm ET.