FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE MEETING

(GIDAC)

Friday, September 13, 2024

8:30 a.m. to 4:18 p.m.

Meeting Roster

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CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. LEBWOHL: Good morning, and welcome. I'd first like to remind everyone to please mute your line or your microphone when you're not speaking. Also, a reminder to everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. For media and press, the FDA press contact is Chanapa Tantibanchachai.

My name is Dr. Benjamin Lebwohl, and I will be chairing this meeting. I will now call the September 13, 2024 Gastrointestinal Drugs Advisory Committee meeting to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We will start with the FDA to my left and go around the table.

DR. ANANIA: Frank Anania.

DR. MEHTA: Ruby Mehta, CDTL DHN.

DR. TRAN: Tram Tran, DHN.

DR. KIM: Yura Kim, statistical reviewer.

DR. ANDRACA-CARRERA: Eugenio Andraca-Carrera, Office of Biostatistics.

DR. WEISSFELD: Joel Weissfeld, Division of Epidemiology.

DR. SEO: If we could have our virtual participants introduce themselves, starting with Dr. Sturmer.

DR. STURMER: Good morning. Til Sturmer, University of North Carolina at Chapel Hill.

DR. WINTERSTEIN: Good morning. I'm Almut Winterstein at the University of Florida.

DR. KAMATH: I'm Patrick Kamath at the Mayo Clinic in Rochester, Minnesota.

DR. LEE: I'm Brian Lee from the University of Southern California.

DR. HELLER: Theo Heller, National Institutes of Health.

DR. COFFEY: Chris Coffey, University of Iowa.

DR. SEO: Jessica Seo, designated federal officer, FDA.

DR. LEBWOHL: Benjamin Lebwohl, Columbia University.

DR. SHAW: Pamela Shaw, Kaiser Permanente, Washington Health Research Institute.

DR. GILLEN: Daniel Gillen, University of California at Irvine.

MS. McVEY: Good morning. Joy McVey, consumer representative, Atlanta, Georgia.

MS. ALSTAT: I'm Danielle Alstat. I am a patient. I have PBC, and I'm the patient rep.

DR. LO RE: Good morning. I'm Vin Lo Re, University of Pennsylvania.

DR. BITTERMANN: Tess Bittermann, University of Pennsylvania.

DR. GOLDBERG: David Goldberg, University of Miami.

DR. HONCZARENKO: Good morning. Marek Honczarenko, industry representative, SUN Pharmaceuticals.

DR. LEBWOHL: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of

opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Seo will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Lebwohl.

The Food and Drug Administration, or FDA, is convening today's meeting of the Gastrointestinal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208,

Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of

supplemental new drug application, or sNDA, 207999 S-011, for obeticholic acid, trade name Ocaliva, 5 milligram titrated to 10 milligram oral tablets, administered once a day, submitted by Intercept Pharmaceuticals, Incorporated, to fulfill the accelerated approval postmarketing requirements specified in the Ocaliva approval letter dated May 27, 2016.

The supplemental NDA 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, or UDCA, with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. This is a particular matters meeting during which specific matters related to Intercept Pharmaceutical, Incorporated's supplemental NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208 (b)(3) to Dr. Benjamin Lebwohl. Dr. Lebwohl's waiver involves his investment holdings in a healthcare sector mutual fund. The waiver allows this individual to participate fully in today's deliberations.

FDA's reasons for issuing the waiver are described in the waiver documents, which are posted on FDA's website on the advisory committee meeting page, which can be found at www.fda.gov, and by searching on September 13, 2024 GIDAC. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they

have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Marek J. Honczarenko is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Honczarenko's role at this meeting is to represent industry in general and not any particular company. Dr. Honczarenko is employed by SUN Pharmaceutical Industries, Incorporated.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue.

Thank you, and I'll return the floor to

Dr. Lebwohl.

DR. LEBWOHL: We will now proceed with FDA introductory remarks, starting with Dr. Ruby Mehta.

FDA Introductory Remarks - Ruby Mehta

DR. MEHTA: Good morning. My name is Ruby Mehta, and I'm a cross-discipline team leader in the Division of Hepatology and Nutrition, in the Office of New Drugs, CDER, FDA. On behalf of my team, I welcome everyone attending the advisory committee meeting, both in person and virtually. I would like to thank the advisory committee members; the applicant, Intercept Pharmaceuticals; FDA colleagues; and the general public for attending this advisory committee meeting.

Today, we will be discussing the confirmatory studies submitted for obeticholic acid for the treatment of patients with primary biliary cholangitis with or without concomitant ursodeoxycholic acid. Primary biliary cholangitis may be used synonymously as PBC, and ursodeoxycholic acid may be referred to as UDCA in today's presentation and discussion.

Primary biliary cholangitis is a rare cholestatic liver disease that causes destruction of small bile ducts. The disease progresses very slowly. Patients may progress to cirrhosis and its complications, leading to liver transplantation or death. PBC predominantly affects middle-aged women.

FDA-approved treatment includes UDCA that was approved under traditional approval pathway in 1997; however, about 40 percent of PBC patients do not respond to UDCA. Second-line therapies include Ocaliva, elafibranor, and seladelpar, all approved via accelerated approval program using alkaline phosphatase and total bilirubin as surrogate endpoints. Off-label treatment of PBC includes use of fibrates. Despite the availability of these drugs, there remains an unmet medical need for UDCA non-responders, UDCA intolerant patients, and in patients with associated symptoms such as pruritus and fatigue.

For the remaining part of this talk, I will be using obeticholic acid synonymously as OCA. OCA

is a synthetic derivative of chenodeoxycholic acid. OCA is a farnesoid X receptor agonist. The postulated mechanism of action is that OCA reduces bile acid biosynthesis, which leads to its anti-inflammatory and anti-fibrotic properties; however, OCA is less polar compared to the endogenous bile acids.

This slide describes the regulatory framework of drug approval at the FDA. Traditional approval can be based on a clinical endpoint, which includes how a patient feels, functions, or survives, or a validated surrogate endpoint, for example, systolic blood pressure or hemoglobin A1C. Accelerated approval is intended to facilitate and expedite the drug development of new drugs to fill an unmet medical need for a serious or life-threatening condition. Accelerated approval can be based on a surrogate endpoint that is reasonably likely to predict clinical benefit.

For drug development in PBC, FDA has agreed with use of alkaline phosphatase and total bilirubin as surrogate endpoint; however, there

remains uncertainties of clinical benefit when a drug is approved through an accelerated approval pathway using surrogate endpoint. So what does it mean? In simple language, there is uncertainty whether the improvement in laboratory numbers, or values, that occur as a result of the treatment with a new drug will translate to decreased risk of poor outcomes such as death, liver transplant, or decompensation events; therefore, the FDA requires completion of confirmatory trials to verify and describe the clinical benefit.

For drugs approved through accelerated approval pathway, the drug approval can be withdrawn if the confirmatory trial fails to verify the clinical benefit. These requirements were addressed by a recent legislation, the Consolidated Appropriations Act, which granted FDA additional authorities regarding accelerated approval. This included authorizing FDA to require, as appropriate, that a confirmatory trial be underway at the time of accelerated approval and specifying new expedited procedures for withdrawal of an

accelerated approval.

So to summarize -- this is a busy slide -- before moving to the next slide, I would like to reiterate that applicant received accelerated approval with alkaline phosphatase and total bilirubin as surrogate endpoint in 2016, and a confirmatory trial to verify the clinical benefit, namely a trial showing decrease in risk of poor outcomes, was still required.

A brief overview of regulatory history; to meet the postmarketing requirement for accelerated approval, the applicant began confirmatory Trial 302 in 2015. A second postmarketing requirement trial was issued after approval of OCA; that is, Trial 401, which was intended to demonstrate pharmacokinetics, pharmacodynamics, and safety of OCA in Child-Pugh B and C population. In February 2018, FDA added a boxed warning for hepatotoxicity and reiterated correct dosing in patients with decompensated cirrhosis. Despite issuing the boxed warning, FDA continued to receive spontaneous adverse events and identified 25 cases

of serious liver injury that were reported to the FDA Adverse Event Reporting System and published in the medical literature, describing liver failure or decompensation events in patients with cirrhosis.

In May 2021, the division contraindicated the use of OCA in patients with decompensated cirrhosis, a prior decompensation event, or compensated cirrhosis with evidence of portal hypertension. Subsequent to the safety labeling changes, Trial 401 was terminated because OCA was now contraindicated for population enrolled in the trial.

In December 2021, the applicant proposed conducting an open-label trial using a historic comparator, along with revisions of the composite primary endpoint because Trial 302 did not reach the prespecified 127 events. FDA did not agree to conduct an open-label trial, however, agreed with adding new endpoints, which increased the primary endpoints to 151 events, allowing closure of the trial.

With contraindication added to labeling,

55 percent of subjects in Trial 302 were now classified as contraindicated for OCA per the labeling and will be referred to as USPI-contraindicated population. The remaining 45 percent who were still eligible to receive OCA will be referred to as USPI-labeled population. Dr. Tran will describe these populations later today. In January 2022, the applicant submitted real-world evidence protocol. There was no agreement on statistical analysis plan for this observational study.

The two studies that will be discussed today are Study 302, a randomized, double-blind, placebo-controlled, event-driven trial. A total of 127 events were needed for study closure. In this trial, non-cirrhotic subjects and subjects with Child-Pugh A and Child-Pugh B with PBC were randomized in a 1 to 1 ratio to receive either OCA or placebo. The prespecified composite primary endpoint included all-cause death; liver transplant; MELD of greater than or equal to 15; uncontrolled ascites; hospitalization due to

variceal bleeding; grade 2 or above hepatic encephalopathy; and spontaneous bacterial peritonitis. This study will be discussed in detail by Dr. Tram Tran.

Study 405 is an observational study conducted using U.S. administrative claims linked to two major laboratory service providers, organ procurement and transplantation network, or OPTN; Social Security Death Index, or SSDI; and a commercial obituary search service. Study 405 used laboratory data to identify PBC, define eligibility, and operationalize covariates for baseline adjustments. Study 405 used pharmacy claims to define OCA exposure; diagnoses codes on hospital claims to identify hepatic decompensation outcomes; OPTN to identify date of liver transplantation; and SSDI and/or obituary search to identify date of death. The study will be discussed in detail by Dr. Weissfeld and Dr. Andraca-Carrera.

The applicant's proposed revised indication is as follows: to reduce the risk of death, liver

transplant, and hepatic decompensation in adults with PBC. The remaining part of the indication statement is projected on the slide, which states the conditions in which a drug is to be used. The proposed dosage regimen includes OCA 5 milligram titrated to 10 milligram, administered once daily.

Today, we will be asking the advisory committee members to opine on two discussion and two voting questions. Discuss whether the evidence generated post-approval verifies the benefit of OCA on clinical outcomes in adults with PBC. Specifically discuss the evidence generated in PMR Study 302 and observational study 405. Discuss the safety of OCA, including the incidence of liver transplant and all-cause death in the USPI-labeled and overall study population.

For voting questions, please provide a rationale for your response. Does the available evidence verify the benefit of OCA on clinical outcomes in the USPI-labeled population? And second, is the benefit-risk profile of OCA favorable in the USPI-labeled population?

Thank you for your attention. We look forward to thoughtful and robust discussions today of these issues. I will now turn the meeting to Dr. Lebwohl.

DR. LEBWOHL: Thank you, Dr. Mehta.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including industry's non-employee presenters, to advise the committee of any financial relationships that they may have with industry, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interests and those based upon the outcome of this meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the

committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the presentation from Intercept Pharmaceuticals, Incorporated.

Applicant Presentation - Sangeeta Sawhney

DR. SAWHNEY: Good morning. My name is Sangeeta Sawhney, and I'm U.S. Head of Research and Development at Intercept Pharmaceuticals. On behalf of the Intercept team, we would like to thank the patients and the entire PBC community for their role in generating the data we will share this morning.

Here is the agenda for our presentation today. After my brief introduction, Dr. Brown will review the disease background; Dr. Damokosh will discuss methods used to estimate clinical benefit; Dr. Capozza will review Study 302; Dr. Dara will provide her perspective on the important topic of drug-induced liver injury; Dr. Bessonova will

review Study 405 and other real-world evidence; Professor Jones will provide his overall clinical perspective; and I will return to conclude our presentation. In addition, Dr. Dreyer and Professor Hirschfield are available to answer questions.

PBC is a rare, serious, progressive liver disease that mostly affects women in their mid 50s. UDCA was first approved in 1997 as first-line therapy; however, 45 percent of patients with PBC have an inadequate response or are intolerant, and these patients remain at high risk for end-stage liver disease. Therefore, there is a clear unmet need for second-line therapies with different mechanisms of action.

Ocaliva, also referred to as OCA, in our presentation was the first approved second-line therapy for PBC. It received accelerated approval in 2016 based on Study 301, a randomized, placebo-controlled study, which showed reduction in alkaline phosphatase, ALP, which is widely accepted as a surrogate marker linked to clinical outcomes

in PBC.

OCA has been studied across the PBC disease spectrum, and it's important to understand the evolution of its labeled indication for PBC in this context. Although Study 301, in light purple, excluded patients with decompensated cirrhosis, OCA was originally approved in 2016 with a broad label, including patients with end-stage liver disease. Importantly, patients in Study 301 were followed in a 5-year, long-term safety extension.

Study 302, shown in dark purple, was a randomized, placebo-controlled study that was established as a postmarketing requirement to confirm benefit based on clinical outcomes. It began enrolling patients before OCA became commercially available, and it included patients with more advanced disease in order to allow accrual of events in a timely manner.

Study 405, shown in light blue, was an observational study which largely aligns with the 2021 USPI population, and it used real-world evidence to assess clinical benefit. Since OCA's

approval in 2016, we have learned that patients with more advanced disease are not an appropriate population for OCA, and this was reflected in a change to the USPI in 2021.

In addition to contraindications for patients with advanced disease, as summarized on the left, the 2021 USPI also provided recommendations for monitoring and management, including discontinuation if a patient developed criteria for a contraindication while on therapy. Approximately half of the patients enrolled in Study 302 would now be contraindicated based upon these label changes.

With this as background, let's now turn to the key topics for our discussion today. There are four areas where our position is not aligned with the FDA. These include interpretation of Study 302 for confirmation of benefit; Study 302 USPI subgroup liver transplants and deaths; and study 405. You will see the USPI subgroup is noted in quotation marks, which I will explain in a moment. In addition, FDA has raised concerns regarding the

predictability and management of drug-induced liver injury.

Starting with the interpretation of Study 302, it is our position that the ITT analysis in Study 302 is flawed. While FDA concluded that OCA's clinical benefit has not been demonstrated, there was substantial functional unblinding that led to treatment crossover and informative censoring, concepts which Dr. Damokosh will describe shortly. In addition, Dr. Capozza will show that adjustments for these biases show a benefit.

As we assess Study 302, there are two considerations outlined by the FDA that are important to highlight regarding confirmatory trials. Number one, when a confirmatory trial does not meet its endpoint, it does not necessarily mean that the drug is not effective for the indication approved through accelerated approval; and number 2, when trials do not appear to confirm clinical benefit, we must carefully assess each case and consider the underlying reasons.

Next, let's review FDA's comments related to liver transplants and deaths in the Study 302 USPI subgroup. It is our position that these data are unreliable to assess harm, as they are inconsistent with all other available evidence. I previously referred to the USPI subgroup in quotation marks, and here is why. This subgroup was not prospectively defined; number two, it was not randomized; and number three, it was not managed according to the 2021 USPI. In fact, because the study was largely complete before the 2021 USPI update, this subgroup of patients did not even exist during the conduct of Study 302.

Lastly, FDA suggests that subjects early in disease would not be expected to progress to liver transplant or death; however, as Dr. Brown will discuss, disease progression can occur in this group of high-risk patients who have failed first-line therapy.

Here, we see hazard ratios with 95 percent confidence intervals for liver transplants and deaths across Study 302, Study 405, and several

additional real-world evidence studies, which Dr. Bessonova will describe. Looking across the entire forest plot, including FDA's own ITT analysis of Study 405, shown in blue, it is clear that the Study 302 USPI subgroup results are an outlier.

If the hazard ratio of 4.77 for liver transplant deaths in the Study 302 USPI subgroup was indeed real, then we would expect to see similar results in the 301 long-term safety extension, our postmarketing experience since the 2021 label update, and even FDA's own ITT analysis from Study 405, as shown from left to right. The predicted rate of events, based on the hazard ratio 4.77 shown in purple, are in stark contrast to the actual rate of events observed in green. Once again, these data demonstrate that the Study 302 USPI subgroup results are unreliable to assess harm.

Turning to Study 405, FDA stated that the study does not meet regulatory standards for an adequate and well-controlled trial; however, it is

our position that Study 405 is well designed and is consistent with FDA guidance and rigorous prespecified best practices for pharmacoepidemiology. The study protocol and the SAP were submitted for agency's review. In addition, the hazard ratio for event-free survival is consistent with multiple other real-world evidence supporting OCA's clinical benefit.

FDA conducted its own analysis, which only includes liver transplants and deaths, and concluded that clinical benefit has not been shown. Although FDA's ITT-like analysis is not powered for this 2-point composite, the hazard ratio of 0.8 still shows a trend for benefit.

Lastly, let's turn to the important topic of DILI. FDA states that DILI with OCA cannot be predicted or managed; however, all cases of DILI in the USPI subgroup occurred early and were identifiable with routine lab biomarkers and were fully reversible with OCA discontinuation.

In addition to PBC, OCA has also been studied in metabolic dysfunction associated

steatohepatitis, also known as MASH; therefore, I would like to highlight a few distinct differences between the two diseases. First, PBC is a rare disease managed by specialists. Second, the starting dose for PBC is 5 milligrams daily, one-fifth of the 25-milligram dose proposed for MASH. Lastly, since we have more than 8 years and more than 42,000 patient-years of clinical experience with OCA in PBC, safety is well characterized.

In addition, clinicians are experienced in using OCA in appropriate patients with appropriate follow-up under the 2021 USPI. Given that PBC is a rare disease, it is almost exclusively managed in specialty practices, and because OCA is only available through specialty pharmacies, preauthorization requirements guide safe use in appropriate patients.

As you deliberate whether OCA has demonstrated clinical benefit that outweighs risk, it is important to highlight FDA uses a totality-of-evidence approach, and for a rare

disease such as PBC where there remains unmet need, a flexible patient-focused approach is particularly appropriate. The totality of evidence across Study 302, Study 405, three large PBC patient registries verifies benefit. Regardless of study design, data source, or methodology, the point estimate for event-free survival is consistently to the left of unity. This shows that OCA is having a clinically meaningful impact on the long-term outcomes of patients living with PBC.

Thank you, and I will turn it over to Dr. Robert Brown.

Applicant Presentation - Robert Brown

DR. BROWN: Good morning. I am Robert Brown, Chief of the Division of Gastroenterology and Hepatology at Weill Cornell Medicine in New York City. I've been a practicing hepatologist for 30 years and take care of hundreds of people with PBC. I am a paid consultant to Intercept Pharmaceuticals, but I have no other financial interest in the company or in the interest in the outcome of this meeting.

PBC is a rare and serious disease managed by specialists, specifically hepatologists and gastroenterologists. It is a dynamic progressive disease in which autoimmune damage to small intrahepatic bile ducts gives rise to cholestasis and inflammation, leading to fibrosis and ductopenia, and eventually cirrhosis, which can decompensate. This progression is reflected in the changing pattern of biomarkers, starting with alkaline phosphatase, or ALP, and gamma GT. Later on, we see elevations in bilirubin, and eventually evidence of portal hypertension with advanced cirrhosis.

Disease progression does vary among patients, and some patients, even early in their disease, can progress quickly, particularly those with elevated ALP. Disease progression can also occur despite therapy, so it is really important to intervene early to prevent progression to cirrhosis and avoid all of its complications, including portal hypertension.

Turning to outcomes, ALP is the best

non-invasive predictor we have. Monitoring ALP over time is what we do. It's in all our major international guidelines, and both clinicians and their patients understand its importance. This is data from the Global PBC study group.

On the left, we see that elevations of ALP to varying degrees is associated with more rapid progression and significantly increased risks of death or need for liver transplantation. The red arrow represents the threshold for clinical trials of patients who are non-responders to first-line URSO. They are clearly a high risk group. On the right, we see what this elevation in ALP over time translates to. In the lighter purple lines, anyone with any abnormal ALP has an increased risk of death, about 20 percent at 10 years, compared to those in dark purple with a normal ALP.

We knew all along that lowering ALP is important, but it took decades of high-quality registry data to know how important, and it turned out to be more important than we even knew. What happens to ALP without effective treatment? We

learned it does not change based on several placebo-controlled trials in PBC. The placebo arm shown here includes patients who are non-responders to URSO and continue on URSO alone. What you see over 12 months is there is no change at all in ALP. This is absolutely typical of the disease. So untreated ALP does not change, but with treatment, we can lower ALP, and we recognize the patients with the best outcomes have the best liver tests.

So what treatment options do we have today to lower ALP and improve other biomarkers? UDCA is the only first-line treatment; however, 40 percent of patients have an inadequate response, and this spans across the entire disease spectrum. Second-line agents include OCA, which is the only approved FXR agonist and PPAR agonist. These include elafibranor and seladelpar, which were recently approved, and fenofibrate and bezafibrate, which are not approved for PBC but are sometimes used off label. The latter is not available in the United States.

Just as in other disease states such as

hypertension and IBD, we will need different mechanisms to get all of our patients to the lowest possible ALP to optimize outcome. In fact, recent data has shown the potential benefit of triple therapy on biomarkers. UDCA targets the bile acids pool and thereby impacts cholestasis and inflammation. PPAR agonists also only impact cholestasis and inflammation. In contrast, FXR agonists target all three pathogenic mechanisms.

So how do we use obeticholic acid today? Candidates for OCA are my patients with PBC who have inadequate response to UDCA and who, based on staging and clinical assessment, are either non-cirrhotic or have an absence of current or prior decompensating events or portal hypertension, as evidenced by ascites, varices, or persistent thrombocytopenia; and we do these assessments every day in our clinical practice.

So how do we manage our patients on OCA? We start at a low dose and we monitor our patients per our standard practice with labs, imaging, and clinical assessments. We know to stop OCA if

patients progress to decompensation, new portal hypertension, or worsening LFTs. As a result, OCA is now standard in hepatology practice, and as a field, we have experience with OCA for more than 8 years. We have seen an improvement in patient outcomes firsthand, and this has been confirmed in independent research and real-world data.

I'll now pass the presentation to Dr. Damokosh.

Applicant Presentation - Andrew Damokosh

DR. DAMOKOSH: Good morning. My name is Andrew Damokosh. I'm Head of Biometric Sciences at Intercept Pharmaceuticals, and I'll provide perspective on the analysis method conducted in Study 302. First, I'll review the primary objective of Study 302. Next, I'll explain why functional unblinding is a concern, including informative treatment crossover and informative censoring. I'll conclude with the impact of functional unblinding on the interpretability of the study conclusions.

Let's start with the study's objective,

which was to assess the benefit of OCA on subjects who received OCA compared to those who did not. The prespecified primary method of analysis was an intention-to-treat approach, or ITT, conventionally referred to as "analyzed as randomized."

In this approach, all follow-up time is included regardless of what is referred to as intercurrent events or ICEs. ICEs are events that occur over the course of the study that -- and this is crucial -- may impact the interpretation of the end point of interest. A good example of an ICE is treatment crossover, where patients randomized to placebo initiate OCA. Any occurrence of ICEs will not be accounted for in the estimate of clinical benefit from the ITT analysis; therefore, the ITT analysis cannot answer the primary objective.

On the next slide, I will review the overarching concern as it relates to Study 302. On this slide, we see change in mean ALP over time for the placebo arms of Study 302 and two other PBC studies. The two panels on the right indicate the established natural history of PBC, where ALP in

untreated patients is stable or increasing over time. In stark contrast, mean ALP in Study 302 steadily decreased over time.

This occurred for two important reasons: one, some placebo patients initiated commercial treatment; and two, others discontinued from the study with high ALP. This leads to a control arm that includes patients who are treated and others who are at lower risk of disease progression due to loss of patients with high ALP. This observed behavior is driven by functional unblinding.

Functional unblinding arose from patients having regular access to their liver biochemistries, in particular ALP. As Dr. Brown mentioned, patients and their clinicians are well educated on the prognostic importance of ALP. Armed with information regarding changes in ALP during the study, they may assume they know their randomization assignment and make treatment decisions accordingly. Those with ALP improvements are more likely to continue study drug, but those with worsening ALP are more likely to take

corrective action by either initiating a commercial therapy or discontinuing the study.

In 302, this occurred more in the placebo arm, leading to a biased estimation of the treatment effect. With worsening ALP, one possible decision is to initiate commercial therapy such as OCA. We refer to this as informative treatment crossover. The figure depicts the time to initiating any available commercial therapy. An event here is defined as initiating commercial therapy, including fibrates and OCA. Censored patients are patients who discontinued study and never received commercial therapy.

The FDA concluded that the overall proportion of patients on commercial therapy was not importantly different between the two arms and that informative treatment crossover had minimal impact on the ITT analysis; however, the treatment arms are balanced only when looking at the end of the study. We must also consider what happens over the course of the study. The highlighted area shows that placebo patients initiated commercial

therapy earlier, as early as 9 months, and more frequently than OCA patients. Early intervention with treatment is likely to impact the disease progression of PBC. Since the ITT approach does not account for the higher rate of informative treatment crossover in the placebo subjects, it underestimates the clinical benefit.

Another option for patients with worsening ALP is to discontinue the study completely. This can lead to informative censoring. Informative censoring occurs when the reason for study discontinuation is related to the probability of having an event.

Recall the ALP curve in the placebo group I presented earlier. One reason for the downward trend is due to early discontinuations in patients with elevated ALP or higher risk patients. As a result, the event rate in the placebo arm is underestimated due to higher risk patients discontinuing the study. This represents informative censoring and leads to a biased estimation of clinical benefit in the ITT analysis.

To determine if informative censoring occurred in Study 302, we looked at the rate of study discontinuation based on changes in ALP and total bilirubin. The figure shows the cumulative incident of study discontinuation prior to experiencing an outcome. The red line is patients without biochemical improvement, while the purple line is patients with biochemical improvement. If there was no informative censoring, we would expect the two lines to overlap; however, you can see that there is clear separation. Those with biochemical improvement discontinue sooner and more often. Since there are nearly twice as many placebo patients without biochemical improvement compared to OCA, informative censoring biases the estimate of clinical benefit towards the null.

So where does this leave us? How can we best interpret the results of Study 302 in the context of the study's objective? The ITT approach does not account for informative treatment crossover, nor does it account for informative censoring biases we observed. To adjust for

informative treatment crossover, we conducted an as-treated analysis, where randomized placebo patients who received at least one dose of commercial OCA were reclassified to the randomized OCA treatment group.

To adjust for informative censoring, we used the inverse probability of censoring weights methodology or IPCW. While these post hoc results aren't confirmatory, Dr. Capozza will show that the results from both analyses show a greater magnitude of clinical benefit compared to the ITT analysis.

I would like to close with three key points. First, the ITT analysis cannot answer the primary objective as it did not account for the important biases outlined; second, correction for these biases support the clinical benefit of OCA; and third, since these sensitivity analyses are inconsistent with the ITT analysis, the ITT results are not robust and cannot be used as the sole basis for confirming OCA's benefit. Thank you, and I will now turn the podium over to Dr. Capozza, who will review the Study 302 results.

Applicant Presentation - Thomas Capozza

DR. CAPOZZA: Good morning. I'm Tom Capozza, Vice President of Clinical Research at Intercept Pharmaceuticals, and I'll present the efficacy and safety data for Study 302.

Now, as you heard, Study 302 was designed to answer the primary research question of whether there's a difference in clinical outcomes between subjects not treated with OCA and subjects treated with OCA. In contrast to Study 301, which was the basis of accelerated approval, Study 302 enrolled patients with more advanced disease. In fact, the mean ALP at study entry for Study 302 was over 400. This was done to assess a broader range of PBC disease spectrum and to allow for a timely capture of outcome events.

A total of 334 patients with PBC were enrolled with 166 randomized to the placebo arm and 168 to the OCA arm. The primary endpoint was an ITT analysis of an outcomes composite, including death, liver transplant, and other events related to end-stage liver disease. Now importantly, the

study design did not prohibit crossover to commercial Ocaliva or initiation of fibrates.

On this slide are the key milestones for Study 302. The first patient was enrolled in February of 2015. OCA became commercially available in 2016, and the last patient was enrolled in December of 2020. Now, in May of 2021, the USPI updated to contraindicate OCA use in patients with compensated cirrhosis with portal hypertension, Child-Pugh B/C cirrhosis, or any decompensated liver disease; and in September of 2021, as enrollment and retention challenges mounted, an agreement was reached with FDA to expand the primary endpoint and to perform a retrospective analysis of USPI-indicated or contraindicated subgroups based upon the May 2021 label update.

Ultimately, the independent data monitoring committee recommended the study be stopped early due to feasibility challenges, and the FDA agreed. The last patient visit was in December of 2021.

Here, we see the expansion of the primary

endpoint for Study 302, which was finalized prior to data lock and unblinding. It included additional liver disease outcomes such as progression to new portal hypertension without decompensation, progression of hepatic impairment to Child-Pugh B/C status or decompensation, and any of the portal hypertension syndromes. The primary prespecified analysis for Study 302 involved an ITT approach in which subjects were analyzed as randomized and not censored for discontinuation of investigational product or initiation of fibrates or commercial Ocaliva.

As you heard from Dr. Damokosh, the ITT analysis for Study 302 is flawed due to biases related to treatment crossover and informative censoring. Now, to adjust for these biases, as-treated and IPCW sensitivity analyses were conducted.

In the top row of this slide, we see the primary expanded outcome results for Study 302 in the overall population. The study did not meet its primary endpoint with an ITT analysis hazard ratio

of 0.84 and a confidence interval that includes 1; however, in the second row, we see the sensitivity analysis which adjusts for both treatment crossover and informative censoring, demonstrating the benefit of OCA with a hazard ratio of 0.69 and a confidence interval that excludes 1.

The bottom two rows show the retrospectively defined USPI subgroup. The ITT analysis results in a hazard ratio of 0.88 with a broad confidence interval and the adjusted analysis results in a hazard ratio of 0.66 that also includes 1. All four point estimates for the expanded primary endpoint are to the left of unity, indicating a consistent trend toward benefit with OCA treatment.

Before we review the USPI subgroup analysis in more detail, it's important to highlight three key limitations. First, the subgroup was not prospectively defined; therefore, there's potential for misclassification, as all of the data needed to define these subjects was not prospectively collected or recorded in the case report forms at study entry.

Second, patients in this subgroup were not stratified at randomization according to their baseline status, which could lead to potential imbalances between the study arms. And finally, because the last patient was enrolled 5 months before the 2021 label came into existence, patients were not managed according to the 2021 label. This means patients could continue OCA treatment during the study, even after they developed a clear contraindication.

Let's take a close look at the USPI subgroup results for death and liver transplant. In the top row, we see the overall ITT population with a hazard ratio of 1.15. In the second row, we see the contraindicated subgroup. The event rates are 24 to 26 percent, which are higher than we see in the overall population, and this is to be expected since the contraindicated group represents a more advanced population; however, there is no difference between placebo and OCA, with a hazard ratio of 0.94.

In the bottom row is the USPI subgroup with

a hazard ratio of 4.77. That 4.77 hazard ratio is in stark contrast to the 0.9 hazard ratio we see in the contraindicated subgroup, so it does not seem to be clinically possible for the USPI subgroup to have a greater risk of death and transplant compared to the contraindicated subgroup, which is a more advanced liver disease population. And as Dr. Sawhney showed in her introductory comments, the rate of death and liver transplant seen in this USPI subgroup for Study 302 is not consistent with actual observed data.

I'll now turn to an assessment of hepatic safety in Study 302. I'll first review all of the liver transplants and deaths which occurred in the USPI subgroup, then I'll discuss drug-induced liver injury, and I'll conclude with a review of our cumulative postmarketing data for hepatic safety.

It is our position that the liver transplants and deaths that occurred in the USPI subgroup are not evidence of underlying OCA-related drug-induced liver injury. You'll see that these were high-risk patients at baseline, and disease

progression in this population is not unexpected since PBC is not an indolent disease. Further, the latency argues against drug-induced liver injury, and these events occurred before the 2021 USPI label update.

This is a table of the 8 liver transplants that occurred in the USPI subgroup. On the far-left column, we've used the same patient numbering as was provided by the FDA in their briefing document alongside their treatment assignments. As we see in the highlighted column, 6 of the 8 patients had abnormal bilirubin levels at baseline, and regardless of documented cirrhosis status, elevated bilirubin is indicative of more advanced disease. And we know that serum bilirubin is an independent predictor of prognosis in patients with PBC; therefore, all of these patients that were retrospectively classified as being part of the USPI subgroup, they were nonetheless at high risk of progression at study entry.

Next, I'll talk about patients 6 and 7, the two patients with normal serum bilirubin at

baseline. Patient number 6 is a 58-year-old female who underwent a planned liver transplant due to pruritus with a MELD score of 6, indicative of essentially normal liver function. I'd like to note that liver transplantation due to pruritus is extremely rare. This patient had a long history of pruritus, refractory to numerous medical therapies, even undergoing experimental treatments prior to study entry.

Patient number 7 is a 43-year-old female with alcohol-use disorder, chronic pancreatitis with insufficiency, and insulin-dependent diabetes, as well as a baseline alk-phos of 616 units per liter, more than 5 times the upper limits of normal. Now, while this patient was programmatically classified as being within the USPI subgroup, upon case-level review of her medical records, she had evidence of portal hypertension at baseline with splenomegaly and an endoscopy report with possible esophageal varices. Now, per the 2021 label, due to her portal hypertension, this patient would not be eligible to

initiate OCA treatment today.

Next, let's look at time from contraindication to event. The first thing to notice is that all patients, except patient 6, became contraindicated to OCA years before undergoing a liver transplant. Patient number 1 developed portal hypertension while on placebo before switching to commercial Ocaliva, and went to liver transplant 2 and a half years later.

Patients 2 and 3 developed portal hypertension without bleeding within a year of study entry, and went on to liver transplantation approximately 3 years later. Patient 4 with a baseline bilirubin of 2.6 progressed to Child-Pugh 2B status based on labs, not due to a decompensation event, and went on to transplant nearly 2 years later.

Patient 5 also developed portal hypertension without bleeding within a year of study entry, and went on to a liver transplant about 2 and a half years later. Patient 7 had evidence of portal hypertension at baseline, and went on to transplant

almost 2 years later, and patient 8 with a baseline bilirubin of 2.4 progressed to Child-Pugh B cirrhosis based on labs, not on decompensation, and went on to liver transplant about a year and a half later. Now, the clinical picture from these cases is one of underlying disease progression in high-risk patients with PBC rather than an acute or subacute liver injury due to OCA.

Lastly, looking at time off IP to event, notice that most patients were off investigational product for months to years before the liver transplant, 2 patients having been off OCA for more than a year before their transplant, and three off OCA for about 2 years before their liver transplant. And as I mentioned earlier, all of these transplants occurred before the 2021 label update, which now contraindicates OCA use in patients with portal hypertension, Child-Pugh B/C, or decompensated cirrhosis.

Now, to help visualize the time course of the liver transplant cases, this slide shows a bar graph of the same 8 patients. I want to first

point out that the numbers in the bar represent the time in years. The red diamond represents the timepoint when the patient developed evidence of more advanced disease, in other words, a contraindication to the 2021 label. The black circle indicates when they underwent liver transplantation. The purple bar is the time on OCA, and the white is the time from discontinuation of OCA to liver transplant.

Now, aside from patient 6, who had a planned liver transplant due to pre-existing pruritus, all the other patients developed evidence of more advanced liver disease well before progressing to liver transplant, the space between the red diamond and the black circle.

Now, I'd like to briefly discuss patient 1, who was started on placebo but then switched to commercial Ocaliva, as this case is referenced in the agency's briefing document. This patient progressed to portal hypertension with thrombocytopenia, splenomegaly, and a liver stiffness measurement by Fibroscan of

22 kilopascals while on placebo, as seen in the gray bar. This was before making the switch to OCA.

This patient had undetectable plasma levels of OCA at year 2 and a MELD score of 9 when they permanently discontinued OCA, which is at the end of the purple bar. In addition, excluding patient 6, the other patients had MELD scores ranging from 9 to 15 at the time they permanently stopped OCA. This is below the typical threshold where patients will be considered for liver transplantation. Now, our careful review of these cases tells us that there's no evidence that these patients are experiencing underlying drug-induced liver injury due to OCA; rather, these are high-risk patients with PBC who have experienced disease progression.

Next, I'll review the 5 deaths that occurred in the USPI subgroup. As you can see in the highlighted columns, 4 of the 5 patients clearly had non-liver-related deaths. These 4 deaths were due to complications after hip fracture surgery, a

subdural hematoma, B cell lymphoma, and multiorgan failure with *C. diff* colitis.

Patient 12 is the one liver-related death. This is a 42-year-old female with splenomegaly as well as an abnormal total bilirubin of 2.0 milligrams per deciliter at baseline. Esophageal varices were noted at month 12. She remained on OCA, and then presented with a refractory variceal bleed about a year and a half later. In addition, the events from this case were reviewed and adjudicated by the blinded DILI committee, all unlikely related to OCA.

Based on these details I've just reviewed, the 8 liver transplants and the 5 deaths in the USPI subgroup are indicative of disease progression in a high-risk patient population rather than evidence of an hepatotoxicity or harm related to OCA.

I'll next turn to the DILI adjudication in Study 302. First, it's important to remember that OCA is a bile derivative. It's modified from the primary bile acid, chenodeoxycholic acid. Bile

acids have been studied as therapeutic interventions for years and are known to have the potential to cause direct exposure or dose-dependent hepatotoxicity, and like other bile acids, OCA exposure increases with hepatic impairment. As has been discussed, the 2021 USPI label update now contraindicates OCA use in patients with evidence of more advanced liver disease, and it also provides guidance on monitoring and managing OCA for drug interruption or discontinuation.

Now, in this slide, we see the proportion of patients with an adjudicated potential liver injury event based on severity as assessed by the independent blinded adjudication committee. Of the 334 patients in Study 302, there were 184 patients with events centrally reviewed that were considered as potential liver injury, 99 on placebo and 85 on OCA.

As shown on the left, a higher proportion of events and higher severity events were adjudicated in the contraindicated subgroup, which is entirely

consistent with patients that have more advanced liver disease. As seen on the right, 57 patients in the USPI subgroup had a potential liver injury event with a higher proportion on placebo compared to OCA. While there was one serious event in the placebo arm, no patients in the USPI subgroup had an event on OCA adjudicated as severe or fatal. In terms of causality, there were no cases adjudicated as probably or highly likely related in the USPI subgroup; however, there were 5 cases adjudicated as possibly related, four on OCA and one on placebo. I'll review these next.

Now, of these 4 cases possibly related to OCA in the USPI subgroup, the agency adjudicated three to be related and one to be unrelated. These three OCA patients are shown on this table in addition to the one placebo patient. None of these patients were found to be contraindicated to OCA at baseline and at the time of the event; in other words, they started and stayed on the USPI label.

In the highlighted columns, you see the DILI adjudication committee's assessment along with the

cited clinical confounders. The DILI committee based their severity and causality assessment on the drug-induced liver injury or DILIN criteria. At a level set, adjudication as possibly related means the available evidence does not definitively exclude the possibility of a causal role, but another etiology, the confounder, is more likely to be the cause of the injury. All of these cases had confounders per our committee, including gallstones, background disease, and two on rifampicin. Note, there was one mild severity case on OCA and 3 cases of moderate to moderate-severe severity, two on OCA and one on placebo.

In the highlighted column, you see the onset of the events were within the first 3 to 4 months after starting therapy. Two of the three OCA cases, numbers 14 and 15, had a predominant elevation of transaminases consistent with an hepatocellular pattern despite their background cholestasis, with one case, subject number 6, having an ALP predominant elevation with a normal bilirubin. Importantly, the cases on OCA resolved

and returned to baseline after appropriate interventions, including discontinuation of OCA and managing the confounders like rifampicin or symptomatic gallstone disease. This supports that OCA use is safe in the right patients with monitoring and management.

Finally, I'll review the postmarketing hepatic safety data. On this slide, we see impact of the 2021 label update on our cumulative postmarketing hepatic experience with commercial Ocaliva. The right column shows data from an estimated 25,000 person-years of exposure since the 2021 label update. As you can see, there's been a marked decrease across all hepatic adverse events, including liver injury, liver transplants, and fatal adverse events.

Notably, the majority of the postmarketing data for OCA is generated from solicited reports through regular structured patient engagements by trained pharmacists at every prescription refill, and this helps to maintain reporting rates over time. In addition, our pharmacovigilance group

reconciles the postmarketing data every quarter with the FDA Adverse Event Reporting System to ensure complete capture of all events between the two databases. These postmarketing data provide support that the 2021 USPI now identifies the right patients for the safe use of OCA.

Now, there are multiple layers of risk mitigation and management for OCA. In addition to the 2021 USPI, there are three other layers of protection in practice today. First, as a second-line therapy, OCA is largely prescribed by specialty practices. Second, OCA is distributed through a limited network of six specialty pharmacies, and payers manage access to Ocaliva through prior authorization. Prior authorization requires submission of labs and attestation that the patient is not contraindicated, and importantly, reauthorization is required for refills, ensuring patient eligibility is monitored at regular intervals.

Finally, Intercept also provides a free voluntary support service called InterConnect,

utilized by approximately 70 percent of patients. With InterConnect, practitioners are required to confirm the patients are not contraindicated, and importantly, this is in addition to the payers prior authorization requirements.

I'll now conclude my presentation with a summary of the overall efficacy and safety results for Study 302. For efficacy, we've seen that, one, the 302 ITT analysis is flawed and cannot answer the primary research question on outcomes; two, adjusting for bias shows a trend toward benefit; and three, the retrospective USPI subgroup analysis for death and liver transplant is inconsistent with the totality of other evidence, which shows a benefit for event-free survival.

For safety, there are two key points. One, the risk of OCA hepatotoxicity is low. It is monitorable, manageable, and reversible in the 2021 USPI population; and two, with more than 8 years and over 42,000 person-years of cumulative postmarketing experience, the safety profile of OCA in PBC is well characterized.

Now, given the agency's focus on drug-induced liver injury, we've asked Dr. Dara to discuss her perspective on the profile for OCA. Thank you.

Applicant Presentation - Lily Dara

DR. DARA: Good morning. My name is Lily Dara. I'm being compensated for my time but do not have a direct financial interest in the outcome of this meeting. I'm a hepatologist with expertise in hepatotoxicity and autoimmune liver diseases such as PBC. I also have a specific research interest in drug-induced liver injury.

There are three main mechanisms of DILI that are characterized based on dose relatedness, predictability, and latency. Direct hepatotoxicity is dose dependent, predictable, and has a short latency, and an example is acetaminophen. As I'll discuss in a moment, hydrophobic bile acids likely also fall into this category. In contrast, idiosyncratic DILI, which is associated with specific host HLA polymorphisms, is immune mediated, unpredictable, not dose related,

and has variable latency. Amoxicillin/clavulanate is the most common example.

In the right column is indirect hepatotoxicity, an example of which is immune checkpoint inhibitors. These drugs are not hepatotoxic themselves but activate the immune system to fight cancer, which can then cause unintended hepatotoxicity.

So why do I think bile acids fall into the first column? Bile acids have been studied for decades, and although the exact mechanism of injury is unclear, it's been well established that bile acids sensitize hepatocytes to cell death in a dose-dependent manner. Here we see results from a published study in mice given various hydrophobic bile acids at increasing concentrations seen on the X-axis, and on the Y-axis we see the effect on serum ALT. As you can see, there's a clear dose-response relationship between bile acid dose and hepatocyte injury. This association has been shown in vivo, in vitro, and by various labs.

As a bile acid, OCA also shows a direct,

predominantly hepatocellular pattern of liver injury. Here, we see phase 1 study data from healthy volunteers. On the X-axis we see increasing doses of OCA, and on the Y-axis is change from baseline liver enzymes. As you can see there's a dose-related elevation in ALT with higher doses of OCA to the right, and the same is true for AST. Note, the small increase in alk-phos was still within the normal range; therefore, this suggests hepatotoxicity is direct, predictable, and predominately hepatocellular with OCA, and it is not idiosyncratic.

I think we all agree that OCA as a hydrophobic bile acid has potential for hepatotoxicity; however, DILI adjudication is complex, and it is ultimately a diagnosis of exclusion. We must rule out other confounders such as other liver diseases, other comorbidities, and exposure to other hepatotoxic drugs and herbal supplements. This is relevant here since the population exposed to OCA has an underlying progressive cholestatic liver disease.

Another key consideration in DILI is the concept of latency. Exposure to the drug should be temporally associated to the DILI event. If a drug is discontinued months before the event, the drug is unlikely implicated. We also carefully consider what we know about the drug in terms of phenotype of presentation, and importantly, we must always consider if there's a positive de-challenge, meaning does stopping the drug result in improvement of the liver enzymes?

As clinicians, our first imperative is to do no harm, and I personally care a lot about DILI and understand the risks, so the question is, can we give OCA safely to patients? And to me, and I think most hepatologists would agree, the answer is yes, because, first, monitoring is routine in UDCA non-responders. We are continually checking the alkaline phosphatase and their liver panels. These patients have persistently elevated liver enzymes. And because many of the drugs we use, such as rifampicin and fibrates, have potential DILI risk, we always check labs monthly when we start a new

drug in these patients.

Second, PBC's a rare disease, and we're dealing with a smaller fraction of UDCA refractory patients who are managed by gastroenterologists and hepatologists who have high awareness of OCA's DILI potential. Third, we know which patients to select, which is early-stage PBC, and if a patient becomes contraindicated while on treatment, like Dr. Capozza showed you, we know to stop the drug. And further, we know to stop OCA if liver tests are abnormal and there's a concern for DILI, and we stop the drug if the patient is not responding to therapy. Finally, the three cases with possible DILI all occurred within the first 100 days and all reversed when the OCA was withdrawn.

Thank you. I'll now hand it over to Dr. Bessonova.

Applicant Presentation - Leona Bessonova

DR. BESSONOVA: Good morning. My name is Leona Bessonova, Executive Director of Medical Affairs Research at Intercept Pharmaceuticals. I will discuss the real-world evidence for OCA,

beginning with Study 405.

Study 405 is an observational, retrospective study that was designed to answer the important question of whether OCA provides a benefit on clinical outcomes based on real-world evidence. Study 405 enrolled patients largely following the USPI who had failed first-line UDCA, and compared patients using second-line OCA to patients who were eligible but not using OCA.

The inclusion and exclusion criteria followed Study 301. It excluded patients with advanced disease and reflects current real-world views. Patients taking fibrates were also excluded. Importantly, all criteria were applied equally across both study arms, and the primary outcome was a composite of time to hospitalization for hepatic decompensation, liver transplant, or death.

Study 405 followed rigorous best practices in pharmacoepidemiology and is consistent with FDA guidances. The prespecified protocol submitted to the agency defined the patient, intervention,

comparison, outcome, and time, and a robust analytical approach was used to minimize bias.

Patients were allowed to contribute multiple control indexes that emulate the times they were eligible for entry into clinical Study 301, but patients on OCA were only able to contribute a single index at the initiation of OCA therapy. Time-to-event analyses were conducted, including prespecified rules about censoring that are appropriate for observational studies assessing the effectiveness of chronic therapies, and this is consistent with the published FDA-sponsored RCT-DUPLICATE initiative.

Study 405 is also consistent with eight guidances for real-world evidence that have been released by FDA since 2018. A fundamental aspect of these guidances is that the databases selected must be fit for use based on an assessment of reliability and relevance for a study's objective. I'll discuss the databases we selected next.

Study 405 utilized the Komodo Healthcare claims database as its primary data source. Komodo

was selected due to its capture of patients with PBC, including those taking OCA with longitudinal follow-up. The database is based on closed claims, and these claims have been stringently reviewed and adjudicated by payers. Komodo contains the data needed to evaluate enrollment criteria and outcomes, including hospitalization for hepatic decompensation, and Komodo was representative of the U.S. PBC population, with prevalence and demographics for this rare disease that align to the published literature.

Study 405 also utilized four supplementary data sources that were linked to Komodo to further strengthen the rigor of data captured. Quest Diagnostics and LabCorp provided laboratory results to assess key inclusion criteria, and the U.S. Transplant Registry and vital status data provided date of liver transplant and date of death, respectively. These databases were linked to Komodo using widely used Datavant's tokenization, which has 98 percent precision in the published literature.

Next, I'll talk about patient identification. As shown on the left, FDA raised concerns that patients with PBC were identified with unknown accuracy, and Study 405 used methods with unknown or uncertain reliability when defining PBC with poor response to UDCA; however, in Study 405, patients with PBC were identified for both OCA and control arms using a validated published algorithm.

Patients were required to have at least one inpatient claim with a PBC diagnosis or at least two outpatient claims with a PBC diagnosis on separate days. This algorithm has 94 percent sensitivity and 73 to 89 percent positive predictive value for confirmed and suspected cases of PBC in which the diagnosis was recorded by the clinician in the patient's medical record.

For both arms, patients were required to have a record of having been on UDCA as first-line therapy, had to meet thresholds for ALP and total bilirubin, and were excluded for other liver comorbidities such as PSC. Collectively, the

algorithm used and the additional criteria applied strengthen the accuracy of identifying patients with PBC who have poor response to UDCA.

Because Study 405 was not randomized, it was important to ensure the OCA and control arms were well balanced. As seen on the left, key baseline predictors of outcomes were prespecified by an independent expert medical team, and propensity score-based SMR weighting was used to achieve balance between OCA and non-OCA arms on the important covariates.

The predictors identified for PBC disease progression included liver and non-liver-related factors, for example, the Charlson Comorbidity Index. Looking down the chart, while there were some differences in unweighted baseline predictors, as shown in the gray, the weighting, as shown in purple, ensured the key prognostic factors fall within the prespecified standard mean difference thresholds. This indicated that statistical weighting achieved acceptable control.

The primary analysis for Study 405 followed

an as-treated study design. OCA indexes were censored 90 days after OCA discontinuation. This is the appropriate way to classify exposure to chronic treatments such as OCA, where patients who stop treatment no longer accrue benefit and their disease continues to progress. Both the sponsor and the FDA conducted additional analyses that vary the censoring rules, and we'll turn to these next.

This table from the agency's briefing book summarizes the key censoring rules. The analysis for Study 405 compares patients treated with OCA to patients not treated with OCA in their risk for the 3-point composite outcome of hospitalization for hepatic decompensation, liver transplant, or death. The prespecified censoring rules establish when patients are no longer followed for outcomes because they have a change in treatment, such as stopping OCA in the OCA arm or starting an active treatment like OCA or fibrates in the control arm. Study 405 used an as-treated approach that censored patients for changes in active treatment. This is the standard in epidemiology.

The FDA raised concern about the potential for informative censoring. As Dr. Damokosh explained, informative censoring occurs when a patient's decision to end treatment is related to the risk of an event. To account for this, we conducted the widely used IPCW analysis to adjust for any potential differences in informative censoring between the two arms.

We also conducted two additional sensitivity analyses which varied the censoring rules. Unlike the as-treated primary analysis, which stopped follow-up time 90 days after patients discontinued OCA, both ITT 1 and ITT 2 allowed OCA patients to be followed after this 90-day window, and ITT 2 further allowed patients in the control arm to be followed even if they started OCA; in other words, ITT 2 included treatment crossover.

The ITT approaches are affected by attributing outcomes to the initial study arm treatment even if those treatments changed during follow-up, and this is referred to as exposure misclassification. The FDA briefing book

acknowledges that the main limitation of ITT analyses in observational studies is that they may include follow-up time beyond when clinical efficacy would be expected. The ITT approaches thus have the potential to bias estimates of results toward the null.

Shown in the gray box is the FDA's 2-point composite ITT analysis. This analysis only includes time to liver transplant or death and excludes the earlier event of hospitalization due to hepatic decompensation. However, it's important to note that Study 405 was not powered to evaluate only two of the three prespecified events. In addition, this analysis removes all censoring criteria, and therefore does not account for any real-world treatment changes that occur in either arm. This approach introduces uncertainty in answering the critical question; is taking OCA associated with clinical benefit compared to not taking OCA?

Before I review the primary results for Study 405, I would like to address two important

concerns raised by the FDA regarding the hepatic decompensation outcome, as shown on the left, the potential for misclassification and the impact on the treatment benefit observed. While there can be limitations for identifying certain events in real-world data sources, hospitalization for hepatic decompensation is well captured in claims databases such as Komodo, where the claims have undergone stringent payer review. In fact, the positive predictive value of using this approach is greater than 80 to 90 percent in a number of published studies across liver diseases. Additionally, even if misclassification exists, there is no reason to believe that payer-reviewed claims for hospitalization due to hepatic decompensation would be substantially different between the OCA and the control arms.

This Kaplan-Meier curve demonstrates the benefit of OCA on the primary composite endpoint of event-free survival. The hazard ratio is 0.37, indicating a 63 percent decreased risk of hospitalization for hepatic decompensation, liver

transplant, or death for patients on OCA compared to patients not on OCA; and separation between the two arms occurred within the first couple of years of treatment.

On this slide, we'll review results for each of the sensitivity and ITT analyses that I described earlier. The first row is the primary as-treated analysis, which demonstrates the association between actual OCA treatment and clinical benefit compared to patients who never took OCA. The second row shows results of the IPCW analysis that addresses potential informative censoring. This yielded a hazard ratio of 0.52, with the confidence interval continuing to demonstrate clear benefit on the 3-point composite endpoint. Despite their limitations, the ITT 1 and ITT 2 sensitivity analyses also suggest benefit, with hazard ratios of 0.59 and 0.64, respectively.

The last row on this table shows the FDA's ITT analysis, which allows for treatment misclassification, thereby introducing a bias toward the null. This analysis doesn't include the

important clinical outcome of hepatic decompensation; therefore, there are far fewer events and a wider confidence interval, demonstrating the imprecision of an underpowered analysis. Even so, the FDA's ITT estimate still demonstrates a trend for benefit in liver transplant and death. In addition, this 0.8 hazard ratio is in stark contrast to the 4.77 hazard ratio for the Study 302 USPI subgroup, which utilized the same methodology and was discussed by Dr. Capozza earlier.

In addition to Study 405, OCA has accumulated a range of other real-world evidence since its approval in 2016. These real-world studies include independent registries with varying methodologies and geographies. I'll discuss three of these studies next.

An external control was created for OCA patients in the clinical Study 301 long-term safety extension. The lead investigator was the Global PBC study team. OCA patients from the 301 LTSE had up to 6 years of follow-up, and non-OCA patients

were matched to Study 301 patients using data captured from the large, well-established registries, contributing over 1300 patients from Global PBC and 2100 patients from UK PBC registries. The analysis examined hard endpoints of event-free, as well as transplant-free survival. Importantly, patients on the OCA arm are consistent with the 2021 USPI; the study was largely conducted prior to commercial availability, which minimizes the issues of treatment crossover; and the analysis was published in Gastroenterology.

Here are the data from the publication. This figure compares OCA patients from Study 301, also called POISE, to patients in the Global PBC control. The hazard ratio is 0.42, indicating a 58 percent decreased risk of the 3-point composite endpoint in OCA versus control patients. An external control was also created for Study 302. OCA patients were matched to an external comparator derived from the Komodo database, and the endpoint was event free survival. And finally, an independent analysis was recently conducted to

evaluate OCA patients from the Italian RECAPITULATE registry to match controls in the Global PBC registry in order to assess event-free and transplant-free survival.

The results of these multiple real-world studies reproduced the event-free survival benefits seen in Study 405, with hazard ratios between 0.33 and 0.42. This consistency is also reproduced across the real-world-based studies that assessed liver transplant and death, with hazard ratios between 0.29 and 0.4.

To summarize, despite differences in data sources, methodologies, and geographies, there's a consistent benefit of OCA on outcomes. Whether we look at Study 302, Study 405, or other real-world evidence, all the point estimates favor OCA. This includes the Study 302 primary ITT analysis and the Study 405 FDA 2-point ITT analysis, despite the limitations discussed for both of these. Taken together, the totality of this data confirms that OCA is having a clinically meaningful benefit on the long-term outcomes of patients living with PBC.

Dr. Jones will provide his clinical perspective next.

Applicant Presentation - David Jones

PROF. JONES: Thank you very much.

My name is David Jones. I'm a hepatologist from Newcastle in the United Kingdom. I'm a paid consultant of Intercept, but I have no personal interest in the outcome of today's proceedings. I'm Chair of the Medical Advisory Board of the PBC Foundation, and this gives me a very broadly-based perspective of the view of PBC patients and clinicians in PBC around the world, and my comments today will reflect the views of those communities. I'm also a clinician myself, managing a large cohort of PBC patients from extensive experience of second-line therapy in practice, and my job here is to put what you've heard before into a clinical context.

I've been managing PBC since the early 1990s, and my experience is one of a dramatic evolution of the disease. This is now a very different disease to the one I first encountered.

When I first managed patients, the majority would die of this disease; now, the disease should be, in my view, thought of as being fully controllable. PBC deaths and transplants are actually unusual these days, and this change is the result of progress in many areas, but I think three are absolutely key.

The first is better awareness and earlier diagnosis; understanding of how to identify people at an early stage of the disease and who are at high risk of progression to cirrhosis complications; and of course the advent of effective therapy. It is the combination of these three advances that has, I think, transformed our practice. The ability to identify early in the disease those patients who are at high risk of progression and treat them at that point, the point at which they are most likely to benefit, is absolutely critical, and this model only works, of course, if we have access to a range of effective therapies.

Now, of course, for any drug, it is a

balance of benefits and risks. For me, for OCA, this balance is strongly in favor of benefit. The totality of the evidence and my own personal practical clinical experience suggests to me that OCA use in the right patient leads to a reduction in death, need for transplant, and decompensation avoidance, and the right patient is not a 302 patient. It is very uncommon now for one of our patients in the treatment program to need hospital admission.

I believe that this effect comes from the impact of OCA as an FXR agonist on key disease pathways. We've heard that OCA is anti-cholestatic and anti-inflammatory, but more than that, it's also anti-senescent, and loss of bile ducts through a process of biliary senescence is actually a really important driver of ductopenia, which is itself a key component of the disease, and of course, it's also anti-fibrotic, and it's the combination of the clinical data with the unique mechanistic effects that I think is so compelling.

OCA is the only available FXR agonist, which

gives it a fundamental importance in our treatment armamentarium, and all of this is quantifiable in practice through the biomarkers introduced by Dr. Brown that we use on a daily basis, which are an integral part of our normal clinical practice. But what about risks? Hepatic impairment and decompensation are, I believe, fully manageable by treating the right patients at the right time, and the model of treating high-risk patients at the earliest point in their disease is actually the way to manage safety as well as efficacy. This is how we manage patients in practice day in and day out. We've learned how to do it.

In terms of side effects, much is said about pruritus. I run a specialist symptom control practice. In reality, pruritis with OCA is a relatively straightforward issue, the majority of people don't experience it, and those that do respond to simple treatment paradigms. The mass majority of events in PBC of course is seen in people who are not being treated with OCA. But all this together, safety and side effects are

manageable by treating the right patient, at the right time, with the right follow-up.

So why do I think we need OCA for our patients? Well, I think the mechanistic element is really important. FXR agonism covers all of the key disease processes in a way that no other drug type does, and OCA is, of course, the only FXR agonist we have access to. I think it's fascinating that it appears to be complementary to the PPAR agonists, and the fact that the addition of a PPAR agonist to OCA gives an enhanced effect indicates that they work through different mechanisms, which does rather challenge the sense that OCA and the PPAR agonists are interchangeable. And personally, I believe that the combination of these drugs in the future is going to be the way that we go in PBC.

OCA is, in the view of the PBC community, a safe and effective part of our treatment armamentarium, it is entirely normal in our management programs, and we now have many years of worldwide clinical practical experience with this

drug. We do understand the need for safety data and efficacy data; of course we do. Safe and effective treatments are what we want as clinicians, and we in the clinical community in PBC, as well as the patients, will be more than happy to work with the sponsor and the regulatory authorities to find a way forward here.

In closing, I can't emphasize enough that the management of PBC patients to meet the unmet need is all about treating the right patient, at the right time, and with the right follow-up. And with this, I hope that we will continue what has been an astonishing revolution in the outcomes of treatment for this disease. Thank you very much, and I will pass back to Dr. Sawhney.

Applicant Presentation - Sangeeta Sawhney

DR. SAWHNEY: Thank you, Professor Jones.

To conclude our presentation, I will briefly summarize our perspective on the voting questions posed to you today. Regarding question 3, the totality of available evidence from Study 302, Study 405, and three large PBC patient registries

verifies clinical benefit in the USPI label population based on clinical outcomes. As a reminder, Study 405 and the other real-world data reflect a population which is largely consistent with the 2021 USPI, and these data tell us that OCA is having a clinically meaningful impact on the long-term outcomes of patients living with PBC.

We are committed to generating additional evidence to further confirm the benefit in the USPI-labeled population with a new study that will complement existing data. To that point, we have already submitted a proposal for Study 407, which will utilize an electronic health record as a third source of real-world data, and we are currently evaluating data sources as fit for use.

And finally, and most importantly, for question 4, we have presented totality of evidence that supports a positive benefit-risk profile in the USPI 2021 population for OCA in patients living with PBC. Adjusting for bias shows benefit in Study 302 and we see consistent benefit across Study 405 and three large PBC patient registries.

We have shown that the USPI subgroup analysis of death and liver transplants is inconsistent with other data and is clinically implausible.

The 2021 USPI reflects appropriate patients and appropriate follow-up. Furthermore, specialty prescribing and preauthorization ensures safe use of OCA. Ultimately, clinicians know how to use OCA. It continues to be an important second-line option for patients living with PBC. Thank you, and we look forward to answering your questions.

Clarifying Questions to the Applicant

DR. LEBWOHL: We will now take clarifying questions for Intercept. For committee members who are here in person, please raise your hand physically, and Jessica Seo, seated to my left, will acknowledge you and write your name down. For those of you who are here remotely, please use the raised-hand icon to indicate you have a question, and remember to lower that icon after you've asked your question.

When acknowledged, please remember to state your name for the record before you speak and

direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

We'll start with Dr. Goldberg.

DR. GOLDBERG: Thank you. I guess I have two questions. The first would be for Dr. Capozza. There wasn't a lot of talk about pruritus in the different studies, and I just had a question in terms of 302, in terms of the liver transplant and the real-world data.

Are there any data on patients that actually require liver transplants for pruritus due to OCA? I know anecdotally, I took care of a patient that had that. I didn't see the indications for transplants in any of the slides. Then I have a different question for Dr. Bessonova, so I don't know if I should ask that or wait.

DR. SAWHNEY: Certainly. I'll go ahead and ask Dr. Capozza to review the transplants in terms of pruritus.

DR. CAPOZZA: Just to clarify, it was about patients who went to transplant due to pruritus in the setting of OCA use?

DR. GOLDBERG: Correct, both in the 302 and in real world.

DR. CAPOZZA: Right. In 302, to the best of our knowledge, it's the one case that I presented, which is the patient that ended up with a transplant due to pruritus, who was in the study and on OCA. We can't find any others where the transplant was due to pruritus. As you know, there are patients who have pruritus but not specifically linked in that sense.

In terms of the real-world data, I don't have the answer to that, but I will convene with our team and see if there's something we can come back with, unless -- yes.

DR. LEBWOHL: Did you have another question?

DR. GOLDBERG: Thank you. Yes.

DR. SAWHNEY: Sorry. If I could just clarify, that patient who received that liver transplant had severe pruritus, and I think, as Dr. Capozza said, was on multiple interventions, including MARS, likely not the best patient to be enrolled in a study for OCA based on what we know today.

DR. GOLDBERG: For sure.

Then I had a question for Dr. Bessonova as it relates to Study 405. One of the papers that you cited in slide 96 was my paper about the codes used, and just a point, our study was only in people with cirrhosis looking at hepatic decompensation codes, so it was a little bit different.

But my question relates to 405 in the use of the Komodo database. I know you talked about 407, but were there thoughts of actually how valid any of these data are? Because we know in studies that the PBC code is for the exposure, the positive predictive value is 73 percent. And I've been a collaborator where we looked at this in the VA

where, similarly, about only 70 percent of people with the PBC code actually had PBC, so the concern about that.

Then with respect to the outcomes, the ICD codes selected were very broad for hepatic decompensation, and for some, like encephalopathy, it wasn't a code plus medication, as recently proposed by the group at Michigan. So I'm just curious how the codes were selected and why there was no attempt to chart review to validate some of these exposures and outcomes.

DR. SAWHNEY: Certainly. I'll ask Dr. Bessonova to clarify how we handle this in the study, and then I might ask Dr. Nancy Dreyer, based on her broad real-world experience, to address your question.

DR. BESSONOVA: In Study 405, it is correct that we identified the events of hepatic decompensation based on the diagnosis code, and the existing literature does provide a bit of a range of upwards of 80 to 90 percent for a single diagnosis, inclusive of a single diagnosis, of the

hepatic decomp events.

Can I have slide 2, please? We prespecified the diagnostic codes for variceal bleed, ascites, and hepatic encephalopathy, and it's also important to note that these were hospitalizations due to these events, and as a claims database, including closed claims where payers have reviewed and adjudicated the claims, this is a robust way to capture a hospitalization due to this event.

Another thing that I'll mention is the issue of unequal classification between the two study arms, there really isn't a reason to believe why the diagnosis code would be differently recorded in the OCA versus the control arm. And lastly, I will also mention that this benefit on the hepatic decompensation, including the other endpoints as well, has been observed in the other studies that are inclusive of registries where the information is differently captured than it is in the claims. So all of this is supportive and all in the same direction.

DR. GOLDBERG: Thank you. My questions have

been addressed.

DR. LEBWOHL: Dr. Coffey?

DR. COFFEY: Yes. I have I guess a couple of broad questions on Study 302. The case was made by several of the presenters that the primary ITT analysis was flawed, was biased, and that the analysis adjusting for bias showed more of a benefit. A lot of the complications here were related to the change in labeling. That one doesn't seem to have much to do with that, and that's a justification for why treatment crossover or informative censoring would be a problem. It seems to be something that would be more broad and perhaps known at the outset.

So my questions are kind of twofold. One, why use the ITT as the primary analysis if those were potential problems that could come up? And second, was that sensitivity analysis adjusting for bias prespecified or post hoc?

DR. SAWHNEY: Certainly. I will ask Dr. Damokosh to address your questions. As he's coming up, we did propose alternate methodologies;

however, there was a desire from the agency to maintain the prespecified ITT treatment policy as the primary.

DR. DAMOKOSH: Yes, you're right. We should have anticipated that, and I think we did include a potential for crossover by looking at an external control. I think we called it 302 external control and we did conduct that. We didn't consider an IPCW at the time of the study design; kind of wish we had. It might have solved some problems and certainly something to be learned for the future. But we did anticipate that, and that's how we were handling it, and I think you did see some of those results.

DR. COFFEY: Thanks.

DR. LEBWOHL: Dr. Winterstein?

DR. WINTERSTEIN: Yes. Thank you, and thank you for all the detail you presented. I'm trying to get my arms around how comparable the non-user group was in the real-world evidence study. From what I understand, what you presented was that everybody was eligible for involvement when they

failed first-line treatment. So what that would mean is that you basically use a combination of prior exposure to first-line treatment plus an elevated ALP based on the labs.

So for the control group, then, since they did not move on to OCA treatment, they were also not allowed to use fibrate, so that basically means these were patients who did nothing. And I'm curious; how clinically likely is that, that if I'm failing first-line treatment, that nothing else happens? Because if something else happens, then I would be censored.

So I was trying to think about the whole issue with prior authorization that you mentioned and the types of patients that are in the Komodo database. As far as I remember, there's 100 percent Medicare beneficiaries in there, and looking at the distribution of baseline data, we have more Medicare patients, it seems, in the non-treated group, older patients.

Are there issues with the prior authorization piece? Do you have a breakdown of

the percent of patients who were in commercial insurance versus Medicare? And then within Medicare, I would be really interested to see how many were dual eligible, so whether they were also enrolled in Medicaid and whether this could have anything to do with access to OCA, if you could walk me through this.

First of all, why did the non-control group do nothing? And secondly, how comparable were they with regard to insurance status, access to OCA, and involvement in public insurance?

DR. SAWHNEY: Certainly. I'm going to ask Dr. Bessonova just to confirm and make sure that I've captured. So you are interested in how did we actually compare patients who we included in the OCA cohort versus the non-OCA cohort and, second, most importantly, in terms of their insurance status.

DR. WINTERSTEIN: Not much how you compared that but whether they were comparable --

DR. SAWHNEY: Correct.

DR. WINTERSTEIN: -- with the specific data

that I just mentioned; yes.

Then, clinically, is it normal to do nothing? Because as far as I understand, they were censored if they had started fibrate, so we're basically looking at people in the non-treated group who failed first-line treatment and do nothing, and is that normal, or would that potentially mean that there is more progression, or what's going on?

DR. SAWHNEY: Sure. I'll ask Dr. Bessonova to address two parts of your question.

DR. BESSONOVA: In terms of the comparability of the controls and the OCA patients -- can I have slide 2 please? -- the same inclusion/exclusion criteria were applied across both OCA and control arms, including the availability of the laboratory data and continuous enrollment, and importantly, the exclusions of severe liver disease in order to make the population more representative of the Study 301 population on which the accelerated approval is based.

Slide 2, please. We did conduct the propensity score-based weighting exercise in order to ensure that the two cohorts were balanced for an evaluation of the outcomes. Now, the characteristics on which that exercise was based were prespecified in the protocol, and these are the key prognostic variables that were identified by our external medical team of experts, so these are the variables that are predictive of the outcome of interest.

Then the other thing, to address your question about the insurance status -- if I could please have slide 1 -- it is true that Komodo is a very large database in the United States, and it actually does capture the actual patient experience in the real world for patients with PBC in the U.S., and therefore it does include patients across all of the insurance types.

On the left in this slide, you will see the unweighted characteristics of these patients, and you can see the distribution of patients in the commercial insurance, those who are in Medicaid,

those who are in Medicare, and also those dual-eligible patients. And the insurance status was actually one of the variables included in the balancing exercise, so after weighting, you can see that distribution in the right-hand column as well, point being that while patients who entered the study are in the unweighted state and may have had some differences there in the insurance status, the weighting exercise that was prespecified in the protocol was meant to create balance between the two cohorts in the assessment of the outcome of interest.

I think you also had a question of why there might be differences. Again, this is a large database that captures the real patient experience in the U.S., and certainly while we don't have clinician decision making recorded in this kind of database, we do capture all of these different variables that might reflect why a patient may make a decision to start a patient on OCA versus not start a patient on OCA, and we did expect that insurance status would be an important such reason.

DR. LEBWOHL: Thank you.

DR. WINTERSTEIN: I appreciate the data on the insurance. I'm still curious about the clinical understanding there. Treatment failure was defined as an abnormal ALP. On your slide where you're defining the inclusion criteria, it says, "patients on first-line therapy who failed," so failure is an elevated ALP or what is failure?

DR. SAWHNEY: Correct. It is failing UDCA based on an elevated ALP. And I think to answer your question about the clinical aspect of the decision making, I'll ask Professor Jones to address that.

PROF. JONES: Yes. Thank you. It's a really good question and one that's a live one in the community. In answer to it, yes, there are people out there who are untreated without there being a sinister reason to it, and it's something that we need to work on. The UK has audited this, and the use of OCA ineligible patients ranges around -- or second-line therapy ranges from 70 percent down to 30 percent in comparable units.

So at this moment in time, not everybody who would benefit from second-line therapy is getting it. We saw the same thing with urso in the early days. There was a sort of time lag before it started being widely used.

It will be increasingly difficult to do these studies as more and more people go on to it, but at this moment of time and over the last few years, there were plausible groups of people out there who were just not on second-line therapy because they wanted to wait and see, as did their clinicians, so it does happen.

DR. WINTERSTEIN: I'm sorry I'm capitalizing here, but fenofibrate is widely available, but they weren't allowed to use that either, so I'm curious. You have patients who are failing first-line therapy and they get nothing. This is the control arm as defined here. If somebody could explain to me the role of prior authorization in this. Would it be possible that their patients would basically have access to nothing else? That's not a unique question because we have an American database here,

so I'm really curious what the insurance situation is in this regard.

PROF. JONES: I will pass. I can't comment on the insurance side of it for the UK. But in the UK, where you don't need that authorization, it still happens that people, for reasons that we don't understand, don't get second-line therapy.

DR. SAWHNEY: I'll ask Dr. Brown from the U.S. perspective to comment on preauthorization.

DR. BROWN: There are a lot of reasons why someone may not be on a second-line therapy. The use of fibrates for PBC is a relatively recent phenomenon, and most of the experiences with bezafibrate, which is not available in the United States, there are people using fenofibrate with very little data for that actual agent just because it's a PPAR and it's a fibrate, but many clinicians might choose not to use a fibrate without prospective data that supports its use.

Anyone who has significant pruritus at baseline, you might be reluctant to use obeticholic acid, and those patients wouldn't be selected. And

as highlighted, the need to get out fast, as low as possible, is something that's evolved over the last 5 to 10 years. I think many of us in the community tolerated alkaline phosphatases that were far higher than we should have and that I in my practice do today. So I think over time, the use of second-line agents has increased, both off-label use of fibrates and on-label use of obeticholic acid.

DR. WINTERSTEIN: Thank you. So that would mean that the control patients potentially have not standard of care?

DR. BROWN: I guess it would depend how you define standard of care, but correct.

DR. WINTERSTEIN: Thank you.

DR. LEBWOHL: If I could ask a related question about 405, really related to Dr. Winterstein's fundamental question of why the non-OCA patients in this analysis are not getting treated, we heard some clinically plausible explanations, perhaps diffusion of practice, practice styles,, authorization, et cetera, but it

raises the concern about residual confounding; that the people who got OCA were different in unmeasured ways and in fundamental ways that might be related to their outcome.

So one way to evaluate for this is to look at another outcome, a falsification endpoint, one that you would not expect OCA to act upon. Has that been done in 405? Do we know people who were in the OCA arm, had lower rates of unexpected outcomes, heart attacks, cancers, et cetera? Because if they did, that would argue that residual confounding is playing a strong role.

DR. SAWHNEY: Certainly. I'm going to ask Dr. Bessonova. We did look at sensitivity analyses, so Dr. Bessonova can go over those.

DR. BESSONOVA: While kind of a falsification endpoint was not conducted at baseline, we did balance the two cohorts across a slew of both liver and non-liver risk factors and key prognostic factors. However, to answer your question -- can I please have slide 1? -- we anticipated that there could be potential for a

residual unmeasured confounder. Despite all of these important prognostic factors being included in the weighting exercise, there could still be remaining potential that there is something that was unmeasured that could be causing the effect estimate that we're seeing.

So in this quantitative bias analysis, on the left side is a potential unmeasured confounder that has a low prevalence, and on the right side is that potential unmeasured confounder that has a high prevalence in the population, up to 50 percent. And then in this exercise, the strength of the association between this potential unmeasured confounder and both the exposure and the outcome of interest is varied along the axes. And what we see from this exercise is that only a potential unmeasured confounder that has a 50 percent prevalence in the population, highly prevalent in the population, and is strongly associated with both OCA treatment and the outcome of interest, has the potential to gradually move this hazard ratio toward the null, and such a

variable is not anticipated and is highly unlikely, given the kind of rigorous prespecification of the variables that were included into the weighting model.

DR. LEBWOHL: Thank you. Is the sponsor suggesting that the point estimate and effect size is so large that a falsification test would not be necessary because of that effect size?

DR. BESSONOVA: We believe that the point estimate is quite robust because of all of these sensitivity analyses that we have conducted, including the ITT, and this estimate is further strengthened by the other studies contributing to the totality of evidence, the other registry-based studies and all of the other studies reflecting different geographies that all fall within the same ballpark.

DR. LEBWOHL: Thank you. That's it for my question.

Our next question is Dr. Sturmer.

DR. STURMER: Thank you. I have several questions. I'll restrict to two here because I

know time is of the essence. The first one is on 405 to Dr. Bessonova. On slide 91, in this forest plot that we've just seen again, you showed that the OCA patients had quite more elevated liver markers than the control group, and following everything that we heard from Dr. Brown and others, that would indicate that they are at higher risk for the outcomes. When I go to the document, figure 22, however, there is no change, in essence, between the crude and the adjusted analysis, and I wonder whether you could explain this.

DR. SAWHNEY: Certainly.

Dr. Bessonova?

DR. BESSONOVA: So indeed, actually, your observation is quite correct. So we observed that in the unweighted state, patients who were entering into the analysis, the OCA patients had much higher ALP, something on the order of 291 units, whereas the non-OCA patients I think were about 199. Recall that this study data period included patients going to the very beginning, 2016, well before the USPI label. So during that period in

time, we actually did see patients that were more severe that were being started on OCA. So that's why for this specific analysis, we prespecified this balancing exercise in the protocol because we knew to anticipate that this sort of imbalance might be expected, so that's why we did that.

Now, in terms of the unweighted versus the weighted analysis, can I please have slide 2? So exactly what you observed is correct, where actually the weighting exercise, the proper way to do this, we needed to make sure that we were minimizing bias in Study 405, so we did prespecify the weighted analysis. However, even if you look at the unweighted analysis, this weighting exercise doesn't seem to be doing anything to tremendously alter the results in some ways. Even in the unweighted state, where OCA patients do have some residual difference than the non-OCA patients, we still see a demonstration of benefit.

I also want to say -- I will also bring up slide 1, please -- we also do see the robustness of this effect because when we look at the cumulative

incidence rate for the important outcome of hepatic decompensation, we actually see the separation of the curves occurring very early. So even in the first year or two, we see a difference in the risk of this event in the OCA-treated group versus the non-OCA-treated group, and we see a similar trend for liver transplant. So all of these pieces of information and the pressure testing of the 405 result yields that, that is actually quite a robust hazard ratio and something that we're confident in.

DR. STURMER: So in essence, you have no explanation for what we would assume would be strong confounding doesn't lead to a change in estimate.

DR. BESSONOVA: The similarity of the results between the unweighted and the weighted analysis do suggest that residual confounding isn't playing a role here.

DR. STURMER: Thank you.

So my second question is about following the data issues. I looked through the entire document and did not find that you censored for

disenrollment, so is my assumption correct that you do not have enrollment files for these claims data?

DR. SAWHNEY: Dr. Bessonova?

DR. BESSONOVA: In Study 405, one of the prespecified censoring criteria was actually the end of closed claims, so that is a variable that's present in the Komodo database, and that was included as a censoring criteria for both arms.

DR. STURMER: But that's not enrollment files. This is not disenrollment from the insurance plan.

DR. BESSONOVA: So we take this as the disenrollment from the insurance plan as the end of the available closed claims, so either that or the end of the observation period, which was December 31, 2021.

DR. STURMER: I just would like to highlight that we would usually not call this closed claims. Thank you.

DR. LEBWOHL: Dr. Lee?

DR. LEE: Thank you. I had a couple questions regarding just clarifying the study

design for 405 with Dr. Bessonova, and then some questions regarding the interpretation of results for 302 with Dr. Capozza. So starting with 405, it's important to fully understand how the exposure was defined, the outcomes, and then the results as well. For the exposure, it's important that they're well balanced across the two arms. How was the presence of portal hypertension without decompensating events captured, and was there any missing data, particularly with the lab values, and how is this handled in the weighting?

Two is that there are a lot of assumptions with residual confounding, and there were some statements made regarding that there shouldn't be any differential misclassification across the treated and control arms. But the study period does span from 2015 to 2021, and there was an important interval event in 2018 with the label warning. And the label warning was that sicker patients may not be prescribed the treatment group, meaning that the treatment group could in fact be sicker. So was there any consideration of this,

and if so, for example, was there any analysis performed for 2015 to 2018 alone?

Then regarding the outcomes, there was a comment made regarding 90 percent positive predictive value of the outcome, but what is the negative predictive value of the outcome here? And a follow-up question from the prior speaker was, what was the rate of disenrollment before the end of observation, essentially loss to follow-up?

Then finally, the Kaplan-Meier curves were displayed, but, Dr. Bessonova, you commented that they branch off very early, even before 6 months. So is there clinical plausibility that Ocaliva would really prevent outcomes, even in the first couple months, and what is that plausibility? And could this alternatively mean that the two treatment arms really aren't balanced at baseline?

The questions regarding 302 for Dr. Capozza, I think there was --

DR. LEBWOHL: Perhaps, why don't we have the sponsor answer about 405, and we'll move to 302.

DR. SAWHNEY: Sure.

Dr. Bessonova?

DR. BESSONOVA: I will take these one at a time. In terms of the definition of the exposures and how we define both the exposure and the outcome, the definition of exposure, your first question was about our operative definition of portal hypertension, and portal hypertension was identified using the diagnosis code or a platelet cutoff.

Then in terms of the missing lab data, one of our inclusion criteria was actually that patients had to have at least one instance of all five laboratory measures in order to be able to establish the inclusion/exclusion criteria. So while that removed some patients from the analysis because we didn't have lab data from Quest or LabCorp on them, the patients that were included in the analysis, similar actually across the arms, did have available the data to make that ascertainment.

The next question is about the hepatic decompensation in terms of the potential for differential misclassification of that outcome

measure. Because we included all of the diagnosis codes, we looked at all of the diagnosis codes available for that hospital admission -- this included the admission diagnosis and any of the diagnoses during that admission -- we captured the maximum amount of information where patients with an hepatic decompensation could have been identified. Now certainly, we identified it based on the one diagnosis code, and it does have a high positive predictive value. I don't have the negative predictive value for you today. We can try to get it for you after the break.

Then you're actually concerned about the label warning in 2018 and the impact of that in terms of the sicker patients, and potentially looking for the events and sicker patients upon a hospitalization. Actually, if one were to look for specifically these kinds of events of hepatic decompensation -- the ascites, variceal bleed, hepatic encephalopathy -- in the OCA patients specifically and make a concerted effort so you would see those diagnosis codes pop up, that would

then mean that those diagnosis codes were underreported in the control arm, which actually then means that our effect estimate is a conservative one if that kind of event wasn't being screened for in the control arm.

DR. LEE: A point of clarification with that question, my concern is really with the assignment of the treatment arms. For example, after 2018, essentially your study design patients can enter at any time; is that correct?

DR. BESSONOVA: That's correct, any time they fit the inclusion or exclusion.

DR. LEE: So for example, patients who enter your cohort after 2018, they could be less likely to be prescribed your treatment group, assigned to your treatment group, because they're sicker, but if your baseline characteristics of, for example, hepatic decompensation or portal hypertension, is not accurate, you might not be capturing that imbalance across the treatment arms.

DR. BESSONOVA: I think it's a good question. I think it's something that we thought

about by including as robust a panel of those baseline characteristics as possible, including the ALP, total bilirubin, and all of the other comorbidities as well, and then undergoing the balancing exercise to make sure that you actually did have two cohorts that were like to like, so you can compare them for outcomes.

DR. LEE: And with your sample population, what was the level of missingness for the 5 labs, then, if you required all 5 labs?

DR. BESSONOVA: I think we have a slide that demonstrates -- if we can bring up the flow diagram for the eligibility -- where the first step in the eligibility is the availability of the 5 labs -- with the numbers, please, with the proportions. I think the proportion of patients with all 5 labs -- I don't want to say this incorrectly, so I'm waiting for the slide. But anyway, I think the proportion of patients with all 5 labs was somewhere between -- here we go.

If I can have slide 1, please? Thank you. About half of patients entering the analysis, who

met the criteria for the diagnosis code and had the record of OCA, which was how OCA exposure was classified, we had data for about half of those patients from the Quest and LabCorp data.

DR. LEBWOHL: I'm mindful of the time because we are approaching break, but I thought maybe we could take just a couple more questions and a few more minutes. And I'll be asking Dr. Gillen to ask their question next, but perhaps just one question with minimal follow-up so as to maximize inclusion.

DR. GILLEN: Thank you. It will be a little bit of a background, too. I know, as a precursor to this question, that in your 301 study, the OCA effect on alk-phos was about a 33 percent reduction in the mean from baseline over 12 months. So my question is really around 302 and the history, if you will, of the placebo arm.

If we can bring up slide 33, I want to get an understanding and really clarification of the data and where the sponsor is coming out with this. So we see what I would consider to be a dramatic

decrease in ALP on the placebo arm here. I'll point out, by the way, that the X-axes across these three studies are completely different, so that can be quite misleading here, and there are no sample sizes either to deal with dropout. But beyond those things, what we see at 12 months is approximately, just from my eye, about an 18 to 20 percent decrease in ALP.

I'm bringing this up because the sponsor has basically said there are a lot of flaws in the study design, and much of this is probably from crossover of treatment that we're seeing on the placebo arm, and that's the reduction, and I really want to get at this.

If we then look at slide CC-39, say between 6 and 12 months, there's only about a 5 to maybe maximal 10 percent crossover. So how do we explain a 20 percent decrease in the mean over 12 months on the placebo arm when there's only estimated to be a 5 to 10 percent decrease on crossover?

DR. SAWHNEY: So I'll just point out the entry criteria for the 301 patient population

compared to the 302. In Study 301, these were patients who were earlier in their disease, so the mean alkaline phosphatase is about 290 compared to the mean alkaline phosphatase at baseline for the 302, which included patients with much more advanced disease, is over 400.

I'll ask Dr. Malecha to address the second part of your question.

DR. MALECHA: If I could have the slide with the ALP decrease back up. As Dr. Damokosh mentioned, we believe that the decrease in the placebo ALP over time is due primarily to two reasons. One is the treatment crossover, but a second is early discontinuation of high-risk patients, so patients with high ALPs discontinuing. Slide 1 up, please. This figure is observed ALP values, so once a patient leaves the study, their ALP is no longer contributing to the mean, and that's driving a downward trend as well.

DR. GILLEN: Great. I thought you might say that. So can you bring up side CC-44, please?

But now, if I look at 6 months, and I look

at the discontinuation there, it's about 2 to 3 percent. So I see a 20 percent decrease in ALP that's occurring over 12 months, I see very little discontinuation that early on that's occurring there, and I see very little crossover. So I'm asking what the relevant explanation is for the decrease in ALP over, say, 12 to 18 months that we see, and sample sizes, by the way, on your mean plots would certainly help with this, too.

DR. SAWHNEY: Correct. I think the biggest challenge in the study is those patients with the higher ALP who either discontinued the study or crossed over to Ocaliva as early as 6 to 9 months. That's the biggest challenge that impacted the study.

DR. GILLEN: So 3 to 4 patients, then, had a reduction, explained the reduction of approximately 100 --

DR. SAWHNEY: I think it's more than 3 to 4 patients. If I could actually have slide 2, and I'll ask Dr. Bessonova to describe the disproportionate patients between the two groups

who discontinued study.

DR. BESSONOVA: Sure. So this is actually evidence of this trend that we're seeing. The dots on this figure represent all the patients in both arms who either discontinued the study visits or initiated a commercial therapy. Highlighted in the yellow boxes are actually the patients who discontinued the study visits or started commercial therapy, and you can see that they're actually having higher ALP and are discontinuing within the first 2 years. And this is more observable even in the placebo arm than the OCA arm, clearly suggesting that this is a differential trend between the two arms. So it's kind of a descriptive analogy, but it's demonstrating that this trend is taking place.

DR. GILLEN: Yes, you have that data, so it would be good to see if these individuals are actually responsible for the reductions that you have because right now it's conjecture, to be quite honest; and you have the data, so it would be good to see that. And it would also be nice to see if

that same drop in the ALP exists when you restrict to the USPI subpopulation.

DR. LEBWOHL: Thank you.

In the interest of time, we're going to move on just to one last question by Dr. Shaw.

DR. SHAW: Okay. I had a couple questions. I don't know if I can ask the other ones later, but here's a quick clarifying question so we can go to break. This is for CC-63. I did have a clarifying question. Yes, this slide.

My understanding of that USPI subgroup is there was that ruling that drug OCA became contraindicated for certain severity, so this subgroup would be defined by the people at the start of 302; that they would not be contraindicated, they would still be allowed to take that drug. I'm confused by this slide because that red diamond for patient 7 looks like it's at study baseline. Is that just because that's a fat symbol or am I misunderstanding the definition of USPI here?

DR. SAWHNEY: Yes. The manner in which the

USPI label is noted in FDA's documents is actually not consistent. It's not consistent with the 2021 USPI, as the patients were managed. This study started in 2015, and all the information which would be necessary to categorize a patient as USPI 2021, indicated or not, was never collected by design. There was no intent at the time to describe this.

If I can actually have slide 1; for example, we had, of course, platelet counts on all the patients collected prospectively in a systematic manner at baseline; however, we did not have TE data for all patients, which would be important to categorize them as having portal hypertension or not. While we had ultrasound at baseline for all patients to categorize their gallbladder status, there was not a requirement for the study sites to check for whether there was presence or absence of splenomegaly. Similarly, not all patients had, or very few patients had, an endoscopy with documented evidence of varices.

So while this group is labeled USPI from

Study 302, the fact that this was retrospectively defined years after the patients had been enrolled and the data was not systematically collected, the subgroup is not reflective of the population that is indicated per the 2021 label.

DR. SHAW: I guess I'm not exactly sure if I understand that answer. So going back to the slide we were looking at, CC-63, are you saying that you're disagreeing with the definition of the USPI subgroup?

DR. SAWHNEY: We're not disagreeing with the definition of the subgroup. I think what we are saying is there are limitations, and because it was not prospectively defined, there is limited data available to accurately describe, and define, and accurately capture all patients, whether they were indicated or contraindicated.

For example, one of the patients that Dr. Capozza mentions, while they were programmatically categorized as USPI indicated, when we look at their medical records, there is evidence of splenomegaly, there is evidence of

esophageal varices. So that's an example of a patient that's categorized programmatically as USPI but clearly had evidence of portal hypertension at baseline.

DR. SHAW: Alright. Thank you.

DR. LEBWOHL: We will now take a quick 15-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any members of the audience. We will resume at 11:05 EST.

(Whereupon, at 10:50 a.m., a recess was taken, and meeting resumed at 11:05 a.m.)

DR. LEBWOHL: Welcome back. We will now proceed with FDA's presentations, starting with Dr. Tao Liu.

FDA Presentation - Tao Liu

DR. LIU: Good morning. My name is Tao Liu. I'm the clinical pharmacology reviewer for this supplemental NDA. In my presentation today, I will discuss the dosing regimen, pharmacokinetics, and pharmacodynamics findings in Study 302.

OCA is a synthetic derivative of chenodeoxycholic acid and endogenous bile acid. Similar to endogenous bile acids, OCA undergoes extensive metabolism to form two major active conjugated metabolites, tauruo-OCA and glyco-OCA. Similar to endogenous bile acids, these two major metabolites, along with the parent drug, OCA, undergo biliary excretion and enterohepatic recirculation.

In the system of recirculation, the exposure to tauro-OCA and glyco-OCA is about 12-fold and 14-fold higher than that of OCA; therefore, the systemic exposure following administration of OCA is presented as the sum of concentration of OCA, tauro-OCA, and glyco-OCA, which is referred to as the total OCA concentration. Liver dysfunction significantly affects the pharmacokinetics of OCA and its major conjugates. In cholestatic liver disease, such as primary biliary cholangitis, the impaired biliary excretion can also affect the pharmacokinetics of OCA.

Prior to the accelerated approval for

hepatic impairment, a PK study was conducted to evaluate the effect of varying degrees of hepatic impairment on OCA PK. This figure shows the plasma concentrations of total OCA over 200 hours after a single dose administration of 10-milligram OCA.

In this study, the mean AUC of total OCA was about 10 percent higher in subjects with mild hepatic impairment defined by Child-Pugh Class A compared to subjects with normal hepatic function. In subjects with moderate hepatic impairment, defined by Child-Pugh Class B and severe hepatic impairment defined by Child-Pugh Class C, the mean AUC was 4-fold and 17-fold higher, respectively, compared to subjects with normal hepatic function.

In another study conducted after the OCA approval for PBC, the systemic exposure after multiple dose of 10-milligram OCA NASH subjects with mild hepatic impairment increased 8- to 9-fold compared to healthy controls, as shown in the figure on the right while the increase in Child-Pugh A subjects in the previous hepatic impairment PK study was only about 10 percent. These results

suggested that OCA exposure in subjects with hepatic impairment are highly variable and may not be reliably predicted by Child-Pugh classification alone.

Having said that, a major protocol amendment to Study 302 was implemented to lower the dose in PBC subjects with moderate to severe hepatic impairment based on the hepatic impairment PK study results. The dosing regimen for PBC subjects with moderate to severe hepatic impairment is to start with 5 milligrams once weekly for the first 3 months and then dose can be titrated to 5 milligrams twice weekly, and further to 10 milligrams twice weekly based on biochemical response and tolerability.

The dosing regimen in subjects without liver cirrhosis or with mild hepatic impairment remains 5 milligrams once daily for the first 3 months, followed by 10 milligrams once daily based on biochemical response and tolerability. The protocol also allowed dose adjustments for tolerability and resulted in variable dosing

regimen amongst study subjects and over time.

This table shows the planning dose regimen by the hepatic impairment per major protocol amendment in 2017. The number of subjects in the OCA arm is also shown by the USPI populations based on the applicant's assessment per the contraindication implemented in 2021. Our clinical reviewer, Dr. Tran, will further discuss the safety and efficacy findings in Study 302 per the USPI-labeled and USPI-contraindicated population.

In Study 302, the USPI-labeled population included subjects either without liver cirrhosis or with Child-Pugh A liver cirrhosis but without clinically significant portal hypertension. Subjects with decompensated cirrhosis, or prior decompensation event, or compensated cirrhosis with evidence of portal hypertension were classified as USPI-contraindicated population. In Study 302, 95 percent of patients with Child-Pugh A were classified as USPI-contraindicated population. Decompensation in this study is defined as Child-Pugh B/C or medical history of hepatic

failure, fibrosis, and liver cirrhosis, and other liver damage-related conditions. In Study 302, no subjects had Child-Pugh C, severe hepatic impairment.

Because Study 302 was ongoing at the time of major dose adjustment amendment, most patients started with 5 milligrams once daily dose. Among the 24 subjects with moderate hepatic impairment in the OCA treatment arm, only 4 subjects started with the adjusted dosing regimen at 5 milligrams once weekly as outlined in the study Protocol Version 3.

In the USPI-labeled population, 54 out of 81 subjects were titrated up to 10-milligram once daily dose from 5-milligram once daily dose, and 21 of the 54 subjects were subsequently downtitrated from the 10-milligram once daily dose. Of these 21 subjects, 11 were downtitrated due to worsening of pruritus. Dosing regimen other than the 5-milligram and 10-milligram daily dose, such as 5 milligrams every other day, 10 milligrams every other day, and 5 milligrams twice a week, were also noted.

This slide represents the average daily dose in Study 302 and the corresponding trough concentrations over time by liver cirrhosis status at baseline. In the figure on the left, almost all OCA-treated subjects started with 5-milligram once daily dose. The dose was titrated to 10 milligrams around 3 months after treatment in subjects without liver cirrhosis or with compensated liver cirrhosis. Subjects without liver cirrhosis had an average daily dose of about 8 milligrams, while subjects with compensated cirrhosis had an average daily dose of about 6 to 7 milligrams.

In the figure on the right, despite the slightly lower mean [indiscernible - 3:12:13] dose, subjects with compensated cirrhosis had a 2-fold higher mean total OCA concentration compared to subjects without liver cirrhosis. This difference is different from the 10 percent higher exposure observed in subjects with Child-Pugh A in the hepatic impairment PK study. As mentioned in the previous slides, most compensated cirrhosis patients are classified as USPI-contraindicated

population and all of the non-cirrhosis patients are the USPI-labeled population.

The accelerated approval of OCA was based on the effect on ALP and total bilirubin. In Study 302, ALP and total bilirubin were also measured. This slide represents the time profile for ALP and total bilirubin. ALP was presented in the figure on the left and total bilirubin was presented in figure on the right. The figure covers the first 3 years of treatment. The red color represents the USPI-labeled population and the blue color represents the USPI-contraindicated population. Triangles represent the placebo-treated subjects and the circles represent the OCA-treated subjects.

In the USPI-labeled population, a greater mean decrease in ALP from baseline was observed in OCA-treated subjects compared to placebo-treated subjects. In the USPI-contraindicated population, the mean ALP at baseline was lower than the USPI-labeled population. A decrease in ALP was also observed in OCA-treated subjects in this

population; however, the magnitude of change was smaller compared to the USPI-labeled population.

In both treatment arms and populations, mean ALP remained higher than the 1.67-fold of upper limit of normal criterion as part of the biochemical response that supported the accelerated approval. In the figure on the right, the USPI-labeled population had close to normal total bilirubin levels at baseline, while the USPI-contraindicated population had higher total bilirubin at baseline.

After treatment, OCA-treated subjects showed slightly lower total bilirubin in both USPI-labeled and USPI-contraindicated population. Of note, total bilirubin lower than upper limit of normal was also a criterion as part of the biochemical response for the accelerated approval.

In Study 302, a higher incidence of liver transplantation or death was observed in OCA-treated subjects than placebo-treated subjects, particularly in USPI-labeled population. Our clinical reviewer, Dr. Tran, will discuss these

cases later.

Here, we compare the total OCA concentration between subjects who experienced liver transplantation or death versus who did not in the OCA treatment arm. Each circle represents total OCA concentration from individual subjects. The red circles represent total OCA concentration in subjects who received the liver transplantation and blue circles represent the concentration in subjects who died. Black open circles are subjects who resulted in liver transplantation or death.

As shown in the figure on the right, in the USPI-contraindicated population, higher total OCA concentration was associated with liver transplantation; however, the incidence of liver transplantation or death were not limited to subjects with high concentration but associated with a wide range of concentration. As shown in the figure on the left, in the USPI-labeled population, subjects who received liver transplantation or died had a comparable total OCA concentration compared to those who did not

experience these events.

To summarize the clinical pharmacology findings in the USPI-labeled population in Study 302, total OCA concentration was similar to those observed in Study 301, the study used to support accelerated approval. Mean ALP was decreased within 4 months of treatment and was lower in OCA-treated subjects compared to placebo-treated subjects, but remained more than 1.67-fold of upper limit of normal in both treatment arms. At month 12, the biochemical response was about 14 percent in the OCA treatment arm and 3 percent in the placebo treatment arm. In the USPI-labeled population, events of liver transplantation or death were not associated with higher total OC concentration.

Now, I will hand over to our clinical reviewer, Dr. Tran, who will discuss the efficacy and safety findings in Study 302.

FDA Presentation - Tram Tran

DR. TRAN: Good morning. My name is Tram Tran. I'm a hepatologist and medical officer here

in the Division of Hepatology and Nutrition, and I'm going to be discussing Study 747-302, which is the pivotal postmarketing confirmatory trial. I'll be presenting our clinical and statistical review on behalf of the clinical review team and Drs. Yura Kim and Rebecca Hager in Biostatistics.

I'll be discussing key study design aspects of 747-302, including study endpoint definitions and populations of interest, in addition to the ITT safety population. I will review aspects of interpretability of the trial, along with the overall efficacy and safety results, and finally will conclude with the FDA benefit-risk assessment for this trial.

Study 747-302 was a phase 3b/4 randomized, double-blind, placebo-controlled, multicenter, event-driven trial. The study was designed to evaluate the effect of OCA on clinical outcomes in the subjects with PBC. The study enrolled 334 subjects in a 1 to 1 ratio, with the final analysis planned after accrual of 127 primary endpoint events.

The focus of this confirmatory study is on clinical endpoint events to confirm clinical benefit, though biochemical markers were assessed as well. Key entry criteria were abnormal bilirubin up to 5 times the upper limit of normal and/or alkaline phosphatase greater than 3 times the upper limit of normal. After follow-up at month 1, subjects were followed every 3 months through the end of study for clinical events even if they discontinued study treatment.

The overall efficacy and safety were assessed by the intent-to-treat, ITT, population; however, given the safety labeling changes that you've heard about that occurred through the course of the study, the subpopulations of interest were also the USPI-labeled populations and USPI-contraindicated populations. It was especially important to try to understand safety and efficacy in the patient population that would qualify for OCA use under the U.S. label.

Determination of the USPI-labeled and USPI-contraindicated populations was done by the

applicant based on the presence or absence of key clinical severity criteria at baseline. Any subject with a history or evidence of clinically significant portal hypertension, shown in the left column, or decompensated liver disease, as shown in the right column, was determined as contraindicated for OCA use, and were classified in the USPI-contraindicated group.

The criteria for clinically significant portal hypertension broadly ranged from having a history of TIPS, GI bleeding, or ascites, to evidence of having collaterals consistent with clinically significant portal hypertension, to having platelets lower than 150 with a splenomegaly and/or transient elastography greater than 15 kilopascals. If no evidence or history of these criteria were documented at baseline, then they were classified as USPI labeled. This classification is noted throughout the analyses to follow in this presentation.

Aligned with the general disease prevalence, the majority of subjects were white, non-Hispanic,

and female. The average age was 53.7 years. A mean baseline alk-phos was 490 and total bili of 1.6. The overall ITT population broken out by USPI contraindicated and USPI labeled was 55 percent and 45 percent, respectively. In the column on the right, using the applicant's defined criteria for USPI-labeled population and their criteria for cirrhosis, 94 percent were non-cirrhotic and 6 percent had compensated cirrhosis. It is not shown here, but the USPI-contraindicated population were 100 percent cirrhotic, as expected and consistent with the USPI-contraindicated criteria of having portal hypertension or decompensation.

Key points to discuss up front are that the applicant claims that results from Study 747-302 are uninterpretable due to functional unblinding and informative censoring, differential data collection between treatment arms, and initiation of commercial PBC therapies.

The FDA finds in our review that Study 747-302 provides meaningful and interpretable data to inform the benefit-risk assessment of OCA

for the following reasons. This trial was a large, randomized, placebo-controlled trial for this rare disease. This trial met the target number of events to trigger the final analysis, and power in the ITT population was adequate under the prespecified assumptions. The randomized treatment arms were similar in on-study follow-up time, which means time from randomization to the end of follow-up of a subject, irrespective of discontinuation of study drug. Randomized treatment arms were also similar in study withdrawal rates and concomitant other PBC therapy use. And while there were high rates of treatment discontinuation, the study evaluated the treatment effect of OCA under real-life clinical practice levels of treatment adherence in the USPI-labeled population.

The applicant has raised issues about differential data collection methods between the treatment arms, with potential recall bias or data collection frequency that could affect some components of the primary endpoint. You will see

later in the presentation that the observed trends in efficacy are largely driven by biomarker endpoints, which are most likely to be affected by these issues; however, we note that liver transplant and death, the two most important clinical outcomes, are the least likely to be affected by recall bias or differences in frequency of data collection.

Crossover to commercial OCA was another concern raised by the applicant. There are differential rates of crossover to commercial OCA between treatment arms, with more crossover from the placebo arm to commercial OCA. We acknowledge that crossover to commercial OCA makes it potentially more difficult to identify differences between randomized treatment arms because it makes the placebo arm look more similar to the OCA arm. Therefore, the magnitude of both efficacy and safety signal differences observed in the study may be smaller than if there was no crossover. But thinking about this critically, this means that if there are observed safety signal differences

between OCA and placebo on liver transplant or death, placebo crossover could actually underestimate this difference in the as-randomized analyses due to the use of commercial OCA.

Let's move on to discuss 747-302 efficacy analysis. ITT and safety populations were the same 334 subjects, and the protocol prespecified the efficacy analysis to be conducted in the ITT population. Efficacy and safety were also evaluated in the key subgroup of interest, the USPI-labeled population as defined by the applicant criteria, which was 45 percent or 149 subjects of this overall ITT population.

The USPI-labeled subgroup is an inherently meaningful subgroup that we consider to be specified at the time of the study safety labeling change in May of 2021, which occurred before the unblinding of the Study 302. This subgroup was not determined based on any safety data results from Study 302 and was defined by baseline characteristics only. Therefore, the analyses of the USPI-labeled subgroup preserves randomization

and are valid randomized comparisons. Given that a USPI-labeled population is currently the indicated patient population in the U.S., this is the most meaningful subgroup for the evaluation of safety.

Power calculations required that at least 127 events were needed to achieve 80 percent power with an assumed hazard ratio of 0.6, the treatment effect size assumed by the applicant. In December 2021, the definition of the primary endpoint was expanded to increase the number of clinical outcome events. With this expansion in the ITT population, 151 events were observed on the expanded primary endpoint.

Using the originally defined endpoint, 96 events were observed; therefore, with the agreed-upon expanded primary endpoint, the 151 events exceeded the 127 events required to achieve 80 percent power in the ITT population under the assumed effect size of a hazard ratio of 0.6. The applicant acknowledged this in December 2021, stating that the predefined number of events is assumed to be reached and triggered study closure.

The primary endpoint is a composite endpoint evaluating the time until the occurrence of the first event. The events are listed in this table and broken up into three categories, which are applicable to certain subjects depending on their baseline status. In bold are the events making up the original primary endpoint. The others, not bolded, are the additional events added to create the expanded primary endpoint as agreed upon with the applicant in 2021. It is noted that there was flexibility in the definition of some events, with the use of biomarkers such as transient elastography, platelet counts, and Child-Pugh score, which may have impacted outcome assessments.

The first set of events apply to all subjects and are denoted group 1 events. These events originally included death, liver transplant, hospitalization for decompensation events such as variceal bleeding, hepatic encephalopathy, and spontaneous bacterial peritonitis; uncontrolled or refractory ascites; and a new MELD score of 15 or higher, which are seen here in bold. And then

these were expanded to capture similar types of serious events such as empyema or other severe portal hypertension syndromes, which are also very clinically important.

The next two set of events apply to subsets of the trial subjects. The first set of events apply to subjects without decompensation at baseline. The second set of events apply to subjects without decompensation or clinical evidence of portal hypertension at baseline.

We would note that these agreed-upon events in the expanded endpoint showed the most flexibility around biomarkers such as platelets and transient elastography, as opposed to the group 1 events which were more clinically event based. Key secondary endpoints are listed here on this slide: time to first occurrence of any of the first group 1 events, time to first occurrence of original in bold events, and time to liver transplant or all-cause death.

The most common reason for treatment discontinuation in the trial was due to an adverse

event. Additional follow-up in the study was planned for subjects who discontinued study drug either with study visits, phone calls, or review of electronic medical records. While there were differences in on-treatment time between the randomized arms, the on-study follow-up time was similar between randomized arms.

There was crossover in the study to commercial product with more commercial OCA use in the placebo arm, 16 percent, compared to in the OCA arm, 8 percent, as you see highlighted in the red boxes; however, use of other concomitant medications like ursodeoxycholic acid, fibrates, and oral budesonide, as shown in the green boxes, was similar across the two arms. These same trends were observed in both the ITT and USPI-labeled populations.

Here are the primary endpoint results. You see here that for the ITT population, the prespecified primary analysis failed to achieve statistical significance with a p-value of 0.304. When looking at the USPI-labeled population, the

point estimate of the hazard ratio was consistent with the results of the ITT population with an estimated hazard ratio of 0.88 and 0.84, respectively, with the confidence interval including the null value of 1.

This slide might be hard to see, the words are very small, but looking in further detail at the components of the primary endpoint in the ITT population, this forest plot depicts the results for each event comprising the primary endpoint. This includes subjects who experienced each event at any time of the study, regardless of whether another primary endpoint had occurred earlier.

At the top of the figure, there's a trend of harm, or better for placebo on the right side, on liver transplant and death. The events with the highest trends of benefit for OCA are at the bottom of the figure and are reliant on biomarkers endpoints such as platelets, transient elastography, or Child-Pugh score, which has some subjective components. These components at the bottom had high incidence rates, which may be

drivers to the overall results of the primary endpoint events but are considered less clinically impactful than endpoints such as death or liver transplant.

Looking at the endpoints in a different way, this forest plot depicts the results from the prespecified primary and key secondary endpoints for both the ITT and USPI-labeled population. Points to the left favor OCA treatment and points to the right favor placebo. At the top are all the endpoints expanded to include biomarkers, et cetera, while at the bottom is just liver transplant or death. As the endpoints become more focused on the more severe events, i.e., moving down the forest plot, the point estimate of the hazard ratio moves from less than 1, favoring OCA, to greater than 1, favoring placebo, and this is more pronounced in the USPI-labeled population.

In the USPI-labeled population, the key secondary endpoint of time to liver transplant for all-cause death showed a hazard ratio of 4.77 with a 95 percent confidence interval that doesn't

include 1, and a nominal p-value of 0.029.

The Kaplan-Meier plot of transplant-free survival in the USPI-labeled population shows separation between the two treatment arms, with the OCA arm having a lower estimated probability of surviving without liver transplant compared to the placebo arm. As previously noted, the estimated hazard ratio is 4.77. This is in the direction of harm given 11 versus 2 deaths or liver transplant events in the OCA versus placebo arms.

Now, I will discuss some detail on safety in Study 747-302. Overall, in the ITT safety population, 38 subjects received liver transplants, 20 in the OCA treatment arm and 18 in the placebo arm. We note, however, that 7 of the 18 subjects in the placebo arm were found to have had either known commercial OCA exposure or tested positive for OCA in PK testing during the study.

Of the 38, 30 out of 38 were in the contraindicated population, which would be consistent with their more advanced disease status and hepatic decompensation being more likely in

this population. Six of these placebo subjects were also OCA exposed. And finally, 8 subjects total were transplanted in the USPI-labeled population. Of these eight, 7 out of 8 were randomized to the OCA treatment arm and one in the placebo arm.

The placebo subject who was non-cirrhotic was randomized to placebo, which she took for 268 days and stopped; the following day crossed over to commercial OCA and received OCA for 2 years. She then developed hepatic decompensation with ascites, upper gastrointestinal hemorrhage, and portal hypertension. She received liver transplant 3 months after discontinuing commercial OCA. Again, the placebo crossover to OCA could contribute to the underestimation of OCA safety signal of liver transplant in the as-randomized analyses.

This table shows some of the highlighted clinical characteristics of the eight USPI-labeled transplanted subjects. As mentioned, 7 out of 8 were randomized to OCA, but 8 out of 8 had OCA

exposure. Six out of eight were classified as non-cirrhotic by the applicant, which would not have suggested high risk for hepatic decompensation, and the clinical indications for subjects who required liver transplant were progressive jaundice with increases in bilirubin, severe pruritus, and complications of portal hypertension such as GI bleeding.

This graphic summarizes the clinical trajectory of all 13 USPI-labeled subjects who had liver transplant, shown as LT, or died, shown as D. The red lines indicate those 11 out of 13 who were randomized to OCA. The two blue lines are those randomized to placebo.

In the USPI-labeled population, subjects who received liver transplant or died had comparable or total OCA exposure, the PK levels, to those who did not experience these events as per Dr. Liu's presentation, highlighting the potential unpredictable nature of these events, even in those without the high OCA exposure observed in the USPI-contraindicated population.

I would highlight for you the vertical hash marks which show the primary, and primary endpoint events occurred while on treatment for the majority of subjects who received liver transplant. Even though they stopped OCA treatment, they still went on to require liver transplant. Timing of liver transplant after a patient's initial decompensation event may be dependent on many external variables.

Now, we'll examine the deaths in Trial 747-302. Total deaths in the ITT safety population were 28, with most being in the contraindicated population. We would note that 3 subjects randomized to placebo in the overall population had documented OCA-positive quantifiable PK samples prior to death and were also in the contraindicated placebo arm. Of the 5 deaths in the USPI-labeled population, four were in OCA and one in placebo. The causes of death are noted here on the right-hand side of the slide.

In reviewing the one OCA-treated subject who died due to a liver-related cause, at baseline, her laboratory values were a total bilirubin of 2,

ALT 155, alk-phos of 453, and a platelet count of 224, and a MELD score of 9.1, with stage 2 fibrosis on a previous liver biopsy. An upper endoscopy done on day 3 showed esophagitis, gastritis, but no evidence or mention of esophageal varices. Approximately one year later, despite improvement in bilirubin and alk-phos, an upper endoscopy showed large esophageal varices with hypertensive gastropathy, and she was adjudicated as having progression to cirrhosis by the Hepatic Outcomes Committee. She continued receiving OCA.

Two and a half years later on day 889, the subject presented with an upper GI bleed and study drug was stopped. She subsequently had three more episodes of GI bleeding leading to shock, cerebral edema likely due to the shock, and arrest. She died about a month later. The Hepatic Outcomes Committee adjudicated this event as a liver-related death.

Moving on to drug-induced liver injury, or DILI, possible or probable cases of DILI were seen more often with OCA in the overall population with

10.7 percent in the OCA to 4.8 percent in placebo; in the contraindicated subgroup, 16 percent for the OCA arm to 7 percent in the placebo arm; and in the USPI-labeled subgroup, 4.9 percent to 1.5 percent. These were adjudicated by the blinded independent hepatic safety adjudication committee for drug-induced liver injury and causality.

I will review one case of possible DILI of a 45-year-old woman who was randomized to OCA and was in the USPI-labeled subgroup. She was diagnosed with PBC by two liver biopsies, was taking medications for arthritis and pruritus, and had Sjogren's syndrome. Once she started OCA in the study, she developed worsening pruritus with no other noted symptoms or clinical issues.

An ultrasound done showed cholelithiasis. On study day 34, her total bilirubin was 1.1, and on a scheduled visit at day 80, it had increased to 4.2, with an ALT increase from 168 to 764. Notably, the clinician investigator found no other suspected cause, she didn't have any other symptoms -- other than the study drug, which was

stopped a week later at day 87 because her total bilirubin continued to climb to 4.9.

After discontinuing OCA for nearly a month, the bilirubin continued to climb to 6.6, and she withdrew from the study. Follow-up lab tests approximately one month later improved when with her history of cholelithiasis, an elective cholecystectomy was performed with liver biopsy showing portal inflammation, ductopenia, and no bridging fibrosis. The adverse event of a total bilirubin greater than 3 and possible DILI were retrospectively reviewed by two independent HSAC panels comprised of three GI hepatologists each, and adjudication decisions are seen here ranging from possible to highly likely.

The asymptomatic and unpredictable rapid rises, such as seen in this subject, with a total bilirubin up to 6.6 and ALT over 700, would be challenging to predict, and progression of liver injury may continue to occur even after stopping medication.

Now, I will discuss adverse event of

pruritus. Pruritus is a known and expected adverse event related to OCA treatment and was observed in Study 747-302, consistent with previous studies. Across all measures of the adverse events of pruritus, including new onset of pruritus, pruritus requiring additional treatment or stopping the study drug, OCA showed more pruritus than placebo. This was observed in the ITT safety population and in the USPI population as seen here.

In summary, in the overall ITT safety population, OCA-treated subjects had higher numbers of clinical events of liver transplant and death compared to the placebo group. This difference may be underestimated due to placebo crossover with commercial OCA. The overall ITT population, contraindicated population, and USPI-labeled population had higher events of possible or probable DILI in the OCA arms. Higher incidence differences were also noted for pruritus for OCA treatment.

The agency's overall benefit-risk assessment of Study 302 is that it provides interpretable and

informative results for OCA in PBC. Biochemical responses were observed in 10 percent versus 2 percent OCA versus placebo arms in the ITT population and 14 percent versus 3 percent in the USPI-labeled populations; however, the primary endpoint of the study, time to first clinical outcome event, in the ITT population failed to demonstrate efficacy of OCA with a hazard ratio of 0.84 and a p-value of 0.304.

Risk assessment found a signal of harm on liver transplant and death in the ITT population with a hazard ratio of 1.18, and in the USPI-labeled population, a hazard ratio of 4.77 with the confidence intervals noted here. Higher numbers of events for DILI and pruritus adverse events were also observed. Risk mitigation for adverse outcomes would likely be infeasible due to unpredictable nature of hepatotoxicity as observed in the USPI-labeled population who required liver transplant despite being non-cirrhotic at baseline.

I will now turn the presentation over to my colleague, Dr. Joel Weissfeld, to discuss

Study 747-405.

FDA Presentation - Joel Weissfeld

DR. WEISSFELD: Thank you. As you heard, my name is Joel Weissfeld. I reviewed study 747-405 for a Division of Epidemiology in the CDER Office of Surveillance and Epidemiology. My presentation will cover major threats to the validity of Study 405, a real-world data study to evaluate the effectiveness of OCA on hepatic outcomes in PBC patients. My colleague, Dr. Andraca-Carrera, will follow with conclusions from the perspective of Division of Biometrics. My presentation has three parts as outlined on this slide. The first part will cover study design, data sources, and methods. The second and third parts will cover key study results and data relevance and reliability.

The applicant presents Study 405 is an adequate and well-controlled study that confirmed clinical benefit from OCA for PBC. Study 405 describes a 67-month observational, non-randomized cohort study which relied on data from U.S. administrative health insurance data claims.

Study 405 adopted a target trial emulation approach which first articulated a causal question in the form of an imaginary protocol for a hypothetical randomized trial, and then emulated some components of the imaginary protocol with observational data. Study 405 emulated an OCA trial designed to assess clinical outcomes for patients similar to the USPI-labeled PBC population.

Study 405 also implemented a treatment-decision design which conceived each occurrence of observed abnormality in alkaline phosphatase or total bilirubin as a decision point whereby a healthcare provider might prescribe or not prescribe OCA. This design has two implications. First, it defined an untreated control; that is, a comparator not treated with OCA. Second, the particular design implemented by 405 allowed more than one follow-up period from the same patient, a complexity addressed during data analysis by a weighting method.

Study 405 used tools provided by one company, Komodo, to access information on

administrative claims against health insurance and tools provided by a second company, Datavant, to link claims and data sources that provided results from diagnostic laboratory tests, date of liver transplantation, and date of death.

The following eight slides summarize methods used by Study 405 to measure key variables and conduct analyses. Inclusion criteria describe variables used to validate observations for analysis whether treated or not treated with OCA. Inclusion criteria for Study 405 required age at least 18 years; definite or probable PBC defined as one inpatient claim or two outpatient claims with diagnosis coding for PBC; evidence for failed treatment with UDCA; high ALP or bili; and closed claims; that is, medical and drug insurance coverage for at least 12 months before a so-called index date or day zero, for a period of follow-up.

Study 405 implemented a complex method to emulate UDCA treatment failure, a critical eligibility criterion and marker of poor PBC prognosis. The first two sub-bullets on this slide

summarize methods used to emulate a component of the currently labeled indication for treatment with OCA: inadequate UDCA response defined as ALP or bili above upper limit of normal despite at least 270 days of UDCA treatment in the previous 365 days, and at least 60 days of UDCA treatment in the previous 90 days; UDCA intolerance, defined as high ALP or bili observed more than 90 days after a single episode of UDCA treatment lasting no more than 90 days.

One-half of OCA patients and one-quarter of control periods satisfied criteria for UDCA treatment failure by virtue of the third sub-bullet shown on this slide, UDCA discontinued, an expedient criterion defined as high ALP or bili reported at least 6 months after the completion of an antecedent course of treatment with UDCA of any duration; or any UDCA before initiation of treatment with OCA. Note here, Study 405 accepted and OCA dispensing in the setting of previous or concurrent UDCA as sufficient evidence for UDCA treatment failure.

Exclusion criteria describe variables used to invalidate observations from analysis whether treated or not treated with OCA. Study 405 used information available on or before index dates to define exclusion criteria, which captured information on claims which might indicate concomitant liver disease, hepatitis C, hepatitis B, alcoholic liver disease, or primary sclerosing cholangitis; information on claims that might indicate history of hepatic decompensation, variceal bleed, ascites, spontaneous bacterial peritonitis, hepatic hydrothorax or hepatic encephalopathy; and laboratory test indicators for previous hepatic decompensation or hepatobiliary injury.

Other factors not listed on this slide were defined to exclude follow-up periods associated with history of malignancy, HIV, or liver transplantation; history of Paget's disease or recent bone fracture; previous treatment with OCA fenofibrate, bezafibrate; and history of combined treatment with rifaximin and lactulose.

Study 405 defined a period of exposure to OCA by days of treatment supplied by a sequence of OCA dispensings as indicated by pharmacy claims against health insurance, with 90-day treatment gaps allowed between dispensings and 90 days added to a last dispensing.

Study 405 defined three study outcomes: hepatic decompensation event defined by hospital claims with diagnosis coding for variceal bleeding, ascites, or hepatic encephalopathy; liver transplantation identified by link to OPTN registry or consistent claims profile; and death from any cause identified by link to Social Security Death Index or obituary search.

This slide itemizes the diagnosis codes used to identify hepatic decompensation. Bolded type highlights the five codes most often used to identify hepatic decompensation outcomes in order of decreasing frequency: one, other ascites; two, encephalopathy unspecified; three, hepatic failure unspecified without coma; four, esophageal varices with bleeding; and five, secondary

esophageal varices with bleeding.

Weights derived from propensity scores were used to achieve comparability between OCA treated at control with respect to 14 covariates measured at baseline. The committee might consider whether these covariates listed on this slide adequately capture clinical notions of PBC disease severity. The covariates included sex; calendar period; age; health insurance type; months since UDCA treatment failure on UDCA; cirrhosis; clinical evidence of portal hypertension; Charlson Morbidity Index; and five laboratory values: ALP, bili, ALT, AST, and platelet count. Additional information about these covariates can be provided during meeting time allocated for clarifying questions to FDA.

For follow-up and analysis, Study 405 assessed as-treated time to death, liver transplantation, or hepatic decompensation. As-treated analysis censored OCA-treated follow-up upon OCA discontinuation. This censoring criterion might or might not be appropriate. Judgments about the appropriateness of this censoring criterion

might depend on notions about the latency or persistence of therapeutic benefits expected from OCA on clinical outcomes. Dr. Andraca-Carrera will discuss the rule sets used to censor follow-up.

The following three slides summarize key study results. This slide summarizes key as six baseline characteristics for 403 PBC patients treated with OCA; 11,246 periods of observations in PBC patients not treated with OCA, unweighted; and 405.37 periods of observation in PBC patients not treated with OCA, weighted. Please focus your attention on the leftmost data column which describes OCA-treated patients with PBC: 91.6 percent female, mean age 56.2 years; 50.4 percent history of cirrhosis; 23.6 percent history of portal hypertension; 72.5 percent on OCA; and mean ALP 292. Weighting balanced OCA and control groups for these and other baseline characteristics.

Extreme differences were observed before weighting between OCA treated and control for some baseline characteristics. For example, these

histograms summarize distributions for baseline ALP with the histogram on the left before weighting and the histogram on the right after weighting. The applicant's primary analysis assessed outcomes during as-treated follow-up with mean duration lower in OCA treated than control, 436 versus 627 days; censored follow-up more frequently for treatment switch in OCA treated than control, 53.3 percent versus 21.1 percent; and censored and observed the primary outcome -- death, liver transplantation, or hepatic decompensation -- less frequently in OCA treated than control, 1.7 versus 4.6 per hundred patient-years. Dr. Andraca-Carrera will critique the results summarized on this slide.

My remaining slides address matters that concern data relevance and reliability. Study 405 used data with complex provenance that appears traceable and data of undetermined accuracy and completeness to identify: PBC, the patient population of interest; UDCA treatment failure, an important inclusion criterion; history of hepatic decompensation, an important exclusion criterion;

covariates needed to adjust comparisons for baseline differences between OCA treated and control; and clinical outcomes of interest, particularly incident or new onset hepatic decompensation.

We lack direct information about the accuracy and completeness of the methods used to identify the study population, PBC with failed response to UDCA and no history of hepatic decompensation. Misclassification of PBC, UDCA treatment failure, or history of hepatic decompensation might result in artifactual association between OCA and PBC outcomes if errors identifying the OCA indicated population occurred more often in one comparison group than another and described patients with different underlying expectation, or risk, for poor outcome.

A favorable determination about the adequacy of weighting methods used to achieve comparability between treated and control requires high confidence in the accuracy and completeness of information used to exclude patients with non-PBC

reasons for abnormal ALP or bili and ability of measured covariates to capture differences in prognosis fully and accurately. Please note that baseline comparability does not necessarily assure comparability during follow-up if certain time varying factors determine both change in treatment during follow-up and subsequent risk for the study outcome. Dr. Andraca-Carrera will comment upon this matter under the rubric of informative censoring.

We have little information about the accuracy and completeness of the method used to link claims to death and liver transplantation registries. We lack clarity about Datavant tokens and matching algorithms; information about the quality of underlying personally identifiable information in source data; and specific information about the accuracy of matches.

The presence of an hepatic decompensation code on a hospital claim might describe a false positive finding due to coding error; misdiagnosis; work-up, ruling out hepatic decompensation; history

of hepatic decompensation or recurrent hepatic decompensation event; or a true positive finding; that is, incident hepatic decompensation event, the outcome relevant to Study 405. The regulatory context at hand creates an expectation for strong methods to distinguish true positive incident hepatic decompensation events from other false positive possibilities. The codes used to identify the hepatic decompensation outcome were not validated in patients who fulfilled eligibility criteria for Study 405. Hepatic decompensation outcomes were not adjudicated, verified, or validated against a second source of information such as patient medical records.

We regard the potential for misclassification of the hepatic decompensation outcome as a major threat to the validity of results from Study 405. Outcome misclassification emerges as a particular concern if misclassification errors differed in scale between OCA treated and controlled conditions. This slide uses the technical term "differential outcome

misclassification" to refer to this possibility. During time allocated for clarifying questions to FDA, I might be asked how differential outcome misclassification might occur.

This busy slide illustrates that validation studies of hepatic decompensation codes have been reported in medical literature. In response to an inquiry from FDA about the accuracy of methods used to identify hepatic decompensation, the applicant cited Kanwal 2012 and Lapointe-Shaw 2018, the third and fourth validation study listed on this table. FDA recognizes that diagnosis codes when used in certain settings might identify hepatic decompensation with some accuracy. Members of the committee with the pertinent expertise might comment about the relevance of these validation studies in medical literature to FDA's assessment of Study 405.

Claims typically open truncated windows into the clinical history of a chronic disease. Particularly when recognized before cirrhosis or decompensation, PBC describes a condition that

typically progresses slowly over a long period of time. As noted on this slide, these considerations generate concern about the relevance of the follow-up windows available to Study 405 as a possible misalignment between observation window and therapeutic effect expected from OCA on clinical outcomes, including long latency outcomes.

In conclusion, the applicant presents Study 405 as an adequate and well-controlled study that confirmed clinical benefit from OCA for PBC. A regulatory purpose so described obligates relevant data and reliable methods that produce clinically germane results with high confidence. As summarized on this slide, Study 405 might not be regarded as adequate and well controlled because of concerns about the accuracy and completeness of study variables, inferential error due to uncontrolled confounding and outcome misclassification, and insufficient follow-up for long latency outcomes.

Dr. Andraca-Carrera will now address a concern described by the fourth bullet on this

slide, differential censoring possibly leading to post-baseline non-comparability between OCA treated and control. Thank you.

FDA Presentation - Eugenio Andraca-Carrera

DR. ANDRACA-CARRERA: Thank you, Dr. Weissfeld.

Good afternoon. My name is Eugenio Andraca-Carrera, and I'm a statistician within the Division of Biometrics VII, CDER. Today, I will talk about the statistical analysis in the observational cohort study, 747-405.

Dr. Weissfeld has just discussed some of the limitations of the data sources and the methods used in this study. Study 747-405 lacks some important data elements that impact our assessment of the reliability and completeness of the data, so please note that all the statistical analysis in my presentation must be interpreted within the context of these limitations. My presentation will briefly discuss the study design as it relates to the statistical analysis, then I will summarize and discuss the applicant's analyses, and I will

present additional analyses conducted by the FDA review team.

In a randomized clinical trial, the date of a study entry, or day zero, is clearly defined as the day of randomization; however, Study 405 is not a randomized clinical trial, and there may have been more than one calendar day per patient to be considered as the date of a study entry. Under the design of Study 405, patients were eligible to contribute multiple dates of a study entry and associated follow-up times. Each of these follow-up times is called an index, so one patient could have contributed multiple indices to the study.

Patients who were treated with Ocaliva during the study period entered the study as the date of their first treatment dose or dispensing of Ocaliva based on their claims data, and this is represented by the green diamond and corresponding line. Patients could only contribute a single index or follow-up time in the Ocaliva cohort. Patients who had not been treated with Ocaliva and

met the study eligibility criteria at a study visit entered the control cohort. This is represented by the orange diamonds and corresponding lines.

A patient could meet the study eligibility criteria at multiple visits, and therefore they could contribute multiple indices to the control cohort. So all the statistical analyses were based on these indices and not on individual patients, and the statistical methods were used to adjust for the use of possibly multiple indices per patient.

This is a summary of the number of patients and indices in Study 405. There were 403 unique patients who met the study inclusion criteria, were treated with Ocaliva, and were included in the statistical analyses; and because patients could only contribute a single index or follow-up period to the Ocaliva cohort, you can see that there are 403 indices corresponding to 403 patients on this cohort. There were 4,174 patients who met the study inclusion criteria for the control cohort at at least one visit, and some of these patients contributed more than one eligible index or

follow-up period in the control cohort, so we have a total of 11,246 indices that correspond to these 4,000 patients.

As discussed by Dr. Weissfeld, because this is not a randomized clinical trial, the baseline characteristics of the patients and indices in the Ocaliva cohort were different from those of the control cohort, and in order to balance the baseline characteristics and to make the control cohort comparable to the Ocaliva cohort, the applicant applied weights based on a propensity score model. After applying these weights to the 11,246 control indices, we ended up with 405.37 weighted control indices, and these are all used in all analyses.

Next, I will briefly discuss the analyses conducted by the applicant. The primary endpoint was time to the first event of either hepatic decompensation, liver transplant, or death. You have just heard from Dr. Weissfeld's presentation that hepatic decompensation might be subject to outcome misclassification in Study 405. The

applicant's primary analysis was based on an as-treated follow-up, also sometimes known as a while-on-treatment strategy, that followed patient indices from the time of the study entry until they either experienced an event or one of several censoring criteria that constitute a treatment switch, and I will discuss the censoring rules in the next slide. As I mentioned earlier, weights were used to make the cohorts comparable, and the statistical analysis adjusted for the use of potentially multiple indices from a single patient.

During the pre-NDA discussions between the applicant and the agency in 2023, the agency communicated that we were interested in analysis that followed patients after treatment discontinuation or treatment switch. In response, the applicant conducted two sets of analyses labeled ITT 1 and ITT 2 that removed some of the censoring rules used in the as-treated analysis.

These are the censoring rules in the as-treated analysis. This is a time-to-event analysis in which follow-up time is censored when a

patient index experiences any of the events in this rule. Indices in the Ocaliva cohort were censored 90 days after they stopped treatment with Ocaliva. They were also censored when they started using fibrates or at the time of study end on December 31, 2021, or if their period of closed claims ended. The last criterion refers to when an insurance plan stops providing claims information for a patient. A period of closed claims is necessary to capture hepatic decompensations. The control cohort does not include an active control, so treatment switch is defined differently. It's defined by the start of Ocaliva, start of fibrates, restart of UDCA for those who stopped it, study end, or the end of closed claims.

Upon request from the FDA, the ITT 1 and ITT 2 analyses conducted by the applicant tried to approximate an intention-to-treat analysis. In the ITT 1 strategy, the censoring rules for control stayed the same, but patient indices on Ocaliva were no longer censored when a patient stopped treating with Ocaliva. In the ITT 2 analysis, the

censoring rules were further reduced, and indices in the control cohort were not censored when they started Ocaliva or restarted UDCA. But notably, all analyses, the as-treated ITT 1 and ITT 2, include censoring for the end of closed claims, and this is necessary because closed claims are the data source used to capture hepatic decompensation events.

Here the results of those analyses. The primary treated analysis observed 8 events among 403 patient indices on Ocaliva compared to 31.8 weighted events among 405 control indices. The estimated hazard ratio for this analysis was 0.37 with a 95 percent confidence interval of 0.14 to 0.75. Now, there were 14 additional events observed in Ocaliva after the end of the as-treated period, for a total of 22 events. The estimated hazard ratios for the ITT 1 and ITT 2 analyses were 0.59 and 0.64, and you can see here in the rightmost column that the upper bounds of the 95 percent confidence intervals were close to 1.

Our review found that the as-treated

analysis is likely subject to informative censoring. As has been discussed previously today, informative censoring occurs when the reason for stopping follow-up is related to the probability of experiencing an event, and the result is that such analysis might miss observing events of interest and might overestimate a treatment effect. The ITT 1 and ITT 2 analysis partially address this issue, although they still require censoring for issues such as the start of fibrates or the end of closed claims. I'll discuss the evidence of informative censoring in the next few slides.

This slide shows the follow-up time and reasons for treatment switch in the as-treated analysis. The first thing to notice is that the mean follow-up time among indices on Ocaliva in this analysis was much shorter, at 436 days, than the mean follow-up among controls, at 627 days.

One of the main reasons for the difference in follow-up times was due to the higher treatment discontinuation among patients on Ocaliva. The proportion of indices that were censored because of

treatment switch was very different between the two cohorts. Among Ocaliva indices, 53 percent were censored because of treatment switch, and most of them, 48.6 percent, were censored because they stopped using Ocaliva. In contrast, only 21 percent of indices in the control cohort were censored because of treatment switch.

So one follow-up question is, why did 48.6 percent of patients stopped using Ocaliva? And unfortunately, because Study 405 is an observational study, we do not have full post-baseline data on the reasons for treatment discontinuation; however, we have some information to try to answer this question.

This is the section on safety and treatment discontinuation in the 2018 product label for Ocaliva. Additional warnings have been added in updated versions of the label, and I have highlighted sections here that might have been relevant for treatment discontinuation. The label instructed physicians to interrupt or discontinue treatment in patients who developed evidence of

worsening liver function or who experienced clinically significant liver-related adverse reactions, and both of these indicate a patient with a higher risk of experiencing hepatic decompensation, liver transplant, or death.

This slide shows the incidence rate of the primary event of hepatic decompensation, liver transplant, or death per 100 patient-years during the as-treated follow-up time in black bars and during the period between the end of the as-treated follow-up time and the end of the ITT 2 in white bars. During the as-treated period, the incidence rate of events was 1.66 per 100 patient-years on Ocaliva and 4.57 on control, and this difference in incidence rates is consistent with the estimated as-treated hazard ratio of 0.37.

The white bars showed the event rate after the as-treated follow-up has ended, and during this time, the observed incidence rate was 4.42 on Ocaliva and 2.54 in control. So the large difference in incidence rates of events during the as-treated period and afterwards suggest that

either the treatment effect of Ocaliva goes away past 90 days after treatment discontinuation or that patients with higher risk were more likely to stop treatment with Ocaliva, and they observe a higher rate of events afterwards.

Now, I will talk about additional analyses conducted by the FDA review team. In order to evaluate the impact of informative censoring, the FDA review team conducted additional analyses for a composite endpoint of liver transplant or death that excludes hepatic decompensations. This endpoint is clinically relevant, and because death and liver transplants are captured through the Social Security Death Index and through a registry, this endpoint is not as likely affected by the limitations of claims data such as potential misclassification and censoring due to the end of closed claims.

We conducted an ITT-like analysis that followed patients until they experienced an event or the end of the study on December 31, 2021, and these are the results of the analysis of the time

to first event of liver transplant or death. For completeness, we also estimated this endpoint using the censoring rules in the applicant's as-treated ITT 1 and ITT 2 analyses, and as shown here, also the FDA ITT strategy described in the previous slide.

Under the as-treated censoring rules, there were two events observed in the Ocaliva cohort and approximately 12 events in the control cohort. The estimated hazard ratio for the as-treated analysis for this endpoint was 0.27. In contrast, both the ITT 1 and ITT 2 strategies, as well as the FDA's ITT-like analyses, estimated hazard ratios between 0.80 and 1.07 for this endpoint, with 95 percent confidence intervals that include the null value of 1, as shown in the rightmost column of this slide.

Our conclusions for this review are as follows. Dr. Weissfeld discussed how the data in Study 747-405 do not have all the necessary information to assess its relevance, as well as its accuracy and completeness. Because of these important limitations, the analyses discussed in my

presentation should be interpreted with caution. In my presentation, I showed that the as-treated analysis of time to hepatic decompensation, liver transplant, or death is likely subject to informative censoring. We conducted additional analyses for a composite endpoint of time to death or liver transplant, and these additional analyses do not demonstrate efficacy associated with Ocaliva.

Thank you for your attention, and now I will give the podium to Dr. Anania. No? Oh. Thank you.

Clarifying Questions to FDA

DR. LEBWOHL: Thank you.

We will now take clarifying questions for FDA presenters. For panel members who are here in person, please raise your hand, and we'll note that and call in order. If you are attending remotely, please use the raised-hand icon to indicate that you have a question, and remember to lower your hand by clicking it again after you've asked your question.

When acknowledged, as previously, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, again, it would be helpful to acknowledge the end of your question with a thank you, or your follow-up as, "That is all for my question," so that we can move on to the next panel member.

We'll start with Dr. Goldberg.

DR. GOLDBERG: I have a question for Dr. Tran as it relates to slide 45. I guess the clinical trajectory in terms of liver transplantation was different the way you showed the data compared to the company. I'm curious if there were any data as to when people were listed for liver transplantation relative to transplant because I think that helps to address the temporality of taking the medication to needing a transplant, because we know so much can get into when you actually get transplanted.

DR. TRAN: Yes. Thanks. So you can see in slide 45, there were primary endpoint events, as you see with the hash marks, and then some patients had multiple primary events and then stopped treatment, and then waited for liver transplant for some period of time. We do have some narratives that give us some information about when they were listed but the narratives don't give us exact timing for all of the patients who were listed for liver transplant in terms of exact day of listing versus the actual time of transplant.

DR. GOLDBERG: And then one other quick question for Dr. Weissfeld. As it relates to Study 405 and the decompensation outcomes in the two groups, were there any data presented as to whether the OCA-treated group was either more engaged with care with specialists and/or on other medications that may prevent decompensations like beta blockers? We didn't see any data on that.

DR. WEISSFELD: No. Thank you for that question. I don't have any data on those items. Thank you.

DR. GOLDBERG: Thank you both.

DR. LEBWOHL: Dr. Lee?

DR. LEE: This is a question for Dr. Tran. One of the most striking findings that was presented is the notion that in the USPI-labeled population, there was a 4.7-fold higher risk of liver transplant and death; and in the context of a randomized clinical trial, the implication is that OCA is causative in the need for transplant and death, but at the same time, there were only four DILI events mentioned with OCA. So if not from DILI, what is the hypothesized mechanism for this signal?

Then somewhat related is that you showed on slide 48 the patient who developed portal hypertension and progression, and then liver-related deaths, although she had improving bilirubin and alkaline phosphatase, which is not quite the natural history of this disease. So were there any attempts to rule out other causative mechanisms such as portal vein thrombosis or alcohol, things like that?

DR. TRAN: I'll take your first question, which is I think referring to the trajectory of the patient's disease and why some of these patients -- okay. DILI may not be the causative issue here. It may be a direct hepatotoxicity or may be progression of disease, the variability and progression of disease in some of these patients; although we would think that if these patients would be particularly high risk, then you would have seen perhaps some patients in the placebo group who also would have progressed.

So the beauty of maintaining the randomization here is really, I think, remarkable in seeing this unexpected result of the hazard ratio of 4.77. So variability in the progression of disease in some of these patients may be the cause, as well as potential hepatotoxicity, not necessarily DILI.

Then in the case of the patient who had a liver-related death and progressed very quickly despite improvement in their bilirubin and progression to portal hypertension, are there other

causative -- we don't have any other history in the narrative that led to any other potential underlying etiologies besides that.

DR. LEE: Thank you.

DR. TRAN: Dr. Ruby Mehta has additional comment.

DR. MEHTA: Ruby Mehta. This mirrors almost similar findings that we noticed in 2021 when we moved for the labeling changes. We don't know exactly, but could there be an element that there is progression of disease because of OCA, the hepatotoxicity component? That is our main concern here.

DR. LEBWOHL: Mr. Honczarenko?

DR. HONCZARENKO: Yes. Thank you. It's a very much related question to my previous speaker's, a question for Dr. Tran. Obviously with such a high hazard ratio of 4.77 in the USPI-labeled population, have you been able to look into the FDA AE reporting system and database, and confirm or deny these claims?

Then a related question, obviously, there is

a big discrepancy between this analysis in the USPI-labeled population and ITT. Do you think that introduction of this criteria for USPI-labeled population post hoc, after study was essentially enrolled, could have introduced the bias into this analysis?

DR. TRAN: So I'll take the first. I think your first question was about a monitoring system.

DR. HONCZARENKO: The question is related to, with this high hazard ratio, have you been able to look into the safety database and deny or validate these findings?

DR. TRAN: Okay. We can pull up the postmarketing safety database slide. Yes, we have seen in the postmarketing that after the safety labeling change of 2021, we do see that there's still evidence of active events of severe liver-related events, as well as liver transplant and death. So we have received other cases despite the safety labeling change of 2021, which continues to be a concern for us.

Your second question, can you repeat it?

DR. HONCZARENKO: The second question was related to a large difference in hazard ratio between USPI-labeled population and ITT. Do you think that introduction of the USPI-labeled population criteria post hoc, when the study was really fully enrolled, could have introduced this bias?

DR. TRAN: Yes. The contraindicated in USPI-labeled criteria were introduced due to the safety labeling change, but the criteria were applied to baseline. So they had the data at baseline, so nothing changed in terms of the patients -- none of the data was unblinded. We didn't analyze it based on unblinded data. So that's what I think the issue is, and that's why the USPI label, we consider that still maintaining randomization.

DR. ANANIA: Can the chair recognize Dr. Racoosin from our team? Thank you.

DR. LEBWOHL: Please.

DR. RACOOSIN: Judy Racoosin, Deputy Director for Safety in the Division of Hepatology

and Nutrition. To your question about the FDA Adverse Event Reporting System, our Division of Pharmacovigilance colleagues have reviewed these cases. Between May 26, 2021, when we instituted the safety labeling change, and September 9th, FDA has received reports to the FDA Adverse Event Reporting System, seven cases of liver transplant, six of transplant evaluation, and five of liver-related deaths. Of the 18 cases of reports describing liver transplant, transplant evaluation, or liver-related death, 15 reports did not provide sufficient information to determine if the patient had decompensated cirrhosis or compensated cirrhosis with evidence of portal hypertension at the time Ocaliva, or OCA, was initiated.

Importantly, two of the reports suggested that OCA was continued after evidence of portal hypertension was identified. So I think it's important to acknowledge that despite best efforts for FDA and the hepatology community to encourage following the labeling, it may not always be followed. Thank you.

DR. LEBWOHL: Dr. Weissfeld, did you have some comments on this?

DR. WEISSFELD: Yes. I believe Dr. Goldberg asked if information was submitted from Study 405 regarding concomitant medications at the time of entry into the study. I'm sorry; I misspoke. I didn't have any slides to present, but in the study report from 405, there is a table that outlines or provides descriptive information for concomitant medications by generic name observed in greater than 10 percent of OCA-treated subjects.

A few things stand out that may be of interest, and this is after weighting. It's estimated that 37 percent of control versus 31 percent of OCA treated had prednisone exposure before entry into the study; hydroxyzine 17 percent in the control versus 27 percent in OCA treated; omeprazole -- those are probably the two that jump out to me when I look at this table. Thank you. That was it.

DR. LEBWOHL: Dr. Gillen?

DR. GILLEN: Great. Thank you. Daniel

Gillen. This question is for Dr. Andraca-Carrera. I think it was very clearly articulated, the issue with potential informative censoring that was done, and I appreciate the analysis that was done by the FDA, and I view all of these as, to some degree, exploratory or sensitivity analyses.

I wonder if you've considered, and can demonstrate, a middle ground where we might censor at 6 months, or 9 months, or 12 months post-treatment, for example. I don't have a feel for the distribution of time from the stopping of the closed claim, for example, to the end of study, and I'm wondering how long we're letting folks go out for.

DR. ANDRACA-CARRERA: Unfortunately, we do not have those analyses that look at different windows after treatment discontinuation. We'll take it under advisement and we'll conduct it. I do not have those analyses ready.

DR. GILLEN: I think the gist of the request, really, is how long do we go out to attribute something back to OCA? We've kind of let

things go until the end of study, and it would be nice to think about a tipping-point-like analysis, where we can look at what happens as we censor different intervals of time post-treatment.

DR. LEBWOHL: Dr. Kamath?

DR. KAMATH: This is a follow-up of Brian's statement. There has been a disconnect noted between alkaline phosphatase and complications. For instance, in the high-dose urso study, which was discontinued because of harm, the urso group actually had significantly better liver tests but a higher rate of requirement for liver transplantation in cholangiocarcinoma. So that's the hepatology paper, so that disconnect was seen first.

The second is, in what we reported in the OCA toxicity and hepatology, bilirubin seemed to be different from alkaline phosphatase. The alkaline phosphatase did not inform who would do badly. So if the bilirubin was less than 2 and they had complications, discontinuing OCA was associated with improvement, and only 1 out of 4 required

liver transplants. If the bilirubin was greater than 2, 3 out of 4 required liver transplants, so discontinuing medication did not help.

Again, there we saw the disconnect between alkaline phosphatase and outcome, and my thought at that time was high-dose urso may in some way be related to urso plus obeticholic acid, but I was not sure about that. So there is a disconnect that we've seen before. Thank you.

DR. LEBWOHL: Does anyone at the agency care respond to that?

DR. MEHTA: Dr. Kamath, could you please repeat the question?

DR. KAMATH: I think the follow-up of this -- it wasn't really a question, it was a comment -- is that there is a disconnect between alkaline phosphatase and outcome. Just because we see improvement in alkaline phosphatase does not mean there is no harm related to the medication, and in support of that was the high-dose urso study, where the high-dose group did worse with high requirement for liver transplant despite

having improvement in liver biochemistry.

DR. MEHTA: Point well taken. If you could pull the clinical pharmacology slide with alkaline phosphatase at baseline and then at follow-up that Dr. Tao presented, slide number 19, there was a decrease in alkaline phosphatase, at least in the USPI-labeled population. In the patients who had liver decompensation events or were USPI contraindicated, they had lower alkaline phosphatase compared to the ones who did not. We can also look at the the baseline alkaline phosphatases, and they were different. But even in this slide, the alkaline phosphatase did go down; however, the clinical outcomes did not pan out in the same direction, so you're correct.

DR. LEBWOHL: Dr. Winterstein?

DR. WINTERSTEIN: Thank you. Almut Winterstein. I have a few quick clarifying questions. The first is a follow-up on the previous suggestion that there might be selection bias when the USPI-labeled population was created because that was post-randomization, obviously.

Do you have a comparison of baseline characteristics? I appreciate the smaller sample size, or was there any attempt made to adjust for differences in baseline characteristics?

DR. KIM: This is Yura Kim, statistical reviewer. The USPI-labeled population was defined based on baseline characteristics and thus preserves randomization; therefore any comparison between the two arms in this subgroup is statistically valid.

Can we go to slide 134?

DR. WINTERSTEIN: Why would that preserve randomization? You didn't do a stratified randomization or block randomization, so the randomization had a specific entry criteria, which obviously was changed when you imposed the USPI-labeled criteria.

DR. KIM: Yes, exactly --

DR. WINTERSTEIN: There was no preserved randomization.

DR. KIM: The randomization was not stratified by this subgroup --

DR. WINTERSTEIN: Exactly.

DR. KIM: -- yes -- however, it was defined only based on baseline characteristics.

DR. WINTERSTEIN: What I'm asking is, after you did that, whether they're still comparable or not.

DR. KIM: Yes. The slide shows the baseline characteristics and it shows the generally balanced characteristics between the two arms.

DR. WINTERSTEIN: So you consider them balanced? This is the first time I see this, so I'm trying to digest this. There are some differences, right? I don't know how significant they are.

(Pause.)

DR. WINTERSTEIN: Well, they seem to be, but if we look at the ITT population, there are a lot more pronounced, right?

DR. TRAN: Yes. So if you look at the USPI-labeled column between OCA and placebo, you can see that in non-cirrhotic, compensated cirrhosis, alkaline phosphatase, and total

bilirubin, which are the characteristics that we would generally think are going to be potentially predictive of outcomes, those seem to be relatively well balanced between the two groups. Rotterdam criteria are also criteria used for PBC severity, and you can see here between early and moderate, those are also well balanced between the USPI-labeled OCA and USPI-labeled placebo groups.

DR. WINTERSTEIN: Yes. It looks like the ALP is a little bit more off compared -- I don't know how relevant that is. I'm comparing it to the ITT population. I just wanted to get an appreciation for could there be potentially bias created with this selection.

The other question I had relates to the real-world evidence study. That was quite interesting. I hadn't realized this. About half of the entry criteria were realized by patients discontinuing first-line therapy, so they went off that base. Was there still a requirement that everybody had a lab value within a certain period? Because, obviously, it shows up in the propensity

score adjustment, but I'm wondering are there missing values, or how do labs play a role here in balancing baseline characteristics, since there didn't seem to be a requirement for study entry?

DR. ANDRACA-CARRERA: This is Eugenio Andraca-Carrera. I'll try to address the question, but maybe the applicant can also respond. They showed that complete lab values within one year prior to index date were a requirement for study criteria, and those lab values are the ones that are used in the propensity score model to balance the two cohorts. Additional values were collected post-baseline, but they're not used as part of the inclusion criteria.

DR. LEBWOHL: If the applicant would like to clarify --

DR. WINTERSTEIN: Somebody might have been a lab value 11 months before or something like that, before study entry, and that would be sufficient for balance, anything but --

DR. WEISSFELD: If I might address that question.

DR. LEBWOHL: Dr. Weissfeld?

DR. WEISSFELD: If I could have FDA slide 69, I believe it is. So this shows the variables included in the propensity score model. With respect to the laboratory values, you see there's alkaline phosphatase, BILI, ALT, AST, and bilirubin. The heading showed is that the propensity score model adjustment used the most recent value in the minus 365, zero day pre-index period.

A value was required for each one of these values in order to get to the final analysis. So patients could enter this study having a missing value for one of these values at an index, but an index was excluded from the analysis if there was missing data for any of these elements.

There was a certain amount of missing data. I think if you look, for example, at the OCA group, there were 432 patients who qualified for the study, but after requiring that there be no missing data for the baseline covariates, it drops down to 403. So it's a difference of 432 and 403 that

gives you an indication of the magnitude of missing data in the OCA-treated group overall for these baseline characteristics.

DR. LEBWOHL: Would the applicant like to briefly -- thank you.

DR. WINTERSTEIN: That's all I've got, just a clarifying question. But since I have Dr. Weissfeld already on the line, he made a reference to potential misclassification of the decompensated liver failure outcome, and I was curious about his hypothesis on this one. He invited us to ask that question.

DR. WEISSFELD: Thank you. Thank for that question. And you're right, it is a hypothesis. It's a speculation. If I might have FDA slide 81, please, which introduces the notion of differential outcome misclassification. Differential outcome misclassification might be seen as a downstream effect from methods that incorrectly include some observations from some patients already decompensated at baseline, whether from PBC or some other hepatic condition.

In this setting, any hepatic decompensation code that subsequently appears during follow-up on a hospital claim should be regarded as misclassified, a false positive; that is, something other than a new onset or an incident hepatic decompensation, something other than progression of an underlying hepatic condition.

If I might be allowed to continue, I can explain how the outcome misclassification might be differential.

DR. WINTERSTEIN: Right. But I understand the [indiscernible - 4:37:26] might be new onset, but why differential?

DR. WEISSFELD: Yes. If we could have slide 65, please. If I work upstream, and I showed on this slide, Study 405 used diagnosis codes and laboratory data to operationalize certain critical baseline exclusion criteria: history of chronic liver disease other than PBC; history of hepatic decompensation; and evidence for previous hepatobiliary injury. If not completely effective -- and we don't know how effective these

exclusion criteria were -- the application of these exclusion criteria may have allowed study entry to some patients who had already decompensated.

So finally, I have a series of questions that the committee might consider. You might consider might these exclusion criteria have operated less effectively as filters in one exposure group as opposed to another, or the other? When considering this question, the committee should remember that OCA prescription by a medical provider was the method used to distinguish observation time exposed to OCA from observation time not exposed to OCA.

Therefore, the committee might consider, might providers have used knowledge not fully captured by exclusion criteria or baseline covariates to selectively prescribe OCA for some patients but not others? Might prescribers have selectively endorsed OCA for patients assessed as good candidates, earlier stage PBC with relatively favorable prognosis, and avoided OCA for patients assessed as poor candidates, later stage PBC with

less favorable prognosis?

Affirmative responses to these questions establish the foundation for our concern about differential outcome misclassification as a potential source of meaningful bias. So again, it's a linkage of these various possibilities that lead to this hypothesis regarding a differential outcome misclassification.

DR. WINTERSTEIN: Got it.

DR. LEBWOHL: Thank you. I think in the interest of time, because we're starting to run over, I'm going to move on to our our next question, Dr. Lo Re.

DR. LO RE: Yes. Thanks. Vin Lo Re from University of Pennsylvania. This is to you, Dr. Weissfeld, again. You raised a lot of questions about the accuracy, the completeness of the data in Study 405, and I'm juxtaposing that with the presentation from the applicant that they had said that the data were fit for purpose. You showed in your slide on hepatic decompensation, slide 82, various PPVs for the different studies.

These were studies from the VA, from Ontario, from Sweden, and from Australia, and in regards to the accuracy of PBC diagnoses, the applicant presented, as a result, a validation study from Calgary.

So as I'm trying to interpret these data and how fit for purpose they are, I wanted to get a sense from you, these validations were not necessarily performed in Komodo data. How transportable would they be in terms of their accuracy for being able to interpret the endpoints like hepatic decompensation without any kinds of validation? That's one question for you.

A second question for Dr. Tran, you had presented on slide 38 the primary ITT for Study 302 was 0.84. The applicant in their briefing document had presented a corrected for treatment crossover and informative censoring that showed a significant protective effect of OCA, going from 0.84 to 0.69. I didn't hear any necessary comment on did you think that that approach for correcting for the treatment crossover informative censoring was valid, was not.

As I'm trying to interpret these data from both Study 405, Dr. Weissfeld, and from Study 302, Dr. Tran, I'd like to hear your comments as to how your, at least, thoughts are. Thanks.

DR. WEISSFELD: Okay. Thank you. If I understand, the first question is you would like for me to potentially comment on the transportability of the validation studies that have been conducted in medical literature.

DR. LO RE: Yes. So where I'm going is that they're telling us that these studies, these outcomes, PBC decompensation, have been validated, showing us high PPVs. You've showed us the table. But I'm trying to interpret those results in the context of those validations weren't necessarily conducted in Komodo data, which is different. So I'm asking the question, do you think that they are applicable, those validation studies, to the Komodo data or not?

DR. WEISSFELD: I think there are grounds to question their transferability to the current setting. There are factors such as code sets,

ICD-9 versus ICD-10. The population that's being studied in terms of the prior prediction of whether or not you would expect for them to decompensate varies in terms of the clinical setting, whether you're working in a VA hospital, or a liver clinic, or in a general population such as Komodo. It also depends upon the specific code sets that are used to operationalize the outcome.

For example, if you look at the Lapointe-Shaw, for example, it's very little overlap in terms of the specific codes that were validated there with respect to the codes that were used to identify the hepatic decompensation outcome for Study 405, so I would say there are many, many reasons to question their transferability.

Having said that, it might be reasonable for the committee to look at the codes themselves and judge whether or not they have some degree of face validity. So if I would comment specifically about Lapointe-Shaw, I think what they were trying to get primarily is being in the liver hepatic decompensated state, which can be like a chronic

condition.

For example, hepatic varices, a code for hepatic varices would be regarded as decompensated. Those kinds of codes were not included in the primary outcome for Study 405; 405, for example, required that there be esophageal varices with bleeding, which would imply some sort of an acute event. So I would say there appears to be a conscious effort on part of the investigators for 405 to say, "Well, to the extent that we know or don't know the accuracy or validity of any of these codes, let's at least for our primary analysis choose certain codes," which may be an indicator of an acute event. The same thing for encephalopathy. Encephalopathy is usually viewed as somewhat acute. I mean, you either get better or you don't get better, in which case you die. But yes, the short answer to your question is it's a lot of reasons to question the transferability, I think, in our opinion

DR. LEBWOHL: Dr. Tran, if you want to comment on the as-treated, mindful of the hour, and

maybe to limit to a minute or so.

DR. TRAN: Yes. So the ITT versus the post hoc analysis, they did with censoring patients that crossed over, so I'll have Dr. Yura Kim answer that question.

DR. KIM: This is Yura Kim, statistical reviewer. In the analysis you referred to, the applicant included placebo subjects who took commercially available OCA in the OCA arm rather than the placebo arm. These analyses did not preserve randomization and are concerning in that they remove much of the benefit of randomization, which makes the Study 302 leading to interpretable results. Also, if we include placebo subject who got liver transplant, similar to the OCA arm because the patient got OCA, it will make the results worse.

DR. LEBWOHL: Dr. Gillen?

DR. GILLEN: I just want to make a comment on this. If my reading of this document is correct from the sponsor, the 26 patients that ultimately received commercial OCA got reclassified into the

treatment arm. It's not clear exactly how that was done, but that can inherently bias that result because what you're doing is you're putting people that are at risk -- they have to have been at risk a period of time until they transferred over than to be labeled over. As an example, if all 26 people switched at one year, and you force them into the other arm, they had to have been at risk for the event for one year, so you can bias yourself that way.

DR. LEBWOHL: A couple more brief questions, brief answers.

Dr. Sturmer?

DR. STURMER: Yes. Thank you. I have a question about the sponsor mentioned several times inverse probability of censoring weights in their as-treated analysis. I couldn't find any explanation on how these were either estimated or implemented and what the distribution of weights was. And my question for the FDA, were you able to emulate this approach? And if so, did you use baseline information only or time updated

information to estimate these? Thank you.

DR. ANDRACA-CARRERA: This is Eugenio Andraca-Carrera. That question might refer to 302 or 405. I will talk about 405. In 405, the applicant conducted those analyses for this meeting, but they didn't submit it in their clinical history report, so the FDA was not able to replicate them, so I would refer to their methodology.

The FDA looked at post-baseline characteristics that could help us predict treatment switch or treatment discontinuation, and we found significant missing data, which I can discuss further if you're interested. The short answer is, for 405, based on the amount of post-baseline missing data, we didn't think that it was reasonable to conduct our own analyses that were adjusted for censoring weights.

DR. STURMER: Thank you.

DR. LEBWOHL: Dr. Shaw?

DR. SHAW: Hi. Dr. Shaw. Thank you. This is exactly the question I was hoping I could

continue this conversation about, particularly on your slide 97, where you were showing evidence of different lengths of follow-up, 627 days on the weighted controls and 436 days on the OCA arm. To me, there are two basic things.

Emulating a clinical trial, that can be aspirational, but statistically it's also a technical thing. It's a causal inference technique. The first thing you do is you need to define an index state such that you could have done the trial at that time. You align time zero in both arms. My understanding is that was not done in this trial, so that's a little strange. But the second thing is you're going to evaluate a treatment policy. So one of the policies is per protocol and you're going to stay on OCA; the other policy is you're not going to be on OCA.

In the causal inference world, when you get censored, and that can happen a year after the baseline starts, you do inverse probability weighting at that time to weight back to the original population that started. So if you had

done that, then you're getting this true effect, had the people really started and stayed on or not started and never started. I don't understand, if you did that then, how can you have a difference in the length of follow-up? It seems like that's inadequate control or that this doesn't represent that kind of weighting.

DR. ANDRACA-CARRERA: I'm sorry. I'm not quite sure I understand the question. What is being shown here is as treated without any control for censoring weights.

DR. SHAW: Okay. So you have the weighted as simply just for the selection --

DR. ANDRACA-CARRERA: The weighted is because the indices were weighted based on the propensity score model to balance covariates -- .

DR. SHAW: It's a baseline only.

DR. ANDRACA-CARRERA: -- but it's not a weight for censoring; it's a weight for propensity score at baseline.

DR. SHAW: Okay. So these statistics don't take that into account. Thank you.

DR. LEBWOHL: One last brief question.

Dr. Goldberg?

DR. GOLDBERG: Dr. Tran, I guess five of the patients who got transplanted were non-cirrhotic at baseline, and one comment on the explants, so in stage 2. Was there any other explant data made available to FDA for the other four to better understand whether OCA could have contributed to them requiring a transplant? Did they actually have cirrhosis at explants or was there some mechanism that thought that was unrelated to progression of PBC?

DR. TRAN: Yes. We do not have explant data for those patients, for most of the patients, so I cannot answer that question.

DR. GOLDBERG: Thank you.

DR. LEBWOHL: We will now break for lunch. We will reconvene again in this room at 1:30 Eastern Time. Please take any personal belongings you may want with you at this time. Panel members, please remember there should be no discussion of the meeting topic during the lunch break amongst

yourself or among any member of the audience. Additionally, you should plan to reconvene at around 1:20 to ensure that you're seated before we reconvene at 1:30 p.m. Thank you.

(Whereupon, at 12:51 p.m., a lunch recess was taken, and meeting resumed at 1:30 p.m.)

A F T E R N O O N S E S S I O N

(1:30 p.m.)

Open Public Hearing

DR. LEBWOHL: We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the

committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect; therefore, please speak only when recognized by the chairperson.

Before we do get started, because we have a large number of speakers, we really want to be fair to all of the speakers, but we will be keeping strict time. These will be three minutes, and when you have about 10 seconds to go, I'll ask you to

please wrap up, and that really means 10 seconds, and then we'll have to move on. Thank you for your cooperation.

Speaker number 1, please unmute yourself and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MS. POPFINGER: Yes. Hello. Good afternoon. My name is Susan Popfinger. I am 71 years old, and I live on Long Island, New York. I retired two years ago after a 30-year career as a registered nurse. I have no financial relationship with the company that you're hearing from today.

My story is simple. I was diagnosed with primary biliary cholangitis about 20 years ago after some routine blood work showed elevated liver enzymes. So after consulting with the gastroenterologist, my diagnosis was confirmed with a liver biopsy and various scans. At that time, 20 years ago, there was only one treatment for PBC, and that medication was called urso.

Unfortunately, for me, I was one of the 40 percent of the patients that were non-responders to urso, and so as a non responder, my liver enzymes remained high over the next 17 years that I was on the medication.

As you may know, the consequence of high liver enzymes over time is liver damage, and although I was 100 percent compliant with the medication regime and I lived a very healthy lifestyle, the liver damage incurred resulted in cirrhosis of the liver. Almost four years ago, I sought a second opinion of treatment options with a well-known hepatologist in New York City and also a second opinion at the Mayo Clinic in Florida. Both doctors concurred that I should try the newer treatment option at that time, which was Ocaliva.

Within 6 months of this medication, I'm taking the medication, all of my liver enzymes returned to normal. I had no adverse side effects from the treatment, and it was a simple once-a-day pill. Today, I am in what is called compensated cirrhosis. My liver is able to maintain its

functions even though it is severely damaged, and gratefully I'm able to live a full, active life.

I know that had I not been taking Ocaliva, my liver enzymes would have remained high. It is my belief this would have most likely resulted in liver failure with possible transplant or death. I feel that Ocaliva can be a life-saving drug for people that do not respond to urso, the first line of treatment. If this disease can be halted or even just slowed down through normalizing enzymes, it is a great treatment. I can only hope this medication will remain available to me and patients like myself. I do believe it has saved my life. Thank you.

DR. LEBWOHL: Thank you.

Speaker number 2, please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MS. GISSELQUIST: Hello. My name is Jane Gisselquist. I am 77 years old, and I live in

Arizona. I've been a primary biliary cholangitis patient for 31 years, since 1993 when a liver biopsy determined that I had the condition. I have no financial relationship with the applicant. The cost of my Ocaliva is partially paid by the assistance fund. I've been taking the medication since 2016.

Before I go further, let me say that my view on Ocaliva is simple and one I hope you will consider. I don't want to take the chance of not taking Ocaliva, as my drug regimen is working for me, and thank you for letting me share my story. I began my career as an elementary school teacher in Minnesota and later worked in Illinois as an executive for a software company that specialized in serving the USDA. My husband and I moved to Arizona in 2005, and I now do volunteer work.

My PBC journey began with routine blood tests for insurance. The tests showed my liver enzymes were abnormal, which led to consultation with several doctors. I had no symptoms, and I did not have hepatitis. When a biopsy determined that

I had PBC, I'd never heard of it. There was no internet to find out anything about this disease at that time, and my doctor said that he had just one other patient who had PBC. He also told me that in 10 to 20 years, I would probably need a liver transplant. Well, that was scary, but he said we'll put you on ursodiol and do blood tests. I just kept having blood tests every 3 months.

Over the 31 years, I've also had 4 biopsies, many ultrasounds, and a fibro scan. These are to monitor my PBC. When I was 70 and in the doctor's office, he said, "At this age, I believe that you're too old to get a liver transplant, but I think that you'll probably eventually die with PBC, not because of it." That was in 2016 when Ocaliva was first approved by the FDA for PBC. My doctor and his staff helped me work through the steps to get Ocaliva. Since that time, I've taken the lowest dose, and my doctors over the years have said that they believe that there's no reason to put me on a higher dose of Ocaliva because the chances of side effects were greater. I seem to be

doing ok.

In the 31 years that I've had PBC, my liver function tests for PBC have varied. I'm not in the normal range very often, but it doesn't seem to concern my doctors, so I'm happy to continue to take ursodiol and Ocaliva, and live my life. To sum up, I don't want to take the chance of not having Ocaliva because it, along with ursodiol, has been working well for me for the last 7 years.

DR. LEBWOHL: Please wrap up for time.

MS. GISSELQUIST: Thank you.

DR. LEBWOHL: Thank you.

Will speaker number 3 please approach the podium and introduce yourself? Please state your name and any organization you're representing for the record. You have three minutes.

MS. JONES-ASAD: Good afternoon. I am LaToya Marie Asad. I'm 48 years old and grew up on the south side of Chicago, raised by my mom and lived with my two sisters. I went on to earn a master's degree in gerontology and now work for a major health insurance company in Illinois. I've

also been a PBC patient since 2019.

I'm on the East Coast today to attend a patient advocacy training sponsored by the Global Liver Institute. I have shared my living with PBC personal journey virtually with the company today, Intercept, in honor of International PBC Day. I'm currently on the first-line therapy for PBC, not Ocaliva, but like many other people, I want patients to have full access to other PBC treatments such as Ocaliva. I'm grateful for the opportunity to share my story with you today.

In January 2019, I started experiencing chronic fatigue and really wasn't sure what was going on. I thought because I was living in Chicago where the weather is cold and snowy, that that was explanation for my symptoms. I thought it was just the winter blues, so I kind of ignored it until the end of the month. I didn't have the energy to do most things that I normally would do. I reached out to my PCP to see what was going on. He got me in for some labs and recommended that I eat better and exercise more. He really didn't

have a diagnosis or anything. So for most of January into February, I continued to experience chronic fatigue to the point where I just couldn't get out of bed.

I continued to work, so it was a struggle. I dragged myself out of bed and showed up to work, but not really giving a hundred percent. I followed up with my doctor again to say, "Hey, what's going on? I can't get to the gym because I don't have the energy." I crashed. I literally just went to bed and could not get up. So my doctor followed up with labs for 3 months and said it looked like I had elevated alkaline phosphatase. He wanted to continue to monitor it, but the chronic fatigue continued.

Finally, I said, "What are next steps? It's affecting every aspect of my life." He really ignored my symptoms and concerns, and finally I took matters into my own hands. His feedback was it could be your bones or your liver. Because I never had issues with my bones, I figured, let's start with the liver. Eventually, I was able to

get in to see a hepatologist at a local hospital, and within days I was diagnosed with primary biliary cholangitis. I was frightened, unaware, and had never heard of the condition before.

DR. LEBWOHL: I'm afraid we're just about a time, if you could wrap up in about 10 seconds.

MS. JONES-ASAD: So I'm here today to share my journey with PBC. It's something I'm living with and learning to manage. I'm receiving support from organizations, but I'm here to encourage you as a committee to keep in mind the human aspect of this condition and support patients that need these treatments. Thank you.

DR. LEBWOHL: Thank you.

We'll now hear from speaker number 4. Speaker number 4, please approach the podium. Please begin to introduce yourself. Please state your name and any organization that you are representing for the record. You have three minutes.

MR. MITCHELL-THAIN: My name is Robert Mitchell-Thain. I'm CEO of the PBC Foundation.

I'm not representing the PBC Foundation as such; I'm representing the patients we serve, 16,000 and 85 countries, including 3,000 here in the U.S. I have no personal disclosures in terms of Intercept. The PBC Foundation is part funded by many industry partners, including Intercept, Gilead, and Ipsen, and many other companies involved in PBC.

Ten years we've been doing this, and I don't think I've ever witnessed such a collective of wisdom, so desperate to do the right thing, get in the way of itself doing the right thing. It's truly astounding as a patient community to watch this. COBALT reached almost farcical levels of achieving everything it didn't want to do, and it did that because it let the patients down. You asked patients to let their disease continue, and they said no, loudly.

405 suits the patient needs but doesn't meet your standards, and we have to come together and find a way, a middle way, to do this. So we're asking, first of all, for OCA to remain on the market. If you take it off the market, people with

PBC will die prematurely. For some people who do not respond to the PPARs, it's their only option. For those who cannot tolerate the PPARs, it's going to be their only option. But whilst we do this, we're going to ask you to come together as regulators, industry, clinicians, and this time with patients, to find a way to have the data that works for everybody. We have three drugs that are now starting from a clean slate. Let's use this opportunity to get our heads together to create an absolute appropriate study for everybody.

So that's the thinking in the room because if we get this wrong, people will die. How many? Not many, but too many. And if we get this wrong, how many kids are going to graduate without their mothers being in the room? If we get this wrong, how many children are going to be born never ever getting to meet their grandmother?

I want to share with you, finally, the paragraph from our petition that has been signed by almost 2 and a half thousand patients. The paragraph reads, "We would like to highlight that,

in our view, OCA is an important part of clinicians' therapeutic toolkit in PBC and that we see potential benefit and accept potential risk. It takes many years to prove that therapy works and is safe over many years. It took years to prove OCA works, and for PBC patients, we're prepared to wait those years to prove OCA is also a benefit based upon current real-world evidence." I ask you as a collective, please, please do better.

DR. LEBWOHL: Thank you.

Speaker number 5, please unmute and turn on your webcam. Speaker number 5, begin and introduce yourself. Please state your name and any organization you are representing for the record. You have three minutes.

DR. STEIN: Hello. My name is Lance Stein. I'm the Medical Director of Hepatology and Transplant at Piedmont Atlanta Hospital in Atlanta, Georgia. I have conflicts of interest to report. I've consulted for both Intercept and GSK in the field of PBC. I'm on the Speakers Bureau for PBC for Intercept, Gilead, and Ipsen, all players in

the PBC space.

I just want to take a moment to talk about Speaker number 4 and his comments because he really speaks to all of our patients. I was very moved by what he had to say, and I really hope you all listen to the community of patients and what they are going through with this disease.

Moving on to what I wanted to prepare and say to you all, OCA's approved now 8 years ago. We started using it at that time as prescribers for our patients. I currently have 12 patients taking the medication and prescribed it to over 20 patients in the last 8 years, some of which I no longer follow or have transitioned, all for one reason or another. It's been shown historically with ursodiol as first-line therapy that the reduction of alkaline phosphatase in this disease leads to a reduction in liver-related outcomes and mortality. As far as we understand, any therapy leading to reduction in biomarkers, including alkaline phosphatase, will continue to show long-term positive outcomes in this disease state.

With eight years of experience, the adverse event profile of OCA is well established. There is some patient intolerance that can lead to discontinuation, and this intolerance mostly is related to pruritus, which is occurring more commonly at higher doses. The Global PBC and UK PBC data sets, which you have shared today, have shown that the principle of alkaline phosphatase, reduction in PBC with therapy, is translated also with the second-line therapies. The real-world data sets are unique in a field where a phase 4 trial in this disease state is impossible. We tried to enroll patients into the phase 4 trials, and we could not because patients refuse to be enrolled into a placebo-controlled trial when there was active therapy available for their disease to halt the progression of their disease.

The real-world data sets, which we have, are very believable. We are performing liver transplants across the country and at our center at the lowest rates in history, presumably due to the administration of ursodiol and second-line

therapies. We and our clinic continue to utilize obeticholic acid in our patients as second-line therapy and those not meeting alk-phos reduction goals. We use it in compensated cirrhotic patients also. We, however, do not use it in patients with cirrhosis and portal hypertension with cirrhosis, and the history of prior decompensation because of its known risks.

It's clear in our clinics that patients with liver cirrhosis and decompensation are at increased risk for drug-induced liver injury, and that is part of what is labeled on the black box, and we avoid it. It is unclear exactly what the true denominator is for this risk, as is often --

DR. LEBWOHL: Please wrap up in the next 10 seconds or so.

DR. STEIN: The importance of this data is clear. Our patients need access to this medication, and our patients have been doing well on this medication for years. I hope you all do the right thing and allow this to continue to be a treatment choice, when appropriate, for individual

patients.

DR. LEBWOHL: Thank you.

Speaker number 6, please unmute and turn on your webcam. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

DR. MAYNE: I'm Dr. Tracy Mayne, Senior Vice President of Regulatory and Life Sciences Research at Slipstream IT. I have no financial interest in Intercept but was previously Vice President of Global Medical affairs. I designed and wrote the 405 and COBALT external control protocols, oversaw the analyses, and was the Intercept lead on the POISE external control.

Dr. Sturmer wondered why there wasn't a large difference between weighted and unweighted 405 outcomes. Comparability in 405 was a two-step process. Patients had to meet all POISE criteria to be included, so they were pretty well balanced before weighting. There were no differences in unweighted baseline, total bilirubin, albumin,

platelets, cirrhosis, portal hypertension. Unweighted baseline differences on ALT and AST were less than half of standard deviation, and ALP less than a standard deviation.

Given unweighted comparability, it would have been problematic if weighting did make a large difference. The indexes between OCA and controls were aligned, based on meeting POISE inclusion criteria and being eligible to be prescribed OCA at that visit; and yes, of course, we have the enrollment files.

The FDA theorized doctors may have differentially selected OCA patients because they were healthier, but the unweighted ALTs, ASTs, and ALPs were higher in the OCA-treated patients. The evidence contradicts their channeling bias hypothesis.

Dr. Winterstein, fenofibrate is not indicated for PBC in the U.S. and is infrequently used, about 12 percent of patients. It is not standard of care. The FDA stated it had inadequate details on Datavant tokenization and concerns with

data quality. Did the FDA conduct an audit of the Komodo data and Datavant tokenization? If so, did they issue any 483 objections? If they didn't, then they were unable to find empirical evidence supporting the theoretical concerns.

In 599, the FDA showed that when patients discontinued OCA, their event rate went from 1.7 to 4.4 events per hundred patient-years. They state this could be treatment effect but could also show informative censoring. The event rate in controls was 4.6. If sicker patients near decompensation are taken off drug, shouldn't their event rates be higher, not equal to the background event rate of untreated patients? And when controlled patients went on OCA, they saw a very similar reduction in events. These data are far more consistent with treatment benefit than informative censoring.

The FDA ITT analysis showed a 20 percent event reduction in OCA patients. If you take the Intercept OCA treatment and control event rates, and apply them to the additional FDA observation time, you get an expected 29 percent event

reduction. Alan Burkhard, check my math. Drugs work while you take them, they stop working when you discontinue.

The FDA analysis demonstrated the expected residual treatment benefit. For the record, the Intercept ITT analyses were prespecified and publicly presented a year before the FDA said they requested them. The engine of science is replication using different populations in the U.S., EU, different data sources, clinical trial claims, registries, different approaches, nested trial emulation, random index, ITT as treated. Intercept independent scientists and the FDA have shown remarkably consistent treatment benefit in the real world.

I ask the committee, please remember, the space between those lines in the Kaplan-Meier curves are real patient lives and real liver transplants. If more data are needed, require a PMR, but taking Ocaliva off the market will result in avoidable deaths and liver transplants in the real world. Thank you.

DR. LEBWOHL: Thank you. We're at time.

Speaker number 7, please approach the podium. Will speaker number 7 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MS. HUNT-METZBOWER: I'm Abigail Hunt-Metzbower. I am a PBC patient and an advocate and volunteer with the PBCers Organization. I do not get any support from Intercept or any other pharmaceutical companies, and I'm not being compensated for telling my story.

In late November of 2003, I experienced what the emergency doctor called a gastro attack. I was terrified. I was in severe pain and thought I had internal bleeding. I was told I needed to see a gastroenterologist. I had several lab tests and met with gastro doctor the week before Christmas. He said he believed I had primary biliary cirrhosis. He said that I needed to have a liver biopsy, which was scheduled for January 6th.

My mother and I sat in the car that day and

cried, not knowing anything about PBC. The biopsy was one of the most painful things I had ever experienced. A few weeks later, it was confirmed that I had PBC with some scarring. I was told that I probably had 15 to 20 years before I would need a transplant, and I started on urso, which was the only approved medication at that point that had helped many facing this destructive disease.

The thing about an autoimmune disease like PBC is that most of us do not just get PBC. Our bodies become our own worst enemies. Within a couple months, I became unable to get up and down without my husband's help. I just did not have the strength. After several more tests, I was told I had diabetes, NASH, autoimmune hepatitis, rheumatoid arthritis, fibromyalgia, among other things. I was given more medicines, which were supposed to help me get my life back to a new livable normal.

Over the next several years, I had good days and bad days, and my weight became an issue which had to be addressed, and in 2007 I had a gastric

bypass and lost 123 lbs. But even with all that weight loss, my liver was still not happy, and for many more years, my labs kept getting worse. My doctor increased my urso, but it was not having the benefit that it had before.

Last year when my gastro retired, I reached out to fellow PBCers and talked to several doctors at our conferences, who recommended that I see Dr. Hamilton at Johns Hopkins. I had learned that he had been part of the trials for Ocaliva. When we met, he said he felt I was a good candidate and that the medicine would help to bring my levels to normal. I was hopeful but nervous. His team said they would help me get the approval and would submit for the patient assistance to help with the cost. My insurance did approve, and I got the assistance.

Two months later, the lab work showed that Ocaliva was working well for me. To say I was grateful is an understatement. I felt like maybe I could make it another 20 years without a transplant or dying. Over the years, I've made it my personal

mission to share my story and encourage others to do the same. I am one of the fortunate people with PBC. I am able to take urso and benefiting from adding Ocaliva to the treatment plan. Sadly, there are many of us that do not respond to urso. For many, Ocaliva is the only option. Having treatment for this is what we all pray for, and we need this medicine to stay so we have a good quality of life. Thank you.

DR. LEBWOHL: Thank you.

Speaker number 8, please unmute yourself and turn on your webcam. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MS. KROL: Good afternoon. I'm Suzanne Krol. I am 65 years old and live currently in Southwest Virginia. I have no financial relationship with the sponsor. I'm a former nurse who had never heard of PBC, just like most people haven't.

In 2007, when I was first diagnosed, it was

still called primary biliary cirrhosis. I was diagnosed at stage 4 PBC with stage 2 cirrhosis. I tried urso for 6 months or so, which caused projectile vomiting, so that was a no-go. There weren't any other treatment options at the time, so you're on your own. I used detox, massages, energy work, acupuncture, and acupressure, which gave me 9 and a half years until my liver just decided it was going to stop. I went downhill rapidly. My MELD score started going up in November of 2015, and I received my liver transplant in May of 2016.

I wasn't supposed to make it according to my surgeon. He had told my family they had missed the window for my transplant. I'm a tad bit stubborn, though, so 2 days later I was back and ready to go, and 6 hours later they had a liver. That was 2016. In 2018, I developed recurrent PBC stage 2 to 3 per biopsy. My cholesterol levels are not very high, so fenofibrate I felt was a questionable choice, so I chose Ocaliva. So far, so good with that, and my liver numbers are within normal range, for the most part.

Fibroscan had me at stage 0 to 1 3 years ago, and currently, I just had another Fibroscan at stage 1 or 2. My understanding is the second time around with PBC can be more aggressive, so the fact that I'm still at a relatively low stage after 6 years on Ocaliva is pretty good. I just take one 5- milligram pill in the middle of the day and that's it. I don't take anything else for my PBC. I believe that my PBC would have progressed much further had I not had access to this drug. It's not a cure. I don't believe any of the new drugs are a cure, to my understanding. It just helps slow down the disease and hopefully have a little bit better of a life. Thank you.

DR. LEBWOHL: Thank you.

Speaker number 9, please unmute and turn on your webcam. Will speaker number 9 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

DR. ZUCKERMAN: Thank you. I'm Dr. Diana Zuckerman, President of the National Center for

Health Research. We're a nonprofit, public health research center that scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products, so I have no conflicts of interest.

Thank you for the chance to share our views today, and thank you to this committee for your important work. My expertise is in clinical trial design and data analysis, not in liver disease. Prior to my current position, I was a postdoc in epidemiology and public health at Yale Med School, and was a faculty member and PI at Yale and Harvard. I also investigated FDA approval standards while working in the U.S. Congress, HHS, and the White House. I'm a founding board member of the Alliance for a Stronger FDA, which educates Congress about the need to financially support the essential work of the FDA.

After accelerated approval, confirmatory trials are essential to keep those drugs on the market, and when drugs are not confirmed to be safe and effective, patients tell us that we owe it to

them to rescind approval and urge the company to either design better studies or conduct studies to determine if there's a subgroup of patients who will benefit and those who are likely to be harmed. We agree with FDA's criticisms today and note that the European Medicine Agency recommended revoking approval for OCA.

Study 740-302 was a randomized-controlled trial that did not meet its primary endpoint. In fact, the probability value was greater than 0.30, which is 6 times higher than what's needed to reach statistical significance. And in the relatively small USPI-labeled population, 11 OCA patients died or needed a liver transplant compared to only two in the placebo group. So if some placebo patients took commercial OCA, this difference would have been even greater.

Study 747-405 was an observational study with major flaws, as you've heard. The composite endpoint included two objective measures, death and transplantation, but also included decompensation, which could be miscoded. And the company's

as-treated strategy was flawed because many OCA patients left the study because of complications and had serious health problems even after they left the study. So the FDA conducted its own intention-to-treat type of analysis based on death or liver transplant, and the difference was not statistically significant.

In conclusion --

DR. LEBWOHL: Please wrap up in the next 10 seconds or so.

DR. ZUCKERMAN: -- we concluded that the data do not meet the FDA required standards of adequate and well-controlled trials and results do not prove that OCA is effective. In fact, the OCA patient's health may be more likely to deteriorate even after they stop taking OCA. Thank you very much.

DR. LEBWOHL: Our time is up. Thank you.

Speaker number 10, please unmute and turn on your webcam. Will speaker number 10 begin and introduce yourself? Please state your name and any organization you are representing for the record.

You have three minutes.

MS. SOBEL: Hello. I am Deborah Sobel from Illinois. I am a PBC patient. I do own shares in the sponsor. I am not being compensated for my participation. My late sister Sarah and I were diagnosed with PBC in 1998. I have been taking Ocaliva since 2016. I spoke to the committee at that time about both Sarah and my shared experience.

Sarah and I were treated similarly, but suddenly in 2004, she went downhill. She received her first transplant March 2006. The second 60 days, 60 days later, she went into a coma on June 26th, and on June 29th the fight for her life was over. We put Bruce Springsteen on for her, and she died.

Today, I strongly believe that Ocaliva must remain available. For many, it is the only treatment that works. Forty percent of PBC patients do not respond to ursodiol. Still, it is available, and like Sarah with her transplant, though a dangerous option, the underlying condition

may not have gone away and will continue to attack the new liver, and may result in the need for a new transplant.

Ocaliva is an option that works for many and should remain available; otherwise, what is to become of these patients? If additional study of Ocaliva is sought, who would go into that study thinking they may go on a placebo? Who would take that chance? Who would risk their life in that way? Treatment is oftentimes complicated. That said, I would give the world for Sarah to have had Ocaliva available to her. Let the doctors do their work. Let them monitor our progress and decide which works best for us. Don't take away progress.

Like many, I am fine on Ocaliva, no issues. My PBC is under control. Each patient is so different. Where things went horribly wrong for Sarah, I'm stable after 25 years. I am haunted forever by the difference in us as sisters and as patients. One of my most vivid memories of Adcom 2016 is the committee member who spoke to me after the vote. He patted his breast pocket, and he told

me he carried Sarah's story with him.

That is Sarah's legacy. That is her gift to the PBC patient. Let it continue to work for the people it helps. How many sacrifices must families make? My family, any family; how many of us do they have to lose before you understand this option needs to remain? Thank you.

DR. LEBWOHL: Thank you.

Speaker number 11, please unmute and turn on your webcam. Will speaker number 11 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MS. STRATTA: Good afternoon. I'm Leslie Stratta, and I'm joining you from Houston, Texas. I'm speaking to you today as a patient and patient advocate. I have no interest and I'm not receiving any compensation for speaking to you today. I was diagnosed with primary biliary cholangitis, PBC, in 2007. I did not have any symptoms or any reason to think I was ill, but during a routine doctor visit my labs told a different story.

I immediately started taking urso and was successful in managing my liver enzymes with this first-line therapy along with healthy eating habits and exercise. But in January of 2017 at a follow-up visit with my hepatologist, my labs showed a significant increase in alkaline phosphatase. My practice team was concerned that I had become a non-responder to urso as a primary therapy but offered an additional treatment option, obeticholic acid, or Ocaliva, which would be taken in addition to urso as the second-line therapy had shown positive results in lowering liver enzymes and slowing the progression of PBC.

After some consideration and review, I made the decision to begin taking Ocaliva. It turned out to be a great decision for me. I saw improvement within the first 6 months, and my labs were within normal range within a year, and I've been able to maintain those normal labs.

I can't imagine, and honestly don't like to think about, what might have happened if Ocaliva hadn't been available at that time. I believe that

if I hadn't had the option of taking Ocaliva as second-line therapy, the fear and anxiety that my disease would progress to liver transplantation would have impacted my overall emotional, mental, and physical health tremendously. Living with a chronic disease that has no cure is daunting, but not having treatment options only intensifies that reality.

Slowing the progression of liver damage caused by PBC is of utmost importance. As more cases of PBC are diagnosed and younger patients are diagnosed, patients like myself need to know we have treatment options. While not all PBC patients have the same experiences and not all medicines work the same on every person, it's crucial that we have options to slow the progression and improve quality of life.

While I may not have symptoms and my disease may not have progressed much since diagnosis, I do believe that's, in part, to Ocaliva. It's important for me to continue to advocate for treatment options for myself and others

experiencing varying stages of PBC because it isn't lost on me. Our circumstances can change, and change quickly.

DR. LEBWOHL: Please wrap up in the next 10 seconds. Thank you.

MS. STRATTA: Having treatments like Ocaliva give us the hope and peace of mind we all need until there is a cure. I implore the committee, please don't take away that hope and that peace of mind. Thank you.

DR. LEBWOHL: Thank you.

Speaker number 12, please approach the podium. Will speaker number 12 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

DR. DUENAS: Hi. My name is Dr. Cecilia Duenas. I'm a clinical psychologist and the mother of two little girls. After a long delayed diagnosis, I've been a PBC patient since 2021. I'm here on behalf of the Global Liver Institute, which covered my travel expenses from California. About

a year ago, I did participate in an educational video sponsored by Intercept for which I was compensated; otherwise, I have no financial relationship with the company.

My life journey and my experience navigating the healthcare system will hopefully give you a sense of why I think it's vital for PBC patients to have treatment options such as OCA fully available. I'm a first generation Mexican-American Latina. For me, my diagnosis was incredibly delayed. The average PBC diagnosis is a couple of months in typical Caucasian women. For me, it was over 7 years.

As I continued to deal with elevated liver enzymes and quality-of-life issues, there were significant health disparities. I've had translators call me simply because of my last name, despite having earned my doctorate in the United States. One provider looked at me and said, "Well, you're Latina. You're overweight. You probably have fatty liver disease; just lose weight." So I lost 120 lbs, but my symptoms progressed. They got

worse.

I was bounced around from endocrinologist, to nutritionist, to OB/gynecologist, to psychiatrist, and even a psychologist because everyone just kept assuming it was something else. It wasn't until I fired my entire medical team that I even got a referral to a hepatologist.

I'm a person of color, but I also happen to speak the language and I'm educated in the U.S., but not all my community is educated, nor do they speak the language. A lot of us don't speak English, which is my second language, and even so, I was still bounced around and literally had providers tell me they couldn't see me until a translator came.

So again, I want to emphasize I've personally encountered a lot of health disparities, and I'm not alone. I also wanted to reiterate that not all of us get diagnosed within months. Some of us have to fight for that diagnosis and have to wait. Why is this so important for me and other PBC patients? To have an option of a medication

potentially taken away is like a death sentence. I already waited 7 years just for my diagnosis. Now, I have to figure out what works for me.

For several reasons, and keeping in mind that patients differ, Ocaliva is not the medication I'm currently using; however, the prospect of removing treatment amounts to being sentenced to the possibility of transplant, or even death, or an increase in quality of life. Only 5 percent of rare diseases have medication. To take an option from our rare disease, PBC, isn't justified. There are other medications on the market that have far more deaths, such as Viagra; yet those patients have a choice. We don't have a choice, and up until a couple of months ago, OCA was one of the only choices we had if we were urso non-responders.

DR. LEBWOHL: We're coming to time, so please wrap up in 10 seconds.

DR. DUENAS: It is also important to remember that we don't have a cure for PBC. We can't have something that has given us hope torn and taken away from us because we need all the hope

we can get. Thank you.

DR. LEBWOHL: Thank you.

Speaker number 13 has withdrawn participation, so we'll move on to speaker number 14. Please unmute and turn on your webcam. Will speaker number 14 begin and introduce yourself? Please state your name and organization you are representing for the record. You have three minutes.

DR. KOWDLEY: My name is Kris Kowdley. I'm a hepatologist, and I've cared for patients with PBC for more than 30 years. I am lead author of the 302 study publication and have served as a consultant and speaker for Intercept Pharmaceuticals. I would like to share my perspectives on obeticholic acid as a treatment for for PBC.

I believe that obeticholic acid, if used appropriately, is a safe and effective second-line therapy for PBC. As a hydrophobic bile acid, it is not surprising that OCA could potentially exacerbate or worsen liver disease in patients with

elevated bilirubin, clinically significant portal hypertension, decompensated liver disease, or history of decompensation; however, in patients with earlier stages of liver disease, I believe OCA has an important role as a second-line treatment for those at increased risk of adverse liver outcomes.

As physicians, we must weigh the potential risks of any therapy with the alternative of watching our patients progress, more advanced stages of liver disease, and the possible heartbreaking tragic outcome of a liver-related death. Of course, we are also charged with ensuring that any therapy does not worsen the disease for patients in our care. Obeticholic acid is a drug with potential risks, but we have learned how to use this drug to maximize benefit and reduce risk. I personally have many patients currently on OCA who are doing well and would be disappointed to have to discontinue this therapy.

The treatment paradigm for PBC is evolving rapidly, and we have recognized that the best

outcomes will be realized in patients who achieve normalization of alkaline phosphatase and liver enzymes. It is likely that combination therapy with multiple medications with different mechanisms of action will be necessary to achieve this result. Currently, obeticholic acid is the only FXR agonist approved for PBC and will likely remain a key component of combination therapies to achieve the best possible outcomes for our patients living with PBC.

I remember that my mentor and role model, Dr. Marshall Kaplan, was criticized for studying a potentially, quote, "hepatotoxic drug for treatment of PBC," namely methotrexate, which was subsequently shown to be safe, if not as effective as hoped. Dr. Kaplan's overarching goal was to do anything he could do to help his patients while ensuring that he was not doing them harm.

In conclusion, I believe that OCA is an effective treatment for PBC patients in need for second-line therapy. I recognize that as a bile acid, it may be associated with toxicity if given

to patients with advanced or decompensated liver disease, and patients should be monitored carefully as we would any patient for whom we prescribe medication with side effects or potential toxicity. However, I believe the preponderance of clinical trial and real-world data support full approval of obeticholic acid based on efficacy and safety, and I hope I can continue to use it for my patients with PBC who need second-line treatment for this progressive and potentially fatal liver disease. Thank you.

DR. LEBWOHL: Thank you.

Speaker number 15, please unmute and turn on your webcam. Will speaker number 15 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

DR. GUTIERREZ: I'm Dr. Julio Gutierrez, and I'm a transplant hepatologist at Scripps Health in San Diego, California. My disclosures include being a speaker consultant for Intercept and Madrigal and a director for Altimmune and Livivos,

and I'm not being paid for this.

I've studied PBC for over 20 years, since prior to beginning medical school at Mount Sinai, New York City. From that experience, I was able to see the effects of untreated PBC, but now with currently available therapies, it's extremely unusual for us to transplant patients with PBC. Supporting that, we currently have one patient with PBC on our liver transplant list, whereas in the '90s, it was one of the most common reasons for a liver transplant at Scripps.

As others have already spoken on today, after completion of the POISE phase 3 study, many clinicians, including myself, began using OCA in people with PBC that had incomplete response to first-line therapy. OCA was approved by the FDA and EMA via an accelerated approval that required a long-term confirmatory trial demonstrating safety and a significant reduction in composite liver-related outcomes.

The failure of COBALT has been, in part, blamed on the loss of subjects in the control or

placebo arm. The question is, how to retain subjects who are on placebo when they are an FDA-approved therapy for second line? Currently, we have three. Is it ethical? We now have the same approach with clinical trials focused on metabolic dysfunction, associated steatohepatitis. Should patients remain on placebo as more and more therapies become available?

This approach, unfortunately, does not sit well with my patients when therapies are coming off the market. If I'm treating a patient with OCA at Scripps, they are likely doing very well. These discussions, when I take patients off therapy, will be difficult, and many patients may be scared that their liver was harmed by OCA when I tell them it is no longer approved by the FDA. Especially, this will be tough, given the significant debate about the validity of the results of COBALT.

Also, what about those subjects on placebo who continue to advance their liver disease for the benefit of science as we observe the natural history of progressive PBC like we saw in the '90s?

I'm here today to request the GIDAC consider alternative approaches to determine benefit under the accelerated pathway without harming or hindering drug development and liver disease. Thank you.

DR. LEBWOHL: Thank you.

Speaker number 16, please unmute yourself and turn on your webcam. Will speaker number 16 begin and introduce yourself? Please state your name and any organizations you are representing for the record. You have three minutes.

DR. YOUNES: Hi. I'm Ziad Younes, and I'm a gastroenterologist in Memphis, Tennessee with a lot of experience in both clinical research and treatment of patients with chronic liver disease, including PBC. I've been a speaker for Intercept, consulted, and participated in clinical trials, but also the same with Ipsen and CymaBay, which is now Gilead.

Over the years, I've been able to witness both the severe and damaging effects of uncontrolled PBC, which we have heard very

eloquently from a lot of our speakers earlier today, which is a very, very, very difficult condition to treat. But I've also seen when the disease is well controlled, particularly if we're able to get biochemical response early in the course of the disease, some wonderful long-term outcomes with no progression of disease, and control disease for decades in the patients who are lucky to respond to therapy. And some of our patients are lucky to respond to only ursodiol but, unfortunately, if we are going to treat anybody efficiently, we need all the help we can get, and we do need multiple options.

It's been very clear that a biochemical response with improvement in liver enzymes has been associated with improvement in clinical outcomes. We've seen from our colleagues that are working in liver transplant centers that they have seen a significant drop in liver transplants for PBC because of more effective therapy, including OCA.

Obetecholic acid, or OCA, is a drug that has some issues and potential for side effects like

everything else we use. The most common thing would be something like itching, which if it does happen is reversible with stopping the medication. We may have seen some increase in cholesterol, but that is transient, and that has not been a significant issue in our patients with PBC. One of the big problems is how to select patients.

It's not right to use obeticholic acid, or Ocaliva, in patients who have decompensated cirrhosis or who have portal hypertension because there are adverse outcomes in that particular setting. But, fortunately, for us clinicians that have experience, this is easy to figure out. If we do have a patient who has had ascites, or who has had jaundice, or who has had encephalopathy with confusion and high ammonia level, or has a large spleen, low platelets, or varices, those conditions we should not be treating with Ocaliva or obeticholic acid. But if we're able to select the right patient, we will be saving lives. And like I said, with this condition being so difficult to manage and so difficult to treat, it is very, very,

very important to have as many options as we can, and thank you. I'm going to leave more time for others.

DR. LEBWOHL: Thank you.

Speaker number 17, please unmute and turn on your webcam. Will speaker number 17 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

DR. FLAMM: Good afternoon. My name is Dr. Steven Flamm. I am Professor of Medicine and Director of the Liver Transplant Outreach Program at Rush University Medical School. I am not being paid for this today. I have consulted with Intercept, Gilead, and Ipsen in the past, all in regards to teaching physicians around the country about primary biliary cholangitis.

I have a very large practice in Chicago. I've been here almost 30 years. I literally have hundreds of patients with primary biliary cholangitis, and I've had dozens on obeticholic acid over the years. As this committee knows,

primary biliary cholangitis is an incurable disease, it is an autoimmune disease, and like many other autoimmune diseases, some patients have an optimal outcome with first-line therapy and other patients need second-line therapy, or for some autoimmune diseases, third-line therapy. For those patients to optimize their response, we and the treatment community need to have options that are safe and effective for them, and the more options, the better because patients are very different. Everybody requires different therapy, particularly if they're not doing well.

In my experience with obeticholic acid -- and as I mentioned, I've had dozens of patients on it; this isn't a single-patient testimonial -- I have found it to be efficacious exactly as predicted by the pivotal trial that led to its initial approval. I have found no substantial safety issues at all. In fact, in the real world, and I talk about this with key opinion leaders all over the country, I've never heard anybody have an issue, that I know of, from

obeticholic acid, a major clinical toxicity.

This is an FXR agonist. I would not remove the approval of this drug because of the theory that there are other options for patients, so we don't need this. There are the PPAR drugs that were both recently approved; that's very exciting. The fibrates are not approved for this condition. In fact, there are some warnings about using it in liver patients. And as one of the speakers previously said, most patients are not on this drug and will not be on fibrates, and that leaves obeticholic acid.

I believe the efficacy, although you can't compare study to study, is very similar to the new PPAR products. I have not found any efficacy issues treating a lot of people over the 8 years that this drug has been out. We monitor patients like we do with all the drugs, and we will continue to do so with OCA, if you permit it, and with the new drugs, elafibranor and seladelpar.

DR. LEBWOHL: Please wrap up in the next few seconds.

DR. FLAMM: But it is my sincere hope that the FDA allows the practicing physicians in this country the option of providing this therapy for appropriate patients. Thank you very much for your time.

DR. LEBWOHL: Thank you.

Speaker number 18, please unmute and turn on your webcam. Will speaker number 18 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MR. TYLER: First off, I want to thank the committee for allowing me to speak with you today. I apologize. I cannot speak as eloquently as those who have spoken before me. I have no financial relationship nor compensation for what I'm about to say today.

My name is Bob Tyler, and I'm from Cleveland, Ohio. I'm 66 years old, and I'm one of the few males that has PBC. I was diagnosed 11 years ago, and like most of us when we were told or diagnosed with this, there's shock, there's

confusion, and asking ourselves what even is PBC? Even with the great doctors I've been blessed to have and guide me on my journey, this is a very lonely disease because not only haven't I, but family, friends, and I have to be honest with you, everyone, even the general medical community, knows very little to nothing about it, nor have they even heard of it; thus leaving me and every PBC patient feeling very alone and on an island. But thankfully, we have a very strong support community along with the doctors, researchers, and big pharma, and that's where Ocaliva comes in. They've dedicated time and a lot of money into research to help those of us with PBC.

The PBC patient that is a non-responder to urso, even if it's followed up by adding a fibrate and it doesn't work, OCA is added or given, and it's a fact that we respond to it. It's even been found that if you're on all three medications, urso, fibrate, and Ocaliva, those patients tend to be the most normalized. Yes, I know new medications are coming out, but there's no

guarantee that those will work on every patient either. Right now, OCA is working. It is part of our solution. We have doctors, and we need this as one of our tools to reach for in our toolbox.

I truly believe this to my core, that without it, it just puts the PBC patient further into a lonely place. We and our doctors need the choices, and Ocaliva is one of those. Does Ocaliva work on every patient? Of course it doesn't. The answer's no, but it does work for some, a major part of some, and the some it does work for deserves to have it available to them.

Please don't take it from us. Don't take it from the PBC community. I'm appealing to each of you, be a part of our solution, be a part of our choices, and be a part of our normalization and not feeling so alone because it works. I really appreciate your time. Thank you.

DR. LEBWOHL: Thank you.

Speaker number 19, please unmute and turn on your webcam. Will speaker number 19 begin and introduce yourself? Please state your name and any

organization you are representing for the record. You have three minutes.

DR. GISH: Greetings. This is Dr. Robert Gish. I'm a hepatologist based in San Diego. My disclosures are that I consult for and I'm a speaker for Intercept, for Ipsen, and for Gilead. I've been involved with managing PBC patients for over 30 years. One of the major things that I've done during my PBC career is lead the name change from primary biliary cirrhosis to primary biliary cholangitis with many leaders throughout the world. I've also been very aware and involved with a number of these studies that have led to the real-world evidence of medication efficacy.

I have treated over 70 patients with OCA since this drug was approved. I've been involved with OCA far back, even in the dates that it was being developed for fatty liver disease. In the 70-plus patients, only one patient has proceeded to liver transplantation. I've only seen one case of potential hepatotoxicity from OCA, which of course was recorded to the company and the FDA.

In my opinion, this drug works for my patients. I'm here representing those patients, and I think that the benefits of this medication far outweigh any risks, either known or potential. Also, you can claim that there are two other options for second-line therapy that are now FDA approved, and we have fibrates. You've heard from many of the other experts the problem with fibrates, and we have no data about switching patients from OCA to one of the new second-line therapies.

Also, requiring these hard endpoints is not fair for patients, of course, in placebo-controlled trials, and it's also not fair for the other companies who are set up for failure when they're required to do placebo-controlled trials. The real-world evidence I believe is compelling that improvement or normalization of alkaline phosphatase and other liver enzymes is a powerful surrogate for improved patient outcomes.

I have direct clinical experience, and I strongly advise the GIDAC committee, this drug

advisory committee, to accept real-world evidence and be a leader, not a caboose. I understand what happened in the EU and the EMEA. They don't recognize real-world evidence. They're only going back to old-style therapy outcomes. I believe strongly that OCA should remain on the market. I want my patients who have been successfully treated with OCA to continue on OCA; and, of course, if patients are failing, it's nice to have newer therapies also that are available. Thank you very much for having me here today. Thank you so much.

DR. LEBWOHL: Thank you.

Speaker number 20 has withdrawn participation, so we'll move to speaker 21.

Speaker number 21, please approach the podium. Will speaker 21 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

DR. SHIFFMAN: Thank you. My name is Mitchell Shiffman. I'm director of the Liver Institute of Virginia. I consult for various

companies in the PBC space, and I'm a speaker for Intercept, as well as these other two companies; however, the views I'm going to present today are my own and don't represent that of any of the companies that I work with or my employer.

My clinical team manages well over 200 patients with PBC. We've participated in the original POISE clinical trial and the long-term extension. We've prescribed obeticholic acid to many patients since the drug was first approved in 2016, probably close to 100, and have firsthand seen the positive benefits of this agent, which mirror those in the two clinical trials.

Approximately 50 percent of patients with PBC, as you know, have a positive response when treated, and the long-term extension studies demonstrate that this treatment is maintained over 6 years with reductions in alkaline phosphatase, total bilirubin, and liver transaminases. Fibroscan data over 5 years demonstrates a 40 percent improvement in fibrosis and only a 15 percent progression.

The long-term benefits of OCA are clearly apparent when compared to two large registries, namely Global PBC and UK PBC. When patients treated in the POISE study and its extension were compared to these two cohorts, an impressive reduction in liver transplant-free survival was observed, with hazard ratios of 0.29 and 0.30, remarkably similar when compared to each study. In absolute numbers, 2.3 percent of patients treated with OCA over 6 years required a liver transplant or died, compared to 9.7 and 13 percent of patients in these two registries. Only 0.95 percent of OCA-treated patients developed hepatic decompensation compared to 9.2 percent of patients in the Global PBC study, representing a 10-fold improvement, hardly by chance such a difference was not significant.

The global standard upon which the agency relies upon for full approval is a carefully executed, randomized, placebo-controlled trial, and COBALT attempted to do this. You've already heard about the problems in randomizing patients to

placebo when there's an effective therapy, particularly when they have cirrhosis, advanced disease, and are facing transplantation or death. And as a result, this led to a significant number of dropouts in the control arm, and the toxicity in patients with advanced cirrhosis led to the study's early termination when enrollment would never be realized. Despite all these shortfalls -- things would have derailed many studies -- analysis of this data demonstrated a slight reduction in hazard ratio of 0.77 to 0.82, depending upon the analysis.

For me as a hepatologist treating patients with PBC, these data are very compelling and clearly demonstrate that obeticholic acid is safe and effective in preventing progression of this disease. I, therefore, urge the committee to grant full approval of obeticholic acid for use in patients in primary biliary cirrhosis, and on behalf of all patients with PBC, I would like to thank you in advance for your positive decision.

DR. LEBWOHL: Thank you, and thank you to all of the speakers during the open public hearing

portion, and particularly with your understanding regarding the time constraints.

Clarifying Questions (continued)

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience.

Before moving forward with the charge to the committee, we have a few minutes that we'd like to grant to the applicant with regard to responding to some matters that came up subsequent to their presentation this morning. We're giving you 7 minutes, no more. Thank you.

DR. SAWHNEY: Thank you. I'm going to ask Professor Hirschfield to comment on the Study 302 USPI-labeled subgroup accuracy, and secondly, to clarify the topic that was brought up from Study 405 in terms of hepatic decompensation classification. Then, number 3, I'm going to ask Dr. Dara to comment on the deaths and transplants in the Study 302 USPI-labeled subgroup. Thank you for your time.

PROF. HIRSCHFIELD: Thank you. Gideon

Hirschfield. I'm a hepatologist from Toronto. I'm a paid consultant, but I have no interest in the outcome. In the last year in our program, 837 patients were seen with PBC of which 100 were treated within the USPI label with obeticholic acid, of which approximately 30 percent have cirrhosis. I, therefore, would like to raise a concern as to the way that 302 has been analyzed in regards, retrospectively, to using the USPI label.

In slide 26 of the FDA presentation, it is suggested that 94 percent of patients are non-cirrhotic. I do not find this to be plausible. In all of the phase 3 clinical trials that used the inclusion criteria of the POISE criteria, of which we were involved in developing, the rate of cirrhosis is somewhere between 15 percent to 30 percent. In the development of the COBALT study, the inclusion criteria had an alk-phos above 3 or an elevated bilirubin.

I believe that because of missing data and the fact that that missing data then leads to automatically classifying those patients as

non-cirrhotic, that this is, therefore, misrepresenting that population of patients, and I believe that is important because you have heard that clinically we do not see this adverse effect of obeticholic acid in our clinical practice.

If I could have slide number 1 up, if we then look at the study and the association with outcomes, these patients have elevated bilirubins, and I believe that when you see a patient with PBC with an elevated bilirubin, it is highly likely that they have cirrhosis, and that, therefore, suggests that, to me, what you're witnessing here is not an effect of obeticholic acid, but the disease.

To further finish that point, I would like to make sure the panel is aware of a very important paper that was published in March 2024. It is a real-world paper from Spain from the ColHai group. It has 388 patients with PBC cirrhosis. It has patients treated with urso, obeticholic acid, and fibrates, so a number of different second-line therapies; and it attempts to look at the efficacy

of those second-line therapies and does demonstrate some efficacy.

But more importantly, it resonates a very important message which I believe practicing clinical hepatologists understand, and what you are hearing and seeing is just the progression of disease and not the effect of the second-line therapies. Indeed, the conclusion of that paper was advanced PBC rather than OCA, and fibrates was found to be associated with the decompensating events.

And finally, to go to the point about the real-world data and misclassification, I do not find it plausible from a clinical perspective that there is a difference between how events are being classified between the OCA-treated group and the control group in the 405 study. Thank you.

DR. DARA: Thank you. I get the concern that Dr. Tran and Dr. Mehta raise with the hepatotoxicity, I think.

DR. SEO: I'm sorry. This is Jessica. Would you please state your name before your

comment?

DR. DARA: Oh, I'm sorry. I introduced myself earlier. I'm Lily Dara. I'm a hepatologist. This is actually at the nexus of my clinical practice and my research.

If I can have slide 2 up, please, I completely understand the concern, but one of the things that we need to consider -- it's a key consideration -- is whenever you do DILI adjudication or hepatotoxicity adjudication, there has to be a temporal relationship, a demonstratable temporal relationship between administration of the drug and the event.

When you look at these, even if you don't think about the fact that they had contraindications and the drug would have been stopped at that point, here you're looking at trough levels, plasma total OCA trough, and as you can see, four of the patients had below the limit of quantification trough. So even if the graph shows that the purple line is where the OCA was stopped, many of them didn't even have quantifiable

trough at the time that they were measured before that purple line.

So if you look at the difference, the white line between when the drug was stopped and when the transplant occurred, you're looking at differences of months and years. And in order to adjudicate something as temporally associated, you have to have a latency that makes sense. So these are not DILI events, and I don't know how you can blame a drug that was discontinued for two years for that event.

(Pause.)

DR. LEBWOHL: The applicant had one more minute, but I suppose we can move on. We'll now move on to the charge to the committee. This is Dr. Frank Anania.

Charge to the Committee - Frank Anania

DR. ANANIA: Good afternoon. I'm Frank Anania, the Acting Director of the Division of Hepatology and Nutrition here at the Food and Drug Administration. First of all, I would like to thank today's participants, both those here on site

and those participating virtually. Perhaps the biggest thanks go to the patients and the patient advocacy groups. We do at the FDA appreciate your passion and your drive for us to approve safe and effective therapies for chronic liver diseases.

I also want to thank the applicant, Intercept, not only for their presentations today and their efforts, but they have truly been a trailblazer in studying farnesoid X receptor biology in chronic human liver diseases, and the hepatology community owes them a great deal of thanks for that. I want to thank also the members of the advisory committee. The FDA recognizes the time and effort that you all contribute to serve today and the time you take out of your busy schedules. We thank you for your efforts on behalf of safeguarding public health.

Before I turn the meeting over to the advisory committee in these proceedings, I want to remind everybody listening today and in the room that what will be discussed and what is voted on does not connote a regulatory action. A regulatory

action about this supplemental new drug application will be taken later this fall.

Now, I want to step back today, and how did we get here? How did we get to this meeting? The applicant submitted a new drug application 207999 back in 2016, and they used a pivotal trial, 747-301, and they studied PBC patients with a reasonably likely surrogate endpoint, primarily alkaline phosphatase, but also bilirubin was included in that. They were granted accelerated approval in May of 2016.

Now, under the accelerated approval statutes that Dr. Mehta reviewed today, accelerated approval does require confirmatory evidence of clinical benefit, and hence, we are here today for the advisory committee to advise us on the applicant's findings in supplemental new drug application 207999. In that supplemental application, as you heard from both the agency and the applicant, several studies were required, postmarketing studies, and they were randomized, double-blind, placebo-controlled studies. One was Study 747-302,

which was discussed at length today, and the other was Study 747-401.

You also heard that there were two boxed warnings that the FDA labeled this product, the most significant of which was in May of 2021. So what happened there was the trial that included primarily data for pharmacokinetics and pharmacodynamics in sick patients with cirrhosis obviously could no longer be continued. Now, the applicant went on to propose and submitted real-world data from administrative health claims database Komodo to produce real-world evidence findings, and that is 747-405, which you heard discussed today again.

Now, what I want to do in the next couple of slides, since there clearly is not alignment, I just want to summarize what I saw were the differences of opinion between the agency and the applicant, so we're going to focus on these two studies 747-302, which was the randomized, double-blind, placebo-controlled study that was part of the postmarketing requirement, and we will

also look at 747-405, which were the data the applicant generated with real-world evidence from the Komodo Health database.

As far as the applicant's position in 74-302, they found the data to be not interpretable, and they discussed at length functional unblinding, treatment crossover, and the fact that the USPI labeling changes in May 2021 made it difficult for them to complete the study or to interpret the data. The agency's position on that study is different. The agency's position is that the data were interpretable, that it provided safety and efficacy data in a controlled setting for the intention to treat, as well as for the USPI-labeled population, which was gone over extensively with you today.

Regarding 405, which is the real-world evidence study, the applicant sees it as interpretable. The agency, I think it's safe to say its position is that it's not interpretable because the data were of undetermined reliability and accuracy.

How about clinical benefit? Clinical benefit was the reason why in accelerated approval, applicants need to provide demonstration of that. In 302, the applicant's position is that the clinical benefit could not be verified for the reasons we stated before. The agency's position is that clinical benefit was not demonstrated in that study, either in the USPI population or in the intention-to-treat analysis.

By contrast, in the real-world evidence data that was submitted, the applicant's position is that it confirms clinical benefit, and therefore would fulfill the accelerated approval requirement based upon the statute. The agency's position by contrast is the data were questionably relevant and reliable, and in essence, the study was not adequate or well controlled to confirm clinical benefit.

And finally, in safety, the applicant's position, obviously on 747-302, was that there could be no conclusion about safety. The agency's position, as you heard earlier today, was it had

found that there was an imbalance in number of liver transplants in the USPI-treated population. There was also a small imbalance in deaths compared to the placebo in the USPI-labeled treatment cohort. The applicant's position with RWE, with respect to that study, felt that the study supported adequate safety for OCA use in the USPI population. The agency's position was the study was not designed to characterize safety.

To sum up, there are core issues that the discussion is going to ensue to help us with. Yes, primary biliary cholangitis definitely remains an unmet medical need, and when accelerated approval was granted for OCA, the speakers today all indicated that the landscape had certainly changed in terms of PBC therapeutics for the intended-use population.

I acknowledge that the clinical benefit of other newly approved drugs has also not been verified, and the issue at hand also is in the published literature. There are data that support other therapeutic modalities, which were discussed,

including fibrates. In 747-302, the agency's position is that it did not demonstrate clinical effectiveness but did provide safety data.

Now, the issue about indolence in this disease, I just want to step back, and I think we would all agree, and we heard this from the patients passionately in most cases, that this is an indolent disease. And we would not expect the patients in the USPI-labeled cohort -- who at baseline were reasonably well compensated; they were not cirrhotic -- to have the need for transplant, and it was unexpected compared to the placebo cohort. In fact, if you look at the briefing document from the company, they note that this is a rare and indolent disease and it is slowly progressive.

The other issue I want to point out is that whether we call it drug-induced liver injury or whether it's hepatotoxicity, there is certainly an issue with obeticholic acid. We heard that from Dr. Kowdley today in his testimony in the public forum. This actually led to two boxed warnings for

Ocaliva, and the second of which can contraindicate use in the sicker patients, which you heard about today.

Now, I might add that the hepatotoxicity was also an issue for the applicant, although admittedly, at a much higher dose, in its inability to complete the studies in metabolic dysfunction associated to hepatitis. I think it's fair to assess that the exact mechanism of hepatotoxicity may not be known, but I think it is fair to assess that there is an hepatotoxicity signal.

Regarding Study 405, the applicant asserts that Study 405 fulfills its requirement to demonstrate clinical benefit of Ocaliva as a safe and effective treatment for the intended-use population. The agency's assessment is that this study is inadequate and not well controlled to demonstrate clinical effectiveness.

Now, I want to just review the discussion questions in which the advisory committee will have one hour to discuss both of these. Followed by a short break, there will be two voting questions.

And again, to notify the public and those in the room, these are the four questions that we would like the advisory committee to discuss and vote on.

The first question says discuss whether the evidence generated post-approval verify the benefit of Ocaliva, or obeticholic acid, on clinical outcomes in adults with primary biliary cholangitis, specifically discussing the evidence generated in, one, the postmarketing required study, number 302, and secondly, in the observational study, 405.

The second discussion question posed to the committee is discuss the safety of obeticholic acid, including the incidence of liver transplant and all-cause of death in the United States Prescribing Information, or USPI-labeled population, as well as the overall study population.

Finally, after the break, the committee will vote, and then discuss the rationale for the vote, on the following two questions. The first question, does the available evidence verify the

benefit of obeticholic acid on the clinical outcomes related to PBC in the USPI-labeled population? And finally, is the benefit-risk profile of obeticholic acid favorable in the USPI-labeled population?

I want to thank you all for your attention.

Questions to the Committee and Discussion

DR. LEBWOHL: Thank you.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

Question number 1 is a discussion question. 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 primary biliary cholangitis, PBC. Specifically, discuss the evidence generated in the postmarketing required study, 302, and observational study, 405.

Are there any questions from the panel about the wording of this discussion question?

(No response.)

DR. LEBWOHL: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion. We will do so by means of the same procedure we did earlier today; raise your hand if you're here in person, click the button if you're attending remotely. I'd like to encourage both voting and non-voting members of the panel to participate in this discussion. And please, just as a reminder, we really want to join both of these, part A, Study 302, and part B, observational study, 405. We're hoping to have a discussion of both of these together about efficacy.

First question or first point of discussion is Dr. Goldberg.

DR. GOLDBERG: I'd like to comment more about 405. For the first 5 to 6 years of my career, all I really did was research using large administrative data, and ICD codes, validating them, and I really would agree that I can't really take any of the evidence from 405 to be interpretable in any way. We don't really know if these patients actually had PBC.

I've been involved in the studies of PBC in the VA, where we required manual chart review, and even among people with cirrhosis and PBC codes, only 80 percent of them actually had PBC. We saw a single validation from a Canadian study that had positive predicted value of 73 percent, so we're not certain that people had PBC.

With respect to the decompensation, one of the papers they cited was mine, but most of these studies that validated these codes were in people with cirrhosis. The codes that were used are very different. For example, they used a whole host of

codes for hepatic encephalopathy, which have been shown in recent studies not to necessarily be valid, and there's actually a new ICD-10 code as of October 2022 for HE that most people say it should be used as a code plus the medication. So if I was even a reviewer for a journal, I'm not sure if I would have accepted that, let alone to approve a drug to be used in patients.

DR. LEBWOHL: Thank you.

Just to amplify that, I just wonder if you think that this is differential misclassification, relying on codes, particularly diagnosis codes for PBC. I would imagine someone who's given OCA is much more likely to truly have PBC in Study 405 than someone who was intermittently given urso with interruptions, maybe for a variety of different reasons.

DR. GOLDBERG: Absolutely. I think -- again, this is just speculative -- you have more confidence that those who got OCA do have PBC, and those who didn't could have had other conditions that could have been mislabeled. They

could have had PSC, which is a disease there's no treatment for. They could have sarcoidosis.

So we actually don't know what those people have, and I think without having any sort of chart review to actually prove that those people had PBC by biopsy or diagnosis, I don't see how we could even interpret any of those results as usable in any way.

DR. LEBWOHL: Dr. Kamath?

DR. KAMATH: So following up on Dr. Goldberg's comment, if I see alkaline phosphatase and bilirubin elevation and it's not PBC, then it's typically something bad. It's likely to be lymphoma, granulomatous disease, fungal infection, and of course there's drug-induced liver injury in there. So I'm with Dr. Goldberg that there is going to be misclassification here; so 405, I'm really concerned about the control group in a sicker population.

When we come to 302, the benefit was in the subgroup analysis, so the number of patients are

much smaller. And typically, subgroup analyses are hypothesis generating because they're typically underpowered to show benefit. So all I can say from 302 is you can generate a hypothesis that in a selected group of patients with PBC, OCA might be beneficial, but not across all patients. Thank you.

DR. LEBWOHL: Thank you.

Dr. Gillen?

DR. GILLEN: Daniel Gillen. My response here is going to rely heavily on the word "verify clinical benefit." I'll take 302 first, and I agree that it is difficult to do a study where you have equipoise but you have an approved drug on the market, and I think that's a bigger issue than what we're even discussing here today in terms of drug approval, but I do not believe that that should be an excuse for limiting truly verifiable evidence.

With respect to 302, the reason why I was asking the questions about dropout is when we look at the IPCW analysis, it has no impact on the expanded endpoint. It changes the endpoints in the

third decimal by 0.02. Where you have an impact in trying to account for the crossover, in my opinion, is truly an artifact of the way that that imputation was done. The individuals that ultimately crossed over, quote/unquote, "by definition" were then switched in terms of their treatment indicator, and that bias means that those individuals had to have been at risk, at least up until the time that they crossed over, so you would expect the hazard ratio to come down. It's a fact. You're adding in more time to event on them. So I don't even think that we've proven any subgroup in 302 that there is a verifiable incidence here through the analysis techniques that have been actually given.

I think 405, again, in my opinion, the observational study evidence is clearly going to be outweighed by any type of randomized-controlled study setting, but I do think that there is a very persuasive argument that says that they are censoring individuals. When treatment ceases, there is often a reason that treatment is going to

cease.

Now, I do think that there needs to be more work in terms of when those events occur following the cessation of treatment. How long is the time lag? We need to understand that. If it's happening within 30 days, that's probably something that was going on already at the time that treatment ceased. If it's happening 2 years later, that may be a different story, and it's debatable at that point. But the point is, I do not think that either of these studies have, quote/unquote, "verified clinical benefit."

DR. LEBWOHL: Dr. Coffey?

DR. COFFEY: My comments are kind of similar to Dr. Gillen's. I think when you talk about the verify, I think it's going to be -- I mean, this is one case, and can go in the direction, where these real-world evidence studies are probably going to be better than some of the randomized-controlled clinical trials because of the challenges that came up, the censoring issues and how to do that, and it's going to be very hard to avoid these types of

issues.

I think the team's commended to pull the observational study together. I think it does have challenges to make it interpretable. I agree that if you take the word "verify," it's hard to say that these verify, but I will also caveat that by saying it's hard to see how many studies done after this, without a really clear hit-you-between-the-eyes benefit that easily comes out, could verify this. It's going to be challenging to do studies in this space anyway, so you kind of have to look at this in that perspective.

DR. LEBWOHL: Dr. Honczarenko?

DR. HONCZARENKO: Thank you. I would like to provide a broader perspective about placebo-controlled trials from an industry perspective, obviously. This is an important topic for us because we struggle to design the trials which have sufficient follow-up for patients who are treated, quote/unquote, "with placebo." And very often, even studies that require patients to remain on placebo for a period of 24 weeks, they

suffer from some bias; patients drop out, use of rescue medications. And indeed, a study like Study 302, that requires patients to be on placebo for even up to 5 years, is incredibly difficult to interpret, especially if the outcome of non-treating patients is liver transplantation or even death.

So I would say that considering this long placebo follow-up period, we have to be cautious to say this study is positive or negative. It's just very difficult with all the biases related to the treatment on placebo to interpret this; however, I think there is a signal, albeit not to the level of pivotal significance, a positive signal observed in Study 405. And considering certain signals from observational study and lack of interpretation of Study 302, it may be warranted to design another trial, a rigorous trial, maybe placebo controlled and maybe another other way of controlling the trial, to still confirm and/or deny the clinical efficacy, and most importantly safety, of OCA.

DR. LEBWOHL: Thank you.

Dr. Lee?

DR. LEE: Thank you. My first point is about 405. I think there's a lot of value towards observational studies, and with careful design, you can certainly gain a lot of information, particularly with target emulation. But we've seen with the study design, and Dr. Goldberg pointed out very well, that we don't have validated ways of looking at PBC and hepatic decompensation in patients without cirrhosis. The level of missingness is also of concern, and there are also other methodological flaws that the panel has pointed out.

I think we see from the results in the branching of the curves immediately, there's really no clinical explanation for this other than the fact that the control arm might be sicker at baseline without us even knowing. So for that reason, I don't think that we can really entrust in the validity of 405. It really does not meet the standard of causal inference.

That being said, 302, we have to consider as

a randomized clinical trial. It was very striking to me listening to the public and hearing opinions, and they were very valuable. What does benefit really mean? It was obvious that it means different things to different people. Here, we're charged with a very specific definition of clinical outcomes. We need an improvement in hepatic decompensation, liver transplant, and death to constitute as benefit as a panel.

I think that this system, in terms of full approval from accelerated approval, is really a safeguard. That's an important mandate here. The mandate here is to ensure that the intervention is treating more than a number and really treating the disease, and I think from 302, we haven't shown that it treats the disease.

I know that this has been separated into two questions here, but I find it very hard to divorce the two; and really, not only are we finding that it might not be treating the disease but, in fact, it might be making it worse. I haven't heard a good explanation in terms of why we're seeing the

signal of harm. By definition, I heard Dr. Dara and Dr. Hirschfield talk about how there might be more cirrhotics, or the latency period doesn't make sense, but the basic tenet of a randomized clinical trial is any difference in the event, as long as the randomization is correct, is due to the intervention.

So until there's a good explanation for this that can formulate a good risk mitigation plan, I think my answer for this is really that we have not verified benefit with 302, we cannot consider 405, and, in fact, there might be harm with the sponsor drug here.

DR. LEBWOHL: Thank you.

With regard to safety/harm, of course we'll be discussing that further in question number 2. But continuing in the vein of the question of efficacy and benefit, Dr. Bittermann?

DR. BITTERMANN: Hi. I share a lot of the same concerns about Study 405. I think, fundamentally, the placebo group was likely quite a bit different than the OCA-treated group. What I

thought was pretty remarkable from that study was the percent of patients who discontinued Ocaliva, which was about 50 percent, and while we don't have good understanding of their characteristics, I think that is a bit of a threat to thinking about benefit.

In terms of Study 302, just looking at the point estimates and the confidence intervals, there likely is a fair bit of variability in response, so there may be some benefit perhaps in a small subgroup. But in terms of that word "verify" in the discussion point here, I don't think that that's sufficient to completely verify the benefit.

DR. LEBWOHL: Thank you.

Dr. Shaw?

DR. SHAW: Thank you. Pamela Shaw. I'll go in order. I have concerns about 302 not being able to do its job to verify the benefit, and the reason is this. We saw in 301 that a number was treated but the biomarker went down. So 302's job was to look at the clinical outcomes. But what happened was we had that black box warning, and we realized

the labeled population had to be smaller. So that wasn't 302's fault. It was designed before we knew that, but that interrupted its ability to do its job, which was to verify benefit on the clinical outcomes, so then we had to expand the definition to get enough endpoints to add the biomarkers back in.

So I have problems because we had accelerated approval based on a biomarker, but what we need now is verifying the clinical outcomes. There were a number of other things that the other panel members have mentioned, such as the discontinuations, which I would echo were concerning, and then also in the analysis where there was concerns about the crossover. There was an analysis where the sponsor simply looked into the future and saw people survived a certain amount of time, and then relabeled them onto their arm because after a certain point of surviving, they then took the drug. That statistically is not a compelling analysis, so that did not help me at all. So I had problems with the evidence that 302

couldn't do its job to verify benefit.

For 405, I think Dr. Lee and Dr. Goldberg really nailed some of the difficulties, making this 405 difficult to interpret. I wanted to just mention something that might be also one of the reasons why there doesn't seem to be good comparability despite, I'm sure, a very careful analysis by the sponsor to try to do those weights to achieve that. It was something that hasn't been mentioned yet. I think we ran out of time this morning.

I actually do have concerns about the index date, not about the control arm. The non-starters had multiple index dates. They became available for this analysis as soon as they failed first line, but it's the OCA arm that has one index date, which is when they started the drug. We don't have that period of time when they became available to start the drug; we fast forward to when they started it. And I think that could be a source of possibly how we might have differential misclassification going on because we're not

observing them exactly the same way, is my interpretation.

So that was just another added perspective in addition to the other concerns, which I echo about the non-interpretability of this study. That's the possible reason a lot of emulated trials are done differently than, I think, the way that analysis was done. Thank you.

DR. LEBWOHL: Thank you.

Ms. Alstat?

MS. ALSTAT: Hi. I'm Danielle Alstat. I have PBC. I was diagnosed about 5 years ago when I turned 31, and I just wanted to offer my fellow panel members a patient's point of view when it comes to clinical trials.

So personally, I feel that there shouldn't be a placebo arm at all. I think it's asking a lot from patients, specifically my age, which we're seeing now is becoming very more common. I see that. I run a support group. I have probably 1400 members in my group, and everyday, people are younger and younger than me coming into the group.

So I personally feel that that needs to be changed for the future.

I think asking someone my age to not go on a for-sure treatment and be put on a placebo, I mean, I feel like you're literally putting my life at risk. I could die because of participating in a trial, and I think that that's something that we need to remember when it comes to making the decision, is that these people are me. I'm the patient. I never would have expected that I would have ever had this disease, and now I'm up to five different autoimmune diseases. And I work in healthcare, so I've seen how we treat patients, and I know what it's like to be the patient, and just please keep patients in the back of your mind when you're making these decisions. Thanks.

DR. LEBWOHL: Thank you.

Dr. Goldberg?

DR. GOLDBERG: I just want to raise one point, and as the last speaker, it's important to keep the patient in perspective. I think one thing that is important is that a number of the patients

who spoke, talked about their liver tests normalizing, and I think that's an important thing, but we're really focused today on outcomes.

I think one thing that's important in the briefing document from the company was focusing on alk-phos elevation as a marker of improved outcomes, but those data that they cited are largely from the Lammers paper from 2014, which was in people when the only treatment was UDCA. So we assume that the alk-phos normalization that we could see with OCA would lead to a better clinical outcome, but we actually don't know, and that's what the purpose of these two studies were.

Perhaps UDCA caused alk-phos normalization that improved outcomes for X, Y, and Z, but OCA, the potential benefits of normalization may be counteracted by some potential harms of changes in the bile acid composition or whatnot. So I don't think we can fully just say that because those patients have experienced alk-phos normalization, they're going to have a better survival benefit, based on data that's purely in the UDCA era. Even

if we do decide people are not in favor of it, we're not discounting the patient's voice, but we're basing it on the clinical outcomes data that are presented to us.

DR. LEBWOHL: Thank you.

Dr. Heller?

DR. HELLER: Theo Heller, and I agree. I want to echo what others have said and perhaps amplify it, but we have to be very careful with surrogates. As a practicing hepatologist and seeing patients with PBC, as a number of us are on this panel, our patients are first and central and foremost in our minds. And the reason we're here, and the reason I do what I do, and the reason I went to medical school, for all of us who are physicians, is because of our patients. But it's because it's for our patients that we can't rely on surrogates.

We can't rely on a blood test getting better. We have to know that the patient's going to do better. We know the fever can come down, but the patient still dies of sepsis. It's not the

point, right? We have to focus on what's really important.

So I agree with what's been said. Whatever the reason for the imbalances are, whether it's DILI or not, I don't care. The fact is there's an imbalance, and in a randomized-controlled trial, that has to be explained. What we've been confronted with in both studies, if I can be frank, is a lack of rigor. It's really a complete lack of rigor, and there are such arguments both ways, is this good; is this not good? We're not being presented with high-quality, first-class kind of studies here, whether they're published in top journals or not, and my concern is that we're going to make decisions when there's such greyness about the validity of the data.

So I don't know if ok is is good or not. I don't know if it's safe or not. Do the study. Once the right study has been done, placebo-controlled or not, design a real study, do a real study, and then we can talk about data. But until that happens, what we've seen today, I agree

with what's been said, it's not enough to feel comfortable to say that it should be available for all patients.

DR. LEBWOHL: Thank you.

Ms. McVey?

MS. McVEY: Thank you. Joy McVey, consumer representative. First, I want to thank everyone from the public that's here with us and the people that were online because my heart hurts so heavy right now, and it's because of exactly what you just said; that what we have to work with is just not there. The evidence isn't there. And it's hard because we have the two questions that we have to answer and vote on, and that isn't represented in what we heard from the patient and clinician perspective on those on the ground living with the condition and those treating it.

So I just want to acknowledge that I appreciate the applicant even taking on the issue and wanting to make people's lives better, but we were charged with safeguarding public health, and that's very important to me, and it's very

difficult to do that with what we're presented within the evidence. Thank you.

DR. LEBWOHL: Thank you.

DR. WINTERSTEIN: Everything has been said. I don't want to stretch this out too much. Maybe just one comment, and that is that this is not the first time where we have very convincing results on surrogate outcomes and unconvincing results on the efficacy when there are clinical outcomes evaluated. There are a lot of examples of that with other medications, and that is something -- I'm very empathetic to the patients that have spoken and providers who seem to be also very passionate about this, but the reality is, it appears that this is an example of a disease where a very clear surrogate outcome is treated, which also was a massive problem with the clinical trial execution at the end of the day. But I think we all agree that there hasn't been demonstration of the clinical benefit, and that is not unique in medication history, unfortunately.

DR. LEBWOHL: Dr. Sturmer?

DR. STURMER: Thank you. 302 first; trials are not my forte, but it looks like there is a slight benefit there, albeit not statistically significant. But when looking at table 5 in the FDA document, there also seemed to be some relevant chance imbalances between the placebo and the treatment arm, in favor of the treatment arm, which could very well explain 10 or 20 percent improved outcomes. So this may be something that someone could look into; that there are no data presented for the USPI population, and specifically it's imbalanced there as well.

My forte is the claims data analysis, and I have several concerns about that. It starts with the data, the lack of enrollment files. We didn't even touch the issue about the transition at age 65 from the commercial insurance databases to Medicare and how this was handled, how many patients whose follow-up time actually fell into that period and how many could be linked to Medicare data.

Then I just want to highlight this point, because it was raised during the public session

again, about the consistency between the crude and adjusted. I'm not implying, and I did not imply, the point estimate should move closer to the null, but it should actually move away from the null given the differences in the baseline liver function tests that we observed. So the non-exposed group or the comparator should get sicker by the SMR weighting, and it doesn't, and that concerns me. I just wanted to highlight that point.

Then finally, just a comment, that we can discuss ITT versus as-treated for the rest of the day, but ITT clearly is not biased by informative censoring because that's the exact reason why we use the ITT analysis. Thank you.

DR. LEBWOHL: Thank you.

Dr. Lo Re?

DR. LO RE: Yes. Just to comment about the 405 study first, I know we heard a lot about these data were initially fit for purpose from the applicant, but I think we heard continually questions about the accuracy; the appropriateness;

the completeness of the data, particularly with regard to defining PBC decompensation; concerns about uncontrolled confounding; concerns about misclassification bias.

But that being said, I do think that it is feasible and possible in the future to design such studies like this for rare diseases that would really, however, require going back to medical records to do the appropriate adjudications to ensure the accuracy of the diagnoses, really, in the population that is being treated as we do in other pharmacoepidemiologic studies. So I wouldn't abandon hope or interest in that down the line.

It was challenging to interpret the differences in the beneficial effects that the applicant was demonstrating versus the FDA's ITT-like analysis. That in and of itself and the fact that sometimes sensitivity analyses weren't necessarily consistent, there were differences between what the agency's was showing and what the applicant was showing, to me, raised more questions. So in regards to 405, I just felt like

there were simply too many questions.

Then with regard to 302, I thought that it was interesting that the applicant showed that the beneficial effect was really only after controlling for the -- I forgot what it was exactly, but the agency showed that there was no beneficial effect, so I was left with major questions about that. Thank you.

DR. LEBWOHL: Thank you.

I'm going to do my best to summarize, really, what I thought was a fruitful discussion. First, on Study 302, there was acknowledgement, in general, of the challenges of conducting an RCT under these circumstances, wherein the study drug became commercially available during the conduct of the trial. The mandate is to determine whether we are treating more than a number; we're treating the disease. There might be a benefit, perhaps a slight benefit, but it's not clearly or convincingly a verified benefit, was the consensus that I'm hearing.

The whole point of 302 was to verify this,

and, unfortunately, because of the changing labeling due to the safety concerns, that affected the ability of 302 to verify this benefit. It's not 302's fault, as was said. The efforts to analyze as-treated are difficult to interpret given that the risk was dynamic over time, particularly at the time of crossover. Patients do not want to be on a placebo. Alk-phos normalization correlates with outcomes, we know that from prior studies, but the degree and nature of that correlation might be changing over time, particularly in recent years. As such, we may need to rely on real-world evidence.

But with regard to efficacy from 302, there's no question that the commercial availability of OCA made it harder to prove that this drug was superior to placebo, Study 302, looking at death-transplant to decompensation. But the question is, does OCA reduce the risk of these outcomes? We don't know the answer to this. We didn't know the answer before accelerated approval was granted, and we're still not sure now.

With regard to 405, concerns were raised with regard to accuracy of relying on diagnosis codes, which could be differential misclassification, wherein the non-OCA controls may include those who don't have PBC and have worse prognoses. Missingness is a concern. The imbalance of index dates in the two arms was raised as a concern. The fact that the curves separate so early on is a red flag. The fact that we have two groups looking at the same data, coming to different conclusions based on their models, speaks to the challenges of using observational data in this context. I'm not sure there was a uniform consensus in this discussion, whether there's any signal of efficacy that's interpretable from 405, but the bulk of the comments conveyed a skepticism about coming away with any real interpretation.

So with that, we'll close discussion point number 1, and we will now move on to question 2, also a discussion question. 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.

Are there any questions or issues about the wording of this question?

(No response.)

DR. LEBWOHL: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion. Please raise your hand as you did previously, and then we can get started.

Dr. Goldberg?

DR. GOLDBERG: So as a transplant hepatologist and also someone who spent a lot of time doing daily adjudication for NIH studies and the FDA, slide 45 from the FDA, really, I think is the most concerning one. There are 8 patients who ended up getting a transplant. One had been in the placebo group and then got OCA, but 6 out of 8 had a clinical event while on obeticholic acid.

Now, the fact that the transplant didn't occur for months or not years longer doesn't mean that it's because of the medication; it's because

getting a transplant is really tough in the United States. So these patients all had an hepatic decompensation event, 6 out of 8, while on OCA that led them probably -- again, we don't know the information -- to be listed, and if we had organs that could go around, they probably would have been transplanted at that moment, but they had to wait due to the waiting period.

One out of eight, there was a short interval between when they were on OCA and the event, so I don't think we could discount what was said before that, "Oh, because there was a long period from the drug, stopping it to getting a transplant, that they're not related," no, it's because it takes a while to get a transplant.

There's a signal of concern here, and I will just say, I have treated a number of patients with PBC, and I have not prescribed OCA as second-line therapy. The data related to both early data and also concerns about pruritus in patients who have cholestatic disease, it has not been a medication that I have actually offered to patients as

second-line therapy because of concerns of this.

DR. LEBWOHL: Thank you.

Dr. Lo Re?

DR. LO RE: I was equally concerned with the signal of hepatotoxicity, particularly the same slide that Dr. Goldberg is mentioning. I feel like we know so little about DILI in the setting of chronic liver disease, and with this particular drug, the timing in relation to decompensation, that may have important impact; and the fact that we're seeing so many events I think in terms of decompensation and then going on to transplant I thought was a concerning enough signal; and then couple the fact that the agency's analysis showed an over 4-fold hazard ratio, was of concern. Thank you.

DR. LEBWOHL: Dr. Gillen?

DR. GILLEN: Thank you. Daniel Gillen. A couple of aspects frame my opinion on this. One is that we have experience with this drug that shows that there is some sort of hepatotoxicity at higher doses, so there's some signal that's there. I

realize that we are working at a lower dose -- I get that -- but we understand a little bit of this drug in terms of the dose response that's happening here.

These are small numbers, but I find the sponsor's argument that a hazard ratio of 4.77 simply isn't consistent with what we're observing in our other studies in terms of incidence rates very uncompelling. And the reason why I say that is because they are small numbers. There is a confidence interval that is ranging from 1.03 to 22.09, and 1.9 is actually consistent with those adverse event rates that are a given there. And if you tell me that a 90 percent increase in the hazard for liver transplantation or death is existing with this drug, that's enough to convince me that there is a potential issue here. So I find that a very soft argument that is happening here.

I also think that it is not our job to prove harm. It is not like you have to have a prespecified subgroup for harm like we do when we deal with efficacy. Here, what we have is we have

a particular endpoint that we've boiled down to where we have reasonable evidence and doubt that there may be a very harmful signal that's occurring here, and we have actually ruled out a point estimate of 1.

Do I stand behind all statistical validity in that, given that there are subgroup analyses and different endpoints considered? No, I wouldn't treat it the way I would treat an efficacy analysis in a subgroup, but it's enough to raise reasonable doubt that there could be a harmful signal here that we need to further understand.

DR. LEBWOHL: Thank you.

Dr. Lee?

DR. LEE: My perspective is as a hepatologist who treats PBC and has prescribed obeticholic acid to my patients and, to me, this experience really shows the value and importance of large multinational studies for rare diseases. These events were not very obvious, and we could see, even from the speakers who have a lot of experience and busy practices, how you might not be

able to detect events that could be causing a serious safety problem.

We saw slide 63 presented by the sponsor that all 8 patients who receive liver transplants received Ocaliva, including one crossover. There are 5 deaths, four were in the Ocaliva arm and only one was determined to be liver related. But if we look carefully, one patient died from complications of *C. difficile* infection, one died from a subdural hemorrhage. These could be liver related. Liver decompensation causes immunosuppression, which could have predisposed to a more severe *Clostridium difficile* infection. Liver disease causes coagulopathy, which could be related to subdural hematoma, so we actually don't know that these were not necessarily liver related.

So this signal is concerning to me. And I heard a lot of concerns regarding crossover and how that's challenging, and I do empathize with the sponsor with this, but the reality is, if there was crossover, this should actually attenuate the potential for signal for harm. So the fact that

this could be even more severe in real world is very concerning for me. Thank you.

DR. LEBWOHL: Thank you.

Dr. Kamath?

DR. KAMATH: This is going to the latency period between starting the drug and the presumed drug-induced liver injury. In the 8 patients that we had, latency period was 87 to 379 days, median 210 days, and that's in cirrhosis, which tells us there's accumulation of the drug before you get the toxicity, and if you don't have cirrhosis, it's likely to be longer.

Then, again, like Dr. Goldberg told you, once we list them for transplant and you stop the drug, they actually get a little better, so their MELD score drops. So I'm not surprised that it takes 2 years for them to get a transplant, and especially now where alcohol-related hepatitis patients, they're much more likely to get transplanted. So, in fact, this is the typical course, the long period between the diagnosis and being transplanted.

The other issue is -- I think it's table 29 -- Brian brought up the issue of the subdural hematoma. We also see the cardiovascular events in table 29, so there's hemorrhage, which even if there's no mortality, that's significant morbidity. And cardiovascular, again, is significant morbidity, so those two are always taken as separate. They're way beyond elevation in bilirubin, so that is, again, a concern that I have here.

DR. LEBWOHL: Dr. Heller?

DR. HELLER: Yes. I agree with everything that's been said in terms of the imbalance being the issue and the safety signal only being seen when you collect large groups of patients. I think we also have to be careful when we think about the standard interpretations of DILI. Look at the glitazones, and look at the difference in glitazones and withdrawal. Years later, we saw this large cohort of patients, and then there was this 1 in 1,000, or something, that developed permanent liver failure, but with a long latency.

I think that's something we should remember and not repeat that mistake.

I also think Dr. Gillen's point about the dose-response curve is very important because it works both ways. When you give a high dose, you see an effect in a small population rapidly, but when you give a lower dose, you might need a very large population to see that toxicity. So I think what worries me here is that we're dealing with small numbers. I go back to what I said originally. We need a real study with rigor.

DR. LEBWOHL: With that, I'm going to suggest that -- oh, I see Dr. Kamath has his hand raised.

Please?

DR. KAMATH: I'm sorry. I've lowered my hand.

DR. LEBWOHL: Ah. Thanks, Dr. Kamath.

So with that, I'm going to try to summarize the discussion of question number 2. Having a liver transplant many months or even after a year after stopping OCA could still be OCA related given

the long waiting time for a transplant, and that could be affected by the fact that the MELD score might drop. We should learn a lesson from glitazones, which taught us about latency. We know that this drug, OCA, is hepatotoxic at higher doses, so we have a reason to place a microscope on its use in this lower dose.

This hazard ratio of 4.77 presented in the FDA briefing document this morning is not really an aberration given the wide confidence interval that included some of the other estimates that had been plausibly put forth. For this kind of outcome, we do not have to definitively prove harm. We rely on reasonable evidence or reasonable doubt. We have to recognize these are rare events that individual practitioners might not discern. Some of the liver deaths seen in 302 might have actually been consequences of worsening liver disease or hepatotoxicity.

The population most likely to be protected from death, transplant, et cetera, these important outcomes, are those whose risk is highest, i.e.,

those whose degree of liver disease is coming close to that warning, where it's agreed that OCA should not be given. So with all of that, what I'm hearing is a consensus that the safety of OCA remains a significant concern.

With that, I'm going to propose that we take a 15-minute break, at which point we will return for questions 3 and 4, which are voting questions. We will return at 3:52.

(Whereupon, at 3:37 p.m., a recess was taken, and meeting resumed at 3:52 p.m.)

DR. LEBWOHL: Welcome back. We will now proceed to question 3, which is a voting question. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the

vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed. I'll read question 3.

Does the available evidence verify the benefit of OCA on clinical outcomes -- hepatic decompensation, liver transplant, and death -- in the USPI-labeled population? Please provide a rationale for your vote.

Are there any questions about the wording of this question?

(No response.)

DR. LEBWOHL: If there are no questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds

to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. SEO: I just want to let everyone know it will be a couple minutes while we compile the results for both the virtual and in person participants. Thank you for your patience.

(Pause.)

DR. SEO: This is Jessica Seo, DFO. For the record, the results for question 3 are as follows: 1 yes, 13 noes, and 0 abstentions.

Dr. Lebwohl?

DR. LEBWOHL: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. We're going to start with our remote attendees.

Dr. Sturmer?

DR. STURMER: Yes. Thank you. Til Sturmer. I voted no. 302, the ITT analysis shows a weak benefit but also evidence for potential serious harm, which leads to an unfavorable benefit-harm balance for treatment indicated for early disease, even in a setting where there are few alternatives available; 405, ITT, again, a weak benefit, but serious concerns about specific data source, not claims data per se, but the specific claims data used; study design and analysis, for example, no information or not enough information on censoring weights. Thank you.

DR. LEBWOHL: Dr. Winterstein?

DR. WINTERSTEIN: Almut Winterstein. I voted no. I agree with the interpretation of the results that Dr. Sturmer just provided. For the real-world evidence study, there isn't, in my opinion, an incomplete assessment of confounders and several reasons pointing to a lack of comparability of comparison groups, and specifically disadvantages of the non-treated

group. There is unclear data validity in completeness and potential concerns about differential misclassification; I actually buy that argument.

With regard to the per protocol analysis of the RCT, the crossovers do mask benefit, but this is an acceptable risk of ITT, I think, and is typically accepted. There was a particular problem here with ALP as treatment goal, which was obvious, and therefore removed some of the blinding. I can see that, potentially, and probably triggered more crossovers, but the way this was handled in the per protocol analysis is unclear.

To the extent that I understand it, there might actually have been introduction of immortal time bias, and I really didn't understand exactly how the inverse probability of treatment rates were constructed, but they could actually have introduced bias as well. So I don't see, really, an advantage of this analysis over the original ITT analysis and the analysis that the FDA provided with regard to the safety issue.

DR. LEBWOHL: Dr. Kamath?

DR. KAMATH: I voted no. 302 didn't show benefit. Only the subgroup analysis showed benefit in a smaller group, and that is only hypothesis generating; 502, significant concerns about patients. Ideally, we should have had a manual review of 10 percent of the records to make certain that the diagnosis was correct.

DR. LEBWOHL: Dr. Lee?

DR. LEE: Brian Lee. I voted no. There are serious concerns with the validity of 405, not because it's observational but because of the study design. 302 did not meet its primary endpoint. My concern is that the reduction in alkaline phosphatase is just a red herring for this drug.

DR. LEBWOHL: Dr. Heller?

DR. HELLER: Theo Heller. I voted no. Nothing to add to what's been said.

DR. LEBWOHL: Dr. Coffey?

DR. COFFEY: Chris Coffey. I voted no. I think, due to the points that were raised, but also due to the discrepancy and opinions about how

convincing the various studies are, it's hard to say that this reaches the level to verify benefit. I think equally important, I'm not sure it doesn't show there's no benefit. It's kind of an unfortunate case where a bunch of studies were done, and I feel like the answer that was set out to look for at the very beginning is just as unclear, perhaps, at this point -- maybe more unclear -- than it was because of the uncertainty.

DR. LEBWOHL: This is Benjamin Lebwohl. I voted no for reasons previously enumerated.

Dr. Shaw?

DR. SHAW: Yes. I voted no for reasons that are iterated. I think, specifically, 302, the evidence is really inconclusive with some concerns raised that need to be investigated, and I did find Study 405 to really be because of the design and a lot of questions that were raised uninterpretable. Thank you.

DR. LEBWOHL: Dr. Gillen?

DR. GILLEN: Daniel Gillen. I voted no for reasons that I previously stated.

DR. LEBWOHL: Ms. McVey?

MS. McVEY: Joy McVey. I voted no for lots of the reasons we've discussed already, but I just want to remind the community that we're here to look at the available evidence that we've been provided. That doesn't dismiss the people that are taking this drug that feel like they're going to lose access potentially to it because I care very deeply for that.

DR. LEBWOHL: Ms. Alstat?

MS. ALSTAT: Danielle Alstat. I voted yes because even though I feel like 302 was inconclusive, I do think that the evidence, the real-world evidence, for 405 does show that if it's given in the right dose for the right patient and is followed along, there is a benefit there that shouldn't be ignored.

DR. LEBWOHL: Dr. Lo Re?

DR. LO RE: I voted no. My interpretation of the 302 data was that they were interpretable but that the primary analysis really failed to demonstrate efficacy on the primary expanded

endpoint. I thought the applicant reported that the analysis corrected for both the treatment crossover and the informative censoring demonstrated a protective effect, but I heard a number of concerns with this analysis from the agency.

I think regarding Study 405, while the applicant's as-treated analysis showed a beneficial effect of OCA, I heard a number of concerns, obviously, about the quality and the accuracy of the data, which we discussed, and I just thought there were too many limitations to this study for it to provide definitive interpretation on the benefit of OCA in this study. Thanks.

DR. LEBWOHL: Dr. Bittermann?

DR. BITTERMANN: I voted no. Neither of the two studies provided the evidence needed to verify the benefit for the outcome studied in patients overall.

DR. LEBWOHL: And Dr. Goldberg?

DR. GOLDBERG: David Goldberg. I voted no. I found 302 did not verify a benefit to the

clinical outcomes and I found 405 to be uninterpretable.

DR. LEBWOHL: Thank you.

We will now proceed to question 4, which is also a voting question. I'll read the question.

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

Are there any questions about the wording of this question?

Dr. Shaw?

DR. SHAW: Yes. Thank you. I have a bit of a question about how I interpret this in the sense of there's how the drug is working in patients and there's what the evidence is telling us about this. And, to me, those are two different things, and I'm not sure is this asking the question, has there been evidence of a favorable benefit? Is that a proper interpretation?

DR. LEBWOHL: Could the FDA weigh in?

DR. ANANIA: Thank you for your question, Dr. Shaw. I think your position for this question

should be look at the evidence that was discussed today, the scientific evidence. That's what we're asking you to do.

DR. SHAW: Thank you.

DR. LEBWOHL: Are there any other questions or clarifications?

Yes, Dr. Goldberg?

DR. GOLDBERG: I guess this is a question for Dr. Anania. When weighing the risk and benefit, can that take into consideration what other options there are for patients or specific to this drug in isolation?

DR. ANANIA: These are very good questions. I think, again, what I would like you to do, the agency posing this question, is to look at the available evidence for this particular agent, exclusive of other agents or other issues in the environment. You look at the data that was discussed here by the applicant and the agency, and you decide to address the question as it's written. Thank you.

DR. HELLER: I have a question, too.

DR. LEBWOHL: Yes, Dr. Heller?

DR. HELLER: What if we feel the benefit-risk profile is not accessible given the data that we've been shown? The quality of the data isn't adequate to answer that question.

DR. LEBWOHL: Does the agency care to respond?

DR. ANANIA: Well, you can vote in the affirmative or negative with a rationale or you can abstain with a rationale, if that's what you choose to do, given how you posed the question.

DR. LEBWOHL: Other questions about this question or requests for clarification?

(No response.)

DR. LEBWOHL: If there are no further questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you're unsure

of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. SEO: This is Jessica Seo, DFO. The results for the record for question 4 are as follows: 1 yes, 10 noes, and 3 abstentions.

Dr. Lebwohl?

DR. LEBWOHL: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did in the record.

We will start with the remote attendees, with Dr. Sturmer.

DR. STURMER: Thank you. Dr. Sturmer. I voted no. I gave the reasons in my previous explanation, and I think, again, the benefit-to-harm balance is important in this setting of early-stage treatment. I also want to acknowledge that I do realize that behind all these numbers are patients looking for treatments. Thank

you.

DR. LEBWOHL: Dr. Winterstein?

DR. WINTERSTEIN: Almut Winterstein. I voted no. I was thinking about the process that FDA goes through, drugs approved based on favorable benefit-risk, and if there is no evidence to support benefit, then benefit-risk cannot be favorable because benefit doesn't exist. There are enough safety concerns to assume that nothing can offset a drug that is not beneficial but has some safety issues. The question, of course, now is whether there is enough promise for OCA to remain on the market with another PMR, but that is, I think, not in the purview of the committee to decide and how that would look like.

I agree with Dr. Sturmer that I am very really empathetic about the issues of not having treatment options, but I think even if there were a decision for this drug to remain on the market, it would be important for patients to understand that benefit may actually not be a benefit because it is currently tied to favorable drug levels and nothing

else. So that would speak for something that includes a REMS, where this is made very clear to patients, and that might result in different choices, actually.

DR. LEBWOHL: Dr. Kamath?

DR. KAMATH: I voted no, benefit not proven. Number of events was high in the treatment group, so the possibility of harm cannot be ruled out.

DR. LEBWOHL: Dr. Lee?

DR. LE: Brian Lee. I voted no. I deeply empathize with the high unmet need and the stories from the patients that we heard today; however, the benefit is unconfirmed, and the signal of harm, with increased risk of death and liver transplant, is concerning.

DR. LEBWOHL: Dr. Heller?

DR. HELLER: Theo Heller. I voted no. And I think all of us agree. We see the patients behind the numbers, but without the data, we can't vote that there's benefit. I can't vote that there's benefit.

DR. LEBWOHL: Dr. Coffey?

DR. COFFEY: Chris Coffey. I abstained mostly due to the point I made before. I feel like the evidence on benefit is unclear in terms of whether there is or isn't benefit, which makes it almost impossible to really assess the benefit-risk ratio. I felt like while there are safety concerns, I'm not sure that I'm comfortable saying the benefit-risk ratio is not favorable enough based on that, because of the uncertainty of benefit, and I'm also not comfortable saying that it is.

I feel like there's a need for better data to assess that, and I think up to that point, I mean, to be perfectly honest, if I were a researcher, had I would have one feeling, if I were a patient, had I would have a different feeling, and I don't think the data are strong enough to justify either one in its isolation.

DR. LEBWOHL: Benjamin Lebwohl. I vote no for reasons previously described by members of this panel during the vote explanations thus far.

Dr. Shaw?

DR. SHAW: Thank you. Dr. Shaw. I voted no, specifically because I think the benefit is inconclusive and there were some concerning signals of the safety. We know there's definitely a group that can be harmed, but have we correctly identified the group that can benefit? It's inconclusive, and I think what's really important when we think about that placebo that people often think of as negative, it's the standard of care, is what that is. We've got to make sure we're not doing worse in the standard of care, and that hasn't been proven yet. So that was my driving reason for no.

DR. LEBWOHL: Dr. Gillen?

DR. GILLEN: Daniel Gillen. I voted no. I had previously stated that I don't believe that we have verified benefit, and I think that there is reasonable question regarding harm here. I don't think it's been proven, but I don't think it needs to be, and I think it's a reasonable question.

I do want to take one second given Ms. Alstat's comments and Dr. Heller's comments.

Being on these committees, I've been in this position now a few times with the accelerated approval process. If we're going to utilize this process and we're going to focus on surrogates, I think we all -- the agency, sponsors, we on the adcoms -- need to do a better job of communicating with patients and physicians about the difference between surrogate endpoints and clinical outcomes.

There is a thought, I think, from the public that if something is approved, it is working, and we still have equipoise with respect to clinical outcomes in these settings. That's why it is ethical to randomize people to a product. I think it's an unfortunate position that we're often in, that we have put these out, and it seems like you're giving something and then taking it away without good explanation as to why, and we need to do a better job at this, in terms of communicating this process, and the role of surrogate endpoints, and the limitations of surrogate endpoints.

DR. LEBWOHL: Ms. McVey?

MS. McVEY: Joy McVey. I abstained. Much

like Dr. Coffey, I don't feel like we have the answers necessarily; more research is needed. Dr. Gillen also made a really good point about the accelerated approval process and the position it puts patients in, assuming something is safe when we still don't really know for sure.

DR. LEBWOHL: Ms. Alstat?

MS. ALSTAT: Danielle Alstat, representing the patients of PBC. I had to vote yes because I think a lot of people end up dying waiting for a transplant. And if there is an opportunity for people to be able to take a medication to be able to live a long and healthy life, I think every PBC patient now, and in the future, should have that opportunity. Thanks.

DR. LEBWOHL: Dr. Lo Re?

DR. LO RE: Vincent Lo Re, Penn. I voted no. I thought the benefit wasn't verified. I certainly think we saw a safety concern. Trial 302 showed more possible or probable cases of adjudicated DILI in the USPI population, suggested harm regarding liver transplant/death with the

hazard ratio of 4.77 in this group despite the placebo subjects use of commercially available OCA, potentially underestimating the signal of harm. So I thought that it was fair to assess that there is a hepatic toxicity signal and the signal was concerning.

I also found the presentation of the data on the clinical trajectory of the liver transplant and death in the USPI-labeled population concerning given the events that were occurring during OCA exposure, and the subsequent discussion that suggested that OCA might cause harm even after discontinuation of the drug. Thanks.

DR. LEBWOHL: Dr. Bittermann?

DR. BITTERMANN: Tess Bittermann. I chose to abstain. I, again, reiterate the issues with the data at hand. I do think that there may be a population within the U.S., the USPI population, that may have some benefits, and that's not proven but I think needs to be further studied. Similarly, there may be other subgroups where the benefit of risks clearly outweighs the benefits. I

think there just needs to be better data to understand in whom we can use this medication safely.

DR. LEBWOHL: Dr. Goldberg?

DR. GOLDBERG: David Goldberg. I voted no. It's been discussed already. I think the evidence of benefit presented today was, I think, really limited. While we heard voices today from patients, I don't think we're discounting the voices of the patients because these data represent patients.

As a clinician, the risk-benefit that I'm seeing, the patients who were transplanting and dying, 48.6 percent in the real world that are discontinuing the medication, there are real risks to this medication from patients on these pieces of paper that are of concern, and I really don't see any evidence of benefit that's been presented today.

DR. LEBWOHL: Thank you.

Before we adjourn, the DFO reminds me that the chair must summarize the panel's consensus for

all of the discussion items, as well as the voting questions, so I'll briefly summarize.

For voting question 3, I would say that there was a strong majority, not unanimity, conveying the notion that the benefit of OCA is not verified, and there was discussion of the fact that Study 302 did not meet its primary endpoint. There was acknowledgement that this was for a variety of reasons, including related to the fact that OCA became commercially available. There was also acknowledgement that Study 405 was difficult to interpret due to a number of potential methodological disagreements conveyed in the panel.

As for question number 4, or discussion point 4, which was a question, again, there was not unanimity but there was a majority that voted no, primarily conveyed because the benefit remains unconfirmed and that there is a concern for real possible harm, though abstainers noted that the benefit remains unclear, making it difficult to truly weigh the risk-benefit ratio.

The unmet need regarding second-line therapy

for PBC was raised and acknowledged, and the challenge of knowing whether a drug is hepatotoxic when it is being used to treat a chronic liver disease is a real one. It's difficult to distinguish, at some points, between direct drug hepatotoxicity and failure to arrest advancement of underlying liver disease.

We're also seeing difficulty in the road ahead in terms of future development of second-line therapies given the course of OCA and given the challenges of conducting such trials in the current landscape. We need to do a better job, really, in communicating the difference between surrogate endpoints and hard clinical endpoints, particularly when we communicate this to patients who are looking for effective therapies.

Before we adjourn, I just want to thank the FDA; I want to thank the applicant, Intercept; I want to thank the public for joining us, the OPH presenters, and for my co-panelists for putting in so much time and effort to studying this matter.

Are there any last comments from the FDA?

DR. ANANIA: No. We just, again, thank everybody.

Adjournment

DR. LEBWOHL: We will now adjourn the meeting. Thank you.

(Whereupon, at 4:18 p.m., the meeting was adjourned.)