FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE (GIDAC) MEETING

Virtual Meeting

Friday, May 19, 2023

9:00 a.m. to 4:45 p.m.

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. LEBWOHL: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is April Grant. Her email is currently displayed.

My name is Dr. Benjamin Lebwohl, and I will be chairing this meeting. I will now call the May 19, 2023 Gastrointestinal Drugs Advisory Committee meeting to order. Dr. Seo is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. SEO: Good morning. My name is Jessica Seo, and I am the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We'll begin with our standing committee members, and first is Dr. Assis.

DR. ASSIS: Hello. My name is David Assis.

I'm an associate professor of medicine and hepatologist at Yale School of Medicine.

DR. SEO: Thank you.

Next is Dr. Chang.

DR. CHANG: I am Lin Chang, professor of medicine, gastroenterologist at UCLA.

DR. SEO: Thank you.

Then we have Dr. Coffey.

DR. COFFEY: Hi. I'm Chris Coffey. I'm a professor of biostatistics at the University of Iowa.

DR. SEO: Thank you.

Ms. Hugick?

MS. HUGICK: Good morning. I'm Joy McVey Hugick, and I'm the consumer representative in Atlanta, Georgia.

DR. SEO: Thank you.

Dr. Lebwohl?

DR. LEBWOHL: Benjamin Lebwohl, associate professor of medicine and epidemiology at Columbia University.

DR. SEO: Thank you.

Dr. Mannon?

DR. MANNON: Peter Mannon, professor of medicine, chief of the Division of Gastroenterology and Hepatology at University of Nebraska Medical Center.

DR. SEO: Thank you.

And Dr. Solga?

DR. SOLGA: Hi. It's Steve Solga. I'm an associate professor of clinical medicine and an transplant hepatologist at the University of Pennsylvania.

DR. SEO: Thank you.

We also have our committee's industry representative, Dr. Albrecht.

DR. ALBRECHT: Good morning. My name is Helmut Albrecht. I am currently the chief scientific officer at Alitair Pharmaceuticals and the president at H2A Associates, a pharmaceutical development consulting company.

DR. SEO: Thank you.

Next, we have our temporary voting members, and we'll begin with Dr. Czaja.

DR. CZAJA: Mark Czaja, adjunct professor of medicine and hepatologist from Emory University.

DR. SEO: Thank you.

Dr. Floyd?

(No response.

DR. SEO: Dr. Floyd?

DR. FLOYD: Hi. Good morning. James Floyd, physician/epidemiologist from the University of Washington.

DR. SEO: Thank you.

Next is Dr. Heller.

DR. HELLER: Hi. Theo Heller, senior clinical investigator and hepatologist at the National Institutes of Health.

DR. SEO: Thank you.

Next, Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger, biostatistician at NIAID, NIH. Thank you.

DR. SEO: Thank you.

Dr. Lee?

DR. LEE: Good morning. Brian Lee, assistant professor of medicine and transplant

hepatologist at University of Southern California.

DR. SEO: Thank you.

Dr. Maher?

DR. MAHER: Good morning. Jackie Maher, professor of medicine and gastroenterology, University of California, San Francisco.

DR. SEO: Thank you.

Dr. Rakela?

DR. RAKELA: Yes. I'm Jorge Rakela, professor of medicine, Mayo Clinic in Arizona, transplant hepatologist.

DR. SEO: Thank you.

Ms. Schwartzott?

MS. SCHWARTZOTT: Hi. I'm Jennifer Schwartzott, and I'm the patient representative.

DR. SEO: Thank you.

And Dr. Wilson?

DR. WILSON: Peter Wilson, professor of medicine, endocrinology, preventive cardiology, Emory University.

DR. SEO: Thank you.

We'll now move on to our FDA participants.

First we have Dr. Anania.

(No response.)

DR. SEO: I apologize. It sounds like our review division team may be having some audio issues in the Great Room. It'll be just a moment while they resolve that.

(Pause.)

DR. ANANIA: Dr. Frank Anania, acting director, Division of Hepatology and Nutrition at FDA.

DR. SEO: Thank you.

Next, we have Dr. Mehta.

DR. MEHTA: Dr. Ruby Mehta, clinical team leader, Division of Hepatology and Nutrition.

DR. SEO: Thank you.

Dr. Hayashi?

DR. HAYASHI: Dr. Hayashi, drug-induced liver injury team lead, Division of Hepatology and Nutrition.

DR. SEO: Thank you.

Dr. Stewart?

DR. STEWART: Charmaine Stewart,

hepatologist in the Division of Hepatology and Nutrition, clinical reviewer.

DR. SEO: Thank you.

And Dr. Hager?

DR. HAGER: Rebecca Hager, statistical team leader, Office of Biostatistics.

DR. SEO: Thank you.

I'll return the floor to you, Dr. Lebwohl.

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 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, or FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, or SGEs, 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 new drug application, or NDA, 212833, obeticholic acid, or OCA, 25-milligram oral tablets, submitted by Intercept Pharmaceuticals, Incorporated, for the treatment of pre-cirrhotic liver fibrosis due to non-alcoholic steatohepatitis or NASH. This is a particular matters meeting during which specific matters related to Intercept Pharmaceuticals, Incorporated's 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, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Benjamin Lebwohl, David Assis, and Jacquelyn Maher. Dr. Lebwohl's waiver involves his investment holdings in a healthcare sector mutual fund. Dr. Assis' waiver involves his employer's research contract for a study funded by Intercept Pharmaceuticals, Incorporated, a party to the matter. Dr. Maher's waiver involves her investment holdings in a healthcare sector mutual fund and her employer's research contract for a study funded by Intercept Pharmaceuticals, Incorporated, a party to the matter.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees. 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 in 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 Dr. Helmut Albrecht is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Albrecht's role at this meeting is to represent industry in general and not any particular company. Dr. Albrecht is employed by H2A Associates, LLC.

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 committee of any financial relationships that they may have with the firm at issue. Thank you.

Dr. Lebwohl?

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

FDA Introductory Remarks - Ruby Mehta

DR. MEHTA: Thank you, Dr. Lebwohl.

Good morning to the advisory committee members, FDA colleagues, patient groups, applicant, and members of the audience. My name is Ruby Mehta, and I'm a clinical team leader in the Division of Hepatology and Nutrition.

On behalf of the agency, I would like to welcome you to the gastrointestinal diseases advisory committee meeting, where we will discuss the resubmission of new drug application for obeticholic acid for the treatment of adult patients with pre-cirrhotic liver fibrosis due to non-alcoholic steatohepatitis. I will now provide some brief opening remarks to begin our meeting.

For the remainder of the meeting, I will refer to obeticholic acid by the acronym OCA, non-alcoholic steatohepatitis as NASH, non-alcoholic fatty liver disease by the acronym NAFLD, and drug-induced liver injury by the acronym DILI. NASH is a severe form of NAFLD and and can be progressive. Histologically, NASH is characterized by the presence of fat, inflammation, and hepatocyte ballooning. NASH patients are at risk of progressing to fibrosis, cirrhosis, liver decompensation events, and may require liver transplant. Increasing fibrosis is associated with mortality. Liver-related outcomes occur at a higher rate in NASH subjects with advanced fibrosis or cirrhosis.

NAFLD and NASH progress slowly. NASH is associated with type 2 diabetes, dyslipidemia, hypertension, and obesity. Patients with NASH are more likely to die from cardiovascular disease or non-hepatic malignancy than from a liver-related event. In the United States, estimated prevalence of NASH is 17 million people, and of these,

6 to 8 million people are expected to have NASH with stage 2 or 3 fibrosis. Currently, there are no FDA-approved pharmacological treatments for NASH in the U.S., and NASH remains an unmet medical need.

OCA is a synthetic bile acid and a derivative of chenodeoxycholic acid and functions as agonists of farnesoid X receptor. The farnesoid X receptor is a nuclear receptor and regulates bile acid biosynthesis. It influences the metabolic pathways, including glucose and lipid regulation. OCA promotes cholesterol saturation in the bile, thereby promoting gallstone formation. In the diet-induced fatty liver disease mouse model, OCA-treated mice demonstrated improvement in liver inflammation and fibrosis.

The applicant has proposed the treatment indication as OCA for the treatment of adult patients with pre-cirrhotic liver fibrosis due to NASH. The proposed dosage regimen for which the applicant is seeking approval is OCA 25 milligram. The proposed approval pathway is accelerated

approval based on histological surrogate endpoint.

Switching gears, I will now discuss briefly the two regulatory pathways for drug approval. Traditional approval considers how a patient feels, functions, or survives, or it is based on a validated surrogate endpoint such as systolic blood pressure. Accelerated approval allows for earlier approval of drugs to fulfill an unmet medical need for a serious or life-threatening condition. Accelerated approval can be based on a surrogate endpoint. For this application, we will be discussing an accelerated approval pathway, and my colleague, Dr. Hager, will discuss a regulatory pathway in more detail.

In 2018, FDA posted a draft guidance for the industry developing drugs for treatment in non-cirrhotic NASH with liver fibrosis. FDA has accepted the following surrogate endpoints as reasonably likely to predict clinical benefit in NASH with stage 2 or 3 fibrosis, and these endpoints were prespecified in the phase 3 trial by the applicant. The first is improvement of

fibrosis by one or more stage and no worsening of NASH. The second is resolution of NASH and no worsening of fibrosis. An applicant can demonstrate efficacy on either or both endpoints to support an accelerated approval.

I will now provide a brief regulatory history of OCA intended to treat NASH. The opening IND was submitted in 2010 under which a phase 2, double-blind, placebo-controlled, randomized trial, also known as the FLINT trial, was conducted by the NASH Clinical Research Network. The trial enrolled a whole spectrum of the NASH population, including definite NASH and indeterminate NASH, and fibrosis stages ranging from 0 to 4. The primary endpoint differed from the ones discussed on the previous slide. Based on the efficacy results of the NASH trial, the applicant received breakthrough designation in January 2015. Breakthrough designation confers the advantage of obtaining intensive guidance for efficient drug development.

The phase 3 trial, which is the focus of today's discussion, was initiated in 2015. In June

2017, the FDA communicated a safety issue when a patient enrolled in the phase 2 trial died due to multiorgan failure soon after developing severe cholestatic liver injury. This led to a safety amendment in the phase 3 protocol. A stringent drug-induced liver injury algorithm requiring close monitoring and DILI evaluation, and triggers for treatment interruption and discontinuation, were prespecified. The safety amendment also allowed for drug discontinuation for liver decompensation and other safety issues; for example, intercurrent illness, were prespecified. In summary, there were challenges during the drug development program, requiring major protocol amendments.

The applicant submitted the new drug application in September 2019, seeking approval for the treatment of adult patients with pre-cirrhotic liver fibrosis due to NASH. Following the application review, the agency determined that the potential benefit of drug, based on assessment of surrogate endpoint, did not outweigh the risks. We issued a complete response letter. A complete

response letter is a regulatory document that notifies the applicant that the submission cannot be approved in its current form and describes the deficiencies identified during the review. I will now describe in the next two slides the reason for complete response.

Regarding the efficacy assessment for the original NDA review, OCA 25 milligram met the surrogate endpoint of one-stage reduction in fibrosis with no worsening of NASH. There was a statistically significant treatment difference between OCA 25 milligram relative to placebo of 11.1 percent. OCA 25 milligram failed to meet the second surrogate endpoint of NASH resolution with no worsening of fibrosis. OCA 10 milligram failed to meet either surrogate endpoint.

Safety concerns identified in the complete response letter that occurred in a greater number of OCA-treated subjects relative to placebo included: serious drug-induced liver as a result, including one case requiring liver transplant; cholelithiasis and related complications;

acceleration of conversion to diabetes or pre-diabetes in normal glycemic subjects and hastening of loss of glycemic control in diabetic subjects; worsening of LDL cholesterol that did not spontaneously resolve and required initiation or intensification of statin therapy; and pruritus requiring symptomatic treatment, treatment interruption, or OCA discontinuation.

In the complete response letter, the agency encouraged the applicant to complete the ongoing pivotal trial before resubmitting the NDA; that is to complete the clinical outcomes portion of the trial so that benefits could be weighed against the risks. However, because of the breakthrough designation and unmet medical need, FDA remained open to reviewing the current resubmission based on histopathologic endpoints or surrogate endpoint along with additional safety data.

FDA recommended reanalysis of histopathology utilizing the consensus read approach due to a high rate of pathologists' discordance in the original submission. You will hear from my colleague, Dr.

Hager, that the assessment of efficacy on histology has largely remained unchanged from the original submission. The safety data available in the resubmission now includes, one, safety information in additional subjects, and two, additional information on subjects included in the original submission. This additional safety information has resulted in more precise estimates of the risk concerns identified in the original submission.

Today we are asking your expert scientific advice regarding the benefits and risks of OCA 25 milligram for the treatment of NASH patients with stage 2 or 3 fibrosis. In your deliberations, we would like you to discuss some of the key topics listed here. Although OCA 25 milligram has modest efficacy on histopathology as a surrogate endpoint for the treatment of NASH with stage 2 or 3 fibrosis, the extent of clinical benefit is unknown.

Safety remains a major concern with serious risks associated with OCA 25-milligram use. One of the most concerning risks is DILI, which has a long

latency period, and then there are concerns surrounding the feasibility of mitigating DILI in clinical practice. You will hear a discussion of DILI from Dr. Hayashi. It is also important to consider how healthcare practitioners will manage additional safety concerns that will require additional monitoring and additional medical therapies.

Another challenge is to identify an appropriate subset of NASH population that is stage 2 or 3 fibrosis. Subjects with NASH cirrhosis should not be given OCA because OCA failed to demonstrate efficacy in NASH cirrhosis; therefore, there is no benefit with OCA treatment. Moreover, with increasing fibrosis, OCA-associated adverse events also increased, potentially related to higher intra-hepatic OCA exposure. Because of the unfavorable benefit-risk profile of OCA in cirrhotic NASH subjects, once OCA treatment is initiated, patients must undergo periodic assessment to detect progression to cirrhosis so that OCA can be discontinued in a timely manner

because there is no reasonable expectation of benefit that could be balanced against the potential risks.

Identifying the time point at which the patient transitions from a pre-cirrhotic stage 3 fibrosis to stage 4 fibrosis may be challenging. Non-invasive tests, or NITs, are available for use in clinical practice; however, NITs are not accurate in distinguishing between stage 3 fibrosis and cirrhosis. The benefit-risk profile of OCA 25 milligram in patients with NASH and stage 2 and 3 fibrosis still remains concerning.

Before I conclude my opening remarks, I would like to share the questions which we will be asking you to discuss this afternoon. I will go over them now, and Dr. Anania will present these questions again during the charge to the committee.

Discussion question 1. Discuss the strength of available efficacy data on the histopathologic endpoint, a surrogate endpoint that is reasonably likely to predict clinical benefit in NASH patients with stage 2 or 3 fibrosis treated with

OCA 25 milligram; 2) based on the data presented concerning cholestatic DILI in OCA-treated patients, discuss whether periodic liver enzyme monitoring could mitigate the risk of DILI; two, the frequency of such monitoring; and three, what stopping criteria should be developed to aid clinicians' decisions to discontinue treatment.

The next two questions are voting questions. 1) Given the available efficacy and safety data, do the benefits of OCA 25 milligram outweigh the risks in NASH patients with stage 2 or 3 fibrosis? Vote yes, no, or abstain; provide your rationale for your vote.

Second voting question; clinical outcome events in patients enrolled in Trial 747-303 will continue to be captured to evaluate clinical benefit in support of a future application for traditional approval. At present, which of the following would you recommend: A) approval of OCA 25 milligram at this time under the accelerated approval pathway, based on efficacy data on a histologic surrogate endpoint and available

clinical safety data; or B) defer approval until clinical outcome data from Trial 747-303 are submitted and reviewed, at which time the traditional approval pathway could be considered. Select either A, or B, or abstain. Provide the rationale for your vote.

Thank you for your attention. I will now turn the meeting back to Dr. Lebwohl to proceed with today's meeting.

DR. LEBWOHL: Thank you, Dr. Mehta.

Both the FDA 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 the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant,

including equity interests and those based on the outcome of the 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 Intercept Pharmaceuticals' presentation.

Applicant Presentation - Michelle Berrey

DR. BERREY: Good morning. My name is Dr. Michelle Berrey. I'm the chief medical officer and president of research and development at Intercept Pharmaceuticals, and I will introduce our obeticholic acid program this morning. Before we begin, I'd like to offer my sincere appreciation to the hundreds of clinical investigators, staff, and to the thousands of participating patients who have made OCA for NASH fibrosis program possible.

After my introduction, Dr. Kris Kowdley will

speak to the medical need; Dr. Rohit Loomba will address the use of non-invasive tests to diagnose and monitor NASH; Dr. Tom Capozza will provide an overview of the efficacy of OCA; Dr. Sangeeta Sawhney will review OCA's safety profile; and Dr. Arun Sanyal will provide his clinical perspective. Four additional experts will be available to address your questions. They have been compensated for their time, but have no financial interest in the outcome of this meeting.

We first evaluated obeticholic acid, OCA, in primary biliary cholangitis, a rare cholestatic liver disease. OCA is a synthetic bile acid and a potent FXR agonist with confirmed anti-fibrotic effect. In 2016, FDA granted OCA accelerated approval as Ocaliva in PBC, and it has been approved in over 40 countries. The 5- or 10-milligram dose is consistent with exposures achieved with 25 milligrams in NASH.

Ocaliva was initially indicated across the entire spectrum of PBC, including decompensated cirrhosis. In 2021, our label was updated after

hepatic safety events were reported in patients with advanced liver disease. We contraindicated patients with clinically significant portal hypertension or decompensation and added stopping rules to the label. We have since shown a significant decrease in the number of hepatic events reported. We have also been able to restrict prescribers to hepatologists and gastroenterologists who cared for patients with PBC.

We've accumulated more than 30,000 patient-years of experience in patients with PBC, and through that long-term, real-world experience, we have demonstrated improved transplant-free survival with OCA. Just prior to the PBC approval in 2016, the FLINT study in NASH reported out with the first evidence of an anti-fibrotic benefit in NASH, recognized by the FDA with breakthrough therapy designation. We worked closely with the FDA to design Study 303 as a single registrational trial in pre-cirrhotic NASH.

A second study, Study 304, was conducted in

patients with compensated cirrhosis due to NASH. Although the efficacy endpoint was not achieved, the safety from Study 304 is important, as there were no irreversible cases of liver injury in patients with cirrhosis taking OCA 25 milligrams. The combined programs in PBC and NASH have provided a robust safety database of 40,000 patient-years through clinical trials and postmarketing data.

Our proposed indication is for the treatment of adults with pre-cirrhotic liver fibrosis due to NASH, with a recommended oral dosage of 25 milligrams once daily. Patients with cirrhosis, portal hypertension, or hepatic decompensation are contraindicated.

OCA is not a perfect drug. It has safety concerns that require monitoring and management by specialists, hepatologists and gastroenterologists which we have recommended and successfully implemented in PBC. We propose non-invasive tests be used for patient identification for monitoring of safety and to identify patients with progression to cirrhosis. We have also proposed enhanced

pharmacovigilance and stopping rules for safety or disease progression, and will continue to work with the agency on details.

The goal of therapy in NASH is to prevent progression to cirrhosis. Continued progression of fibrosis results in cirrhosis, the natural history of the disease. An ideal anti-fibrotic response would show reversal of fibrosis by a full stage. This degree of change in fibrosis has resulted in lower rates of hepatic outcome events and mortality. Although these responses are correlated with improved outcomes, it is also clear that halting or stabilizing fibrosis is a success. A patient with stage 3 fibrosis who can remain at stage 3 without progressing to cirrhosis is a success.

Study 303 was designed together with the FDA to determine the proportion of subjects who can avoid progression to cirrhosis. The study has been fully enrolled since September 2019 and is anticipated to require at least another three years to accumulate the outcomes needed for full

approval.

The composite event endpoint that will determine if fewer patients on OCA 25 milligrams are progressing to cirrhosis is events driven. We anticipate a majority of this composite endpoint will be comprised of progression to cirrhosis on the month 48, or end of study biopsy, or by assessment of non-invasive tests.

In December 2018, FDA issued draft guidance for development of therapeutics for NASH. Fibrosis is considered the strongest predictor of adverse clinical outcomes, including all-cause and liver-related death. The ultimate goal of NASH treatment is too slow, halt, or reverse disease progression and improve clinical outcomes. Because of the slow progression of NASH and the time required to accrue clinical endpoints, the FDA recommends histologic improvements in liver biopsies as surrogate endpoints reasonably likely to predict clinical benefit.

The efficacy discussion today is focused on the 18-month liver biopsy. The prespecified

interim analysis population of 931 subjects agreed with the FDA. Improved fibrosis stage at month 18 is capturing those patients least likely to progress to cirrhosis, those with a reversal of disease, but does not capture those with halting or slowing of progression.

The month 18 interim analysis prespecified two alternate primary endpoints based on histology and an agreement with the agency. Importantly, study success required only one of these two primary endpoints to be met. The fibrosis primary endpoint assess the proportion of patients with an improvement of at least one full stage in fibrosis with no worsening of steatohepatitis, which was mandated by the FDA as no worsening in any of the three NAFLD activity score parameters.

I'd like to address three main topics highlighted by FDA, starting with the FDA's characterization of OCA's efficacy as modest with uncertainty regarding the translation to clinical outcomes. Although we have alignment that statistical significance can be discussed only for

the prespecified ITT old population of 931 patients, FDA's briefing book has included an 8.6 treatment effect from the post hoc ITT histology population who were included only for assessments of safety and outcomes.

FDA questions whether the 13 percent treatment difference on the primary fibrosis endpoint is clinically meaningful. The regulatory endpoint underestimates the clinical benefit observed in patients on OCA 25 milligrams. It requires a full-stage reversal of fibrosis without worsening of NASH within 18 months and excludes patients who were able to halt or stabilize disease progression. Non-invasive tests show improvements in hepatocellular injury in OCA patients without a full stage in fibrosis improvement on histology. Subjects receiving OCA 25 milligrams are providing evidence that we are achieving the goal of therapy to halt, slow, or reverse the progression of fibrosis.

The second issue we will address is hepatic safety. We have seen cases of liver injury in the

first 12 months after drug initiation. Two cases cited by the FDA as irreversible provide the basis of the 18-fold higher rate of events as a reason to not approve OCA for NASH. We will review our mitigation proposals, which likely would have avoided these two cases of hepatic injury.

As I illustrated earlier, Intercept has successfully implemented contraindications, monitoring paradigms, and ability to interrupt dosing of OCA in PBC with these same specialists, with a significant decrease in the rate of hepatic safety events. And finally, we believe that most gastroenterologists and hepatologists do have the expertise to monitor and manage disease progression and potential DILI.

The final issue for today, we believe appropriate patients can be identified for treatment with OCA using non-invasive tests. Multiple guidelines have now been published demonstrating the utility of non-invasive tests to identify and manage patients with fibrosis due to NASH without liver biopsy. Specific monitoring

implemented in Study 303 and proposed for labeling recommends visits at 1 month, every 3 months for the first 12 to 18 months of therapy, and every 6 months thereafter. Drug holidays would be mandatory for acute illness, hospitalizations, or investigations of potential liver injury. Stopping rules for permanent discontinuation would be mandated in patients with evidence of progression of disease by non-invasive tests or clinical signs and symptoms. We've seen the GI treating community successfully and safely adopt new treatment paradigms, which Dr. Sanyal will address.

Today, you will hear that OCA has demonstrated a positive benefit-risk that fulfills the requirements for accelerated approval. First, patients with pre-cirrhotic fibrosis due to NASH are facing a life-threatening disease with no available therapy that is able to be diagnosed and monitored using non-invasive tests. Second, OCA has demonstrated a clinically meaningful dose-dependent, anti-fibrotic benefit that has been confirmed by two independent biopsy reading

methodologies in Study 303. The regulatory primary endpoint underestimates benefit.

Third, we now know fibrosis stage is the single strongest predictor of liver-specific and all-cause mortality in individuals living with NASH. Thus, halting or reversing fibrosis are both reasonably likely to reduce outcomes. Study 303 is fully enrolled and progressing towards clinical outcomes. And finally, OCA's safety and tolerability are well characterized. Our proposed USPI provides guidance on patient monitoring with routine tests that would allow hepatologists and gastroenterologists to safely prescribe OCA.

I would now like to turn the presentation over to Dr. Kris Kowdley.

Applicant Presentation - Kris Kowdley

DR. KOWDLEY: Thank you, Dr. Berrey.

My name is Kris Kowdley. I'm director of the Liver Institute Northwest. I'm professor at Elson S. Floyd College of Medicine, Washington State University. I've conducted research and cared for patients with NASH for more than

25 years. I am being compensated for my time but have no financial interest in the outcome of this meeting.

NASH is a serious liver disease. As I will discuss shortly, there is high morbidity and mortality, and it is now the second leading cause of liver transplant in the United States. In addition, we know NASH is on the rise due to its associated comorbidities, including obesity and other cardiovascular risk factors. The estimated number of cases of NAFLD is expected to increase to 128 million by 2040, and similarly, the number of cases of NASH, the more serious form of NAFLD, is expected to increase to 39 million during the same time period.

NASH is a progressive disease. As shown in this figure, 30 percent of NAFLD patients progress to NASH, which affects 26 million Americans. As highlighted in yellow, stages 2 and 3 are indicative of clinically significant fibrosis, and 8 million Americans fall into this category. 2.5 million Americans will further progress to

stage 4 or cirrhosis. Once cirrhosis develops, there's an increased risk of liver cancer, risk of decompensation of liver disease, liver transplantation, and death.

Furthermore, the diagnosis of cirrhosis is accompanied with decreased quality of life, added stress due to the fear of cancer and complications, and functional impairment. Preventing progression to cirrhosis is therefore critically important, and patients with clinically significant fibrosis represent the optimum population for intervention.

It is now very clear that it is fibrosis stage, and not NASH, that predicts mortality and liver outcomes. This was shown in the landmark paper by Hagstrom, was confirmed in a recent large systematic review and meta-analysis by Ng, and more importantly in the prospective study of outcomes from the NASH Clinical Research Network. In the retrospective cohort study, we see a step-wise increase in overall mortality risk as fibrosis stage progresses from F0 to F1, F2 and F3, with a remarkably increased risk in patients with

F4 fibrosis or cirrhosis, shown in the black dotted line.

A recent meta-analysis by Taylor, et al. depicts the risk ratio for all-cause mortality on the left, liver-related mortality in the middle, and liver events on the right, comparing patients with F0 versus F2 in yellow, F0 versus F3 in red, and F0 versus F4 in black. All three risk categories increased by fibrosis stage; however, the increase is even more dramatic as patients move through each stage for liver-related mortality and events. This is largely due to liver-related risks becoming more frequent compared to cardiovascular risks in patients with F2 or higher fibrosis.

Even more compelling are prospective data from the NASH CRN, confirming the increased risk of decompensation and all-cause mortality by fibrosis stage of F2 or higher. Therefore, our treatment goal is to reverse or halt progression of clinically significant fibrosis; and we now have emerging data confirming that reversal of fibrosis reduces the rate of hepatic events and death.

Shown here is a combined analysis of over 1100 patients with compensated cirrhosis due to NASH from two large, randomized, placebo-controlled studies of investigational agents. Although these therapies were not effective, the data show the impact of fibrosis regression during the median 16 months of follow-up; 69 events occurred in patients without fibrosis improvement compared with only 2 events in patients whose fibrosis had improved. This represents a greater than 6-fold reduction in liver-related events and death.

As I previously discussed, we have known for some time that increasing fibrosis stage is associated with worsening outcomes, and more importantly, we now see that reversal of fibrosis stage is also associated with improvement in outcomes. As I mentioned, our goal is to intervene in patients with clinically significant fibrosis to prevent progression to cirrhosis by halting or reversing fibrosis stage. Unfortunately, 20 to 25 percent of patients with F3 fibrosis will progress rapidly to cirrhosis within 2 and a half

to 4 years without effective therapy. This would predict 23,000 deaths per year among those who have cirrhosis.

Despite the urgency of the unmet need in NASH, we currently have limited management options for our patients. Lifestyle modification aimed at weight loss is recommended as first-line therapy; however, very few patients successfully achieve the 10 percent weight loss needed to improve fibrosis. Bariatric surgery may be an option for individuals who meet criteria, but it is a major surgery with associated risks. Liver transplantation is an option of last resort; however, many patients are not candidates for transplant due to multiple comorbidities, and there is a high incidence of recurrence of NASH post-transplantation.

Finally, while some therapies such as GLP-1 analogs are currently being used in the absence of FDA-approved therapies, none have definitively been shown to reverse clinically significant fibrosis, which we know is the most important predictor of adverse liver outcomes.

In summary, clinically significant fibrosis leads to adverse liver outcomes. NASH alone without fibrosis is not associated with adverse liver outcomes. We now see that reversal of fibrosis improves outcomes; therefore, there is an urgent unmet need for an effective anti-fibrotic therapy that can reverse or halt progression of fibrosis in patients with NASH. If such a therapy were available today, it would meaningfully improve the lives of my patients. Thank you very much. I'd like to now hand off to Dr. Loomba.

Applicant Presentation - Rohit Loomba

DR. LOOMBA: Thank you, Dr. Kowdley.

I'm Rohit Loomba, director of NAFLD Research Center and professor of medicine at the University of California at San Diego. I'm being compensated for my time but have no financial interest in the outcome of this meeting. I will discuss the current practice guidance for non-invasive tests, also known as the NITs, and how they are already used in clinical practice. I will also discuss some new data addressing the specific question of

non-invasive identification of patients with pre-cirrhotic fibrosis due to NASH with high specificity.

NITs have been routinely used by hepatologists and gastroenterologists to risk-stratify patients for treatment, identify patients who have cirrhosis, and monitor disease progression. I serve on the AASLD Practice Guidance writing committee, and we recently updated the guidance on clinical assessment and management of NAFLD using NITs.

NITs are preferred over liver biopsy by both patients and their providers. They're easily accessible, and thus allow for serial or frequent monitoring. The AASLD practice guidance recommends a sequential NIT approach for risk stratification. For example, to identify low-risk patients who do not need referral or high-risk patients likely to have cirrhosis, we first use FIB-4, which is calculated using ALT, AST, platelets, and age. Specificity is increased with the use of a second NIT such as a transient elastography on a Fibroscan

machine or a blood test called ELF. This allows us to appropriately risk-stratify our patients at either low or high risk, leaving only a small number of patients who require additional testing such as MRE, MRI, or liver biopsy. This sequential NIT approach is also endorsed in guidelines published by several professional societies, including the AASLD, AACE, ACG, and the AGA.

I would now like to show you how an NIT-based algorithm can be applied to identify patients with stage 2 or stage 3 fibrosis within a population of patients with NASH across all stages of fibrosis, based upon a recent analysis. We believe that the population to which this NIT algorithm was applied includes the majority of patients suspected to have stage 2 or stage 3 fibrosis due to NASH. I will describe on the next slide the results of this analysis, which has been accepted for presentation at EASL and is based upon data from approximately 6,000 patients screened in two phase 3 studies.

As shown on the left, the approach requires

FIB-4 between 1.3 and 2.67, followed by either a Fibroscan or ELF, inclusive of the upper and lower bound cutoffs, as shown on the slide. Furthermore, patients with low platelets, low albumin, or a high conjugated bilirubin are excluded. This NIT algorithm has a high specificity of 91 percent for identifying stage 2 or stage 3 fibrosis, with a high positive predictive value. Of note, this approach enriches for patients with stage 3, which represents 65 percent of the identified patients. Thus, this algorithm can reliably identify patients with pre-cirrhotic fibrosis due to NASH.

As Dr. Kowdley showed you, fibrosis stage predicts mortality in patients with NASH when assessed by liver biopsy. Here we show that NITs such as FIB-4, ELF, and transient elastography are also independent predictors of mortality. This reinforces the utility of NITs in risk stratification and, once again, underscores the urgent need for treatment that can halt, reverse, or slow the progression of fibrosis due to NASH.

Thank you. I would now like to turn the

podium over to Dr. Tom Capozza. Thanks.

Applicant Presentation - Thomas Capozza

DR. CAPOZZA: Thank you, Dr. Loomba.

Good morning. My name is Tom Capozza. I'm a hepatologist and an executive director of clinical research at Intercept Pharmaceuticals, and I will present our efficacy data today. Our NASH clinical development program has shown treatment with OCA 25 milligrams result in clinically meaningful anti-fibrotic effects. This benefit was first established in FLINT, a phase 2 study, and now confirms twice in our pivotal phase 3 Study 303, using two different biopsy read methodologies.

The goal of therapy is to slow, halt, or reverse disease progression; as such, the regulatory primary fibrosis endpoint underestimates benefit. OCA 25 milligram not only meets the primary fibrosis endpoint of reversal at 18 months but also attenuates fibrosis progression, as well as improves non-invasive tests in patients with no change in fibrosis stage. This anti-fibrotic

effect is highly likely to lead to clinical benefit because we now know that liver fibrosis is the strongest predictor of clinical outcomes in NASH.

To set the stage for how efficacy was assessed, I'd like to review the NASH Clinical Research Network, or CRN, scoring system for evaluating biopsies. There are two major domains. On the left, the NAFLD activity score, or NAS, reflects the degree of steatohepatitis. The NAS is the sum of three parameters which create hepatic steatosis, lobular inflammation, and hepatocellular ballooning. On the right, the fibrosis score characterizes the degree of fibrosis and is based on a 5-point ordinal scale from 0 to 4. Stages 2 and 3 are consistent with what we are referring to as pre-cirrhotic fibrosis due to NASH.

Turning now to Study 303, eligible patients had to have biopsy confirms steatohepatitis and pre-cirrhotic fibrosis due to NASH with a fibrosis stage of 2 or 3 as scored by the central pathologist, and an NAFLD activity score of at least 4, with at least one point in each of the

three parameters to identify sufficient baseline steatohepatitis. In addition, there were several notable exclusion criteria, including significant weight fluctuations during the 3 months prior to study entry, a current or recent history of significant alcohol consumption, other known chronic liver disease or the presence of cirrhosis, and any recent history of a significant atherosclerosis cardiovascular event within one year of study entry.

Study 303 was fully enrolled in September 2019 and is an ongoing, randomized, double-blind, placebo-controlled study. The prespecified month 18 interim analysis for accelerated approval is shown in the gray box. Patients with NASH and fibrosis stage 2 or 3 were randomized in a 1 to 1 to 1 fashion to placebo, shown in dark gray, OCA 10 in light blue, or OCA 25 milligrams in teal green. The 25-milligram dose for Study 303 was carried forward based on the results from the phase 2 FLINT trial. The study treatment duration for the interim analysis was 18 months. The

clinical outcome portions of the trial are ongoing, as the study is event driven.

As presented by Dr. Berrey, the month 18 interim analysis prespecified two primary endpoints based on histology. In agreement with the FDA and consistent with their current draft guidance, study success required only one of these two primary endpoints be met. The fibrosis primary endpoint assessed the proportion of patients with an improvement by at least one full stage in fibrosis with no worsening in NASH, and as mandated by the FDA, was defined as no worsening in any of the three NAS parameters This definition is the most stringent interpretation of the regulatory fibrosis endpoint. The steatohepatitis primary endpoint reflects the proportion of patients with resolution of NASH with no worsening of fibrosis.

As I noted earlier, Study 303 is ongoing with the primary end-of-study endpoint a composite of clinical outcome events, including all-cause mortality, liver transplantation, hepatic decompensation, or any progression to cirrhosis.

Here we see the disposition for the 931 patients included in the original month 18 interim analysis, referred to as the ITT old population. This is the same population analyzed for both the original central read and the new consensus read. Placebo is shown on the left, OCA 10 in the middle, and OCA 25 milligrams on the right. The overall discontinuation rate was similar across the three treatment groups. A numerically greater number of OCA 25 treated patients discontinued due to an adverse event, while a greater number of those in placebo and OCA 10 withdrew consent. Of the original 931 who remained ongoing in the study, shown along the bottom, a small percentage discontinued treatment but agreed to remain in the study to be followed for clinical outcomes.

At baseline, patient characteristics, including age, sex, race, ethnicity, BMI, and the presence of type 2 diabetes, were balanced across the treatment groups. Baseline clinical characteristics were also balanced across the

treatment groups and are reflective of our target population for treatment. More than half of the patients were read as fibrosis stage 3, and as expected, there was a significant degree of NASH disease activity as shown by the NAS and liver biochemistries. As discussed by Dr. Loomba, transient elastography, FIB-4, and ELF are non-invasive biomarkers of fibrosis, and these were also consistent with our target population.

Turning to the month 18 interim analysis, scoring of the liver biopsies for the original NDA was performed centrally in a blinded manner by two pathologists with expertise in NASH. Concerns were raised about inter-reader discordance most evident on the NAS parameters, and this led to potential uncertainty with respect to the positive efficacy results. After subsequent discussions with the agency, it was agreed that Intercept would reread and reanalyze the same biopsies using a consensus method approach in alignment with the updated recommendations for NASH clinical trials.

Now, before I review our primary endpoint

results, I'd like to highlight a few key statistical considerations. The strategy to control for multiplicity for the prespecified month 18 interim analysis only applies to the original submission of 931 patients in the ITT old population using the central read methodology. The consensus read methodology confirms the efficacy results of the original reads; however, reported p-values are nominal, and the ITT histology population is only supportive, as it was not prespecified. Importantly, for all primary endpoint analyses, patients with missing biopsies were treated as non-responders.

Here are the results of the fibrosis primary endpoint from the month 18 interim analysis. The original central method is on the left and the consensus method is on the right. As you can see, the results of the two analyses are highly consistent. OCA 25 milligrams met the prespecified interim analysis primary endpoint for accelerated approval. We see a dose-dependent, anti-fibrotic response with both reading methods, with a

statistically significant p-value for the OCA 25-milligram group from the original central read, which was confirmed with the consensus read approach. Both analyses showed a doubling of the treatment effect for OCA 25 milligrams compared to placebo, with an 11-point to 12.8 percent treatment difference.

Looking at the steatohepatitis primary endpoint, the results are again consistent across both methods, where the proportion of responders in both OCA doses was numerically higher than placebo. However, the treatment effect from the original interim analysis was not statistically significant for OCA. Of note, I will only show the consensus method for histology results for the remainder of my presentation, as it is now the recommended approach for NASH clinical trials.

Here we show the anti-fibrotic benefit of OCA 25 milligram was generally consistent across key baseline demographics. As you can see, the point estimates for OCA 25 are all to the right of 1 for age sex, race, and ethnicity. Here, we show

the treatment effect was also seen across disease characteristics of note, such as BMI, diabetes status, and statin use. Overall, the response to OCA 25 milligrams was consistent across these subgroups.

Since fibrosis is the best predictor of clinical outcomes, I'd now like to review the fibrosis results of OCA 25 independent of NASH. For reference, the primary regulatory endpoint is on the left with missing biopsies considered non-responders. In the middle, for the same ITT old population now independent of NASH, 30 percent of patients achieved at least a full stage of improvement in fibrosis with a treatment difference of 14 percent, and on the right, in patients with biopsies available at both baseline and month 18, we see 37 percent of patients on OCA with improvement in fibrosis and a treatment difference of 17 percent.

Now let's look at the same patient shown on the right by fibrosis stage at baseline. For baseline fibrosis stage 2, the treatment difference

for OCA 25 milligrams is 11 percent. For baseline fibrosis stage 3, the treatment difference doubles to 22 percent. The treatment difference is particularly important because these patients are at the highest near-term risk of progression to cirrhosis.

Now, recall that the regulatory primary fibrosis endpoint only captures the reversal of fibrosis by at least one full stage; however, the goal of therapy in NASH is not only to reverse progression but also to slow or halt progression; therefore, a patient who stabilizes and does not progress towards cirrhosis is a success.

Shown here is the proportion of patients that did not progress on OCA. On the left, we see fewer patients who worsened the fibrosis stage on OCA 25 milligrams compared to placebo, indicative of halting of progression, and on the right, we see a greater proportion of patients with at least one full stage of improvement in fibrosis, indicative of reversal. Collectively, we see less progression and more reversal, again suggesting the

anti-fibrotic benefit of OCA 25 milligrams is underestimated by the primary regulatory endpoint.

Next, let's look at the group with no change in histologic fibrosis stage at month 18. As we would expect, after only 18 months, many of the patients with available biopsies at baseline and post-baseline remained in the same histologic fibrosis stage. With NITs, we see evidence of a benefit with OCA beyond histologic stage. Improvements in liver stiffness as measured by transient elastography are shown on the left and improvements in ALT are shown on the right. Despite being counted as non-responders in the regulatory primary fibrosis endpoint at month 18, more patients on OCA are moving in the right direction towards clinical benefit.

Turning back to the overall ITT old population, here we show the least squares mean change from baseline in liver stiffness. On the left at month 18, OCA 25 milligrams improved liver stiffness by an LS mean of 1.6 kilopascals compared to a 1 kilopascal worsening in placebo. On the

right at month 48, treatment with OCA 25 milligrams also shows improvement in liver stiffness, specifically by an LS mean reduction of 2.2 kilopascals. This dose-dependent trend of improvement in liver stiffness at month 18 and at month 48 is, again, supportive of OCA's anti-fibrotic activity.

Lastly, looking at ALT in the overall ITT population, at month 18 there is an LS mean reduction of 31 units per liter from baseline for OCA 25 milligrams, with a mean treatment difference of 17 units per liter over placebo, and at month 48, the pattern of ALT reduction is consistent. In addition, as shown in our briefing document, a similar pattern of reduction was observed for AST and GGT. Overall, this demonstrates an additional beneficial effect of OCA on hepatocellular injury at month 18 and at month 48.

In summary, we have shown a statistically significant anti-fibrotic effect for OCA 25 milligrams in the original analysis on a

stringent regulatory endpoint of fibrosis improvement by greater than or equal to one stage with no worsening in any of the NAFLD activity score components. A 12 to 13 percent treatment effect at month 18 was confirmed by the consensus method. This is clinically meaningful because fibrosis stage is the strongest predictor of clinical outcomes.

The regulatory primary fibrosis endpoint underestimates the overall benefit because in addition to reversing fibrosis, the goal of therapy is also to slow the progress of or halt disease progression. We have shown that fewer patients on OCA 25 milligrams have worsening of fibrosis stage at 18 months, and NITs suggest not only a positive impact on fibrosis, but also a positive impact on hepatocellular injury in patients with no change in fibrosis stage. The totality of data show a clear anti-fibrotic effect of OCA 25 milligrams, which is likely to predict clinical benefit.

I will now hand the presentation over to Dr. Sangeeta Sawhney. Thank you.

Applicant Presentation - Sangeeta Sawhney

DR. SAWHNEY: Good morning. I'm Dr. Sangeeta Sawhney, vice president for clinical development at Intercept Pharmaceuticals, and I will present our safety data. I will cover a description of the safety population, the overall safety profile for OCA, key safety topics as noted here, our risk management plan, and finally, an overall summary of our safety findings. Let's start with the safety population and the overall safety profile.

The safety population includes pooled data from 2,860 patients across three long-term, placebo-controlled studies in patients with pre-cirrhotic NASH and provides the most comprehensive assessment for safety. The ongoing Study 303, as seen on the left, contributes the majority of the patients with approximately 90 percent of safety exposure, and therefore we will present safety data from Study 303 in this presentation.

The new safety data set now has long-term

exposure up to 6 years, which presents a 3-fold increase since the original NDA submission. With a median exposure of 39 months and approximately 700 patients with four or more years of exposure to OCA, this data set allows an adequate characterization of OCA's safety profile.

Consistent with good pharmacovigilance practice, data for all adverse events is treatment emergent, meaning onset date after initiation of investigational product, referred to as IP, up to 30 days from last dose of IP. For cardiovascular events, data is presented for on-study, meaning with onset date after initiation of IP up to the data snapshot.

As Dr. Kowdley shared earlier, patients with NASH have many comorbidities related to metabolic syndrome. Consistent with this observation, 90 percent of patients in Study 303 met criteria for metabolic syndrome at baseline, which requires use of multiple concomitant medications. These are important when interpreting the safety findings.

Throughout my presentation, we will show

placebo data on the left, OCA 10 milligrams in the middle, and OCA 25 milligrams on the right. Type 2 diabetes, obesity, hypertension, and hypercholesterolemia are each reported in over half of all patients. In addition, 12 percent of patients reported the history of cardiac disorder and 20 percent reported a history of gallstones or renal disorder. Most patients across all treatment groups, including placebo, reported an adverse event as shown in the summary table. A higher proportion of patients in the OCA 25-milligram group experienced an adverse event, which led to discontinuation, which was mostly due to pruritus. Of note, these data reflect a median exposure of 39 months. I will cover serious adverse events and deaths in more detail shortly.

Pruritus is a well-characterized adverse drug reaction of OCA. The Study 303 protocol mandated IP discontinuation for grade 3 pruritus and, importantly, analyses for patient-reported outcomes showed similar scores in patients with or without pruritus, indicating that it did not

negatively impact quality of life.

Here we see the most frequently reported serious adverse events by system, organ, and class in preferred term, where the rate was higher in the OCA 25-milligram group compared to placebo. SAEs were reported in 22 percent of patients in the placebo group compared to 26 percent in the OCA 25-milligram group. The higher proportion of serious adverse events in the OCA 25-milligram group was related to acute kidney injury, cholecystitis, pruritus, UTI, and diabetes events, which I will cover in more detail later in the presentation.

Here are the adverse events leading to death summarized for on treatment plus 30 days. With approximately 8,000 patient-years of exposure, a total of 27 deaths were reported, including 8, 9, and 10 in the placebo, OCA 10-, and OCA 25-milligram groups, respectively. Of note, there was no clear treatment-related pattern for underlying etiology. Off-treatment adverse events leading to death, i.e., which occurred more than

30 days from last dose of IP, are shown here and, again, no clear treatment-related pattern for etiology was observed.

For the remainder of my presentation, I will focus on key safety topics. These events were selected based on OCA's mechanism of action, underlying comorbidities in patients with fibrosis due to NASH, as well as our prior experience with OCA in PBC. Before I review each safety topic in detail, I'd like to provide an overall snapshot for these events, focusing on risk difference between OCA 25 milligrams and placebo. Rates for each event are shown on the left with risk difference for OCA 25-milligram compared to placebo shown on the right. Pruritus, dyslipidemia, and gallstone-related events are the most common adverse event, and all three are described as an adverse drug reaction in our proposed label. No increase in risk was observed for hyperglycemia, urolithiases, or pancreatitis, based on the updated data. The FDA briefing document notes risk of dysglycemia with OCA, which I will review in detail

during my discussion of hyperglycemia events.

Adjudicated data are shown here for the three safety events for which detailed blinded independent adjudication committees were organized. Rates for hepatic cardiovascular and acute kidney injury events were low overall, but higher in the OCA 25-milligram group compared to placebo. I will describe our proposed risk management plan for these important events later in my presentation.

Turning now to our detailed review, I'll start with hepatic safety. As Dr. Berrey noted, Study 303 was initiated in late 2015. In 2017, a safety amendment was implemented following two serious hepatic events. One fatal event was reported in the long-term extension phase of Study 209, a phase 2 study which included patients with cirrhosis, and one event resulted in a liver transplant in a patient enrolled in Study 303.

Although not referenced in the FDA's briefing document, Intercept and FDA collaborated on a safety amendment based on standard clinical and lab criteria. This was implemented in

Study 303 and led to a marked decrease in potential hepatic safety events, especially severe events. Of note, 50 percent of patients in Study 303 were randomized after the 2017 amendment.

Here we see the protocol specified monitoring measures pre- and post-2017 amendment. In the post-amendment period, the protocol was revised to add instructions for patients and investigators to promptly recognize signs and symptoms suggestive of potential liver injury and specific thresholds for liver lab tests to monitor for potential injury. The drug was to be promptly interrupted if liver injury was suspected and permanently discontinued if a patient was found to have portal hypertension. This specific guidance allowed us to prospectively assess the impact of focused monitoring on the incidence of hepatic safety events. Importantly, the monitoring frequency used in Study 303 is also proposed in our label.

Before I review the adjudicated hepatic safety results, it is important to note three

points. All events were reviewed by the independent Hepatic Safety Adjudication Committee comprised of six DILI experts in a blinded manner following the DILI network methodology. DILI was defined as a liver injury caused by a medication or an herb, leading to abnormal liver tests or abnormal liver dysfunction with reasonable exclusion of other etiologies.

Each event was adjudicated for severity and relatedness to IP. Unlikely relatedness was defined as the probability of relationship to IP less than 24 percent, possible as 25 to 49 percent, probable as 50 to 74 percent, and highly likely as 75 to 100 percent. Of note, FDA's briefing document mentioned readjudication of the 12 cases in an unblinded manner.

It is important to characterize DILI in the setting of chronic progressive liver disease. Thresholds for fatal events based on Hy's law may not be meaningful or appropriate to assess DILI in the setting of chronic progressive liver disease. And lastly, considering that specific monitoring

for liver injury was only introduced with the 2017 amendment, the post-amendment, exposure-adjusted incidence rates are the most appropriate and inform our proposed label.

Turning now to the adjudicated results, here we show the impact of the 2017 safety amendment on adjudicated hepatic events. Data for patients with an adjudicated event pre-amendment are shown on the left and post-amendment on the right. As seen in this table, the pre-amendment period on the left included 400 patient-years of safety follow-up compared to more than 2300 patient-years of exposure in the post-amendment period.

As shown in the yellow box, following incorporation of the safety amendment, the incidence rate for moderate and higher severity, and more than possibly related adjudicated hepatic events in the OCA 25-milligram group, decreased from 1.5 pre-amendment to an exposure-adjusted incidence rate of 0.13 in the post-amendment period. This represents a 10-fold reduction in the exposure-adjusted incidence for patients with a

moderate or higher related event in the OCA 25-milligram group, a notable finding considering 5- to 6-fold increase in patient years of follow-up in the post-amendment period. All three cases in the OCA 25-milligram group post-amendment were reversible with interruption of OCA.

Now I would like to address the clinically significant moderate and higher severity and related cases described in the FDA's briefing document. This table shows 8 of the 12 cases readjudicated by the FDA in an unblinded manner in table 12 of the FDA's briefing document. The cases are in order of time to onset as shown in the last column.

In most cases, the Hepatic Safety Adjudication Committee and FDA's assessment for relatedness were consistent. In the three cases highlighted in yellow, the independent blinded assessment of relatedness by the Hepatic Safety Adjudication Committee was more conservative compared to FDA's unblinded assessment, reflecting the rigor of the blinded Hepatic Safety

Adjudication Committee, and no case was assessed as highly likely by either the Hepatic Safety Adjudication Committee or the FDA.

In the black outline is case number 1, a patient who underwent a liver transplant. This event occurred prior to the 2017 safety amendment, and was one of the two events I highlighted earlier as leading to the amendment. As you can see, potential liver injury events occurred within the first year of treatment, and this informed the monitoring guidance in our proposed label. Apart from the liver transplant which occurred pre-amendment, all of the seven other cases were reversible with interruption of OCA.

There were four late onset events shaded in yellow at the bottom of the table. All four of these events were gallstone related, with two each in the OCA 10 milligram and OCA 25 milligram. One fatal event of ascending cholangitis was reported in a 60-year-old female patient who had diabetes and cholelithiasis at baseline, and had been on OCA therapy for more than 18 months. Her month 18

liver biopsy showed progression to cirrhosis. Two months after her month 18 biopsy, she was hospitalized with acute right upper quadrant abdominal pain and elevated liver enzymes. An MRCP showed complete obstruction. Unfortunately, there was a prolonged delay of 3 to 4 days in addressing the acute obstruction via an ERCP, and OCA was not stopped during this hospitalization.

This review of the clinically significant hepatic cases leaves us with two serious events, one transplant in a patient prior to the 2017 amendment, which could have been mitigated with post-amendment guidance to promptly interrupt investigational product in acute illness, and one fatal case of ascending cholangitis in the OCA 25-milligram group, over more than 2000 patient-years of exposure. Our proposed label contraindicates initiating OCA in the setting of biliary obstruction and instructs prompt interruption of OCA in the setting of symptomatic gallstone disease, actions which will allow avoidance of adverse outcomes related to

gallstones. Further, evidence of progression to cirrhosis on the month 18 biopsy would have been another reason to permanently discontinue OCA in this patient per our proposed label.

Now turning to gallstone-related events, these are more common in patients with NASH compared to the general population, with 20 percent of patients reporting a history of gallstones and 25 percent of patients reporting a history of cholecystectomy. Cholelithiasis was the most common gallstone-related adverse event. 2.5 percent of patients in the OCA 25-milligram group reported a serious gallstone-related event, which was most commonly cholecystitis.

In OCA patients who underwent a cholecystectomy, OCA was safely resumed in the majority of cases, with no further adverse events related to gallstones. Importantly, the relative risk for gallstone-related adverse events with OCA 25 milligram versus placebo was similar in patients with known gallstones, no gallstones, or gallstone status not reported at baseline.

Here we see events related to pancreatitis. No difference was observed between OCA groups and placebo, including biliary pancreatitis. One fatal event of hemorrhagic pancreatitis resulting from a post-procedure complication of ERCP was reported in a placebo patient.

Now we will turn to cardiovascular safety. Considering the background risk for cardiovascular disease in this population, as well as the known effect of FXR agonism on lipids, a comprehensive assessment for cardiovascular safety, including adjudication of cardiovascular events, was performed. This comprehensive evaluation showed an initial increase in LDL and hemoglobin A1c, which attenuated over time. No changes in systolic blood pressure or heart rate were observed. Cardiovascular safety was further evaluated through rigorous assessment of independently adjudicated MACE, and no imbalance was observed in adjudicated MACE events between placebo and OCA groups. Based on these data, there is no clear signal for an excess cardiovascular risk with OCA. Labeling will

recommend that all patients are managed to target parameters for existing clinical guidelines.

After a transient increase with OCA at month 1, LDL levels decreased to near baseline levels by month 18, regardless of initiating a statin. Of note, more than 60 percent of patients had an LDL greater than 100 milligrams per deciliter at baseline, a threshold likely to require management with a lipid-lowering agent. In a separate analysis evaluating overall time averaged LDL over a median 39 months, a difference of 9 milligrams per deciliter was observed for the pooled OCA doses versus placebo.

Study 209 was a phase 2 study designed and conducted to evaluate the impact of adding lipid-lowering therapy to OCA. Data from the study is shown on the left panel. The increase in LDL with OCA was rapidly managed by addition of atorvastatin 10 milligrams daily at week 4 and LDL levels returned to below baseline levels within 4 weeks of adding atorvastatin. On the right panel, we see data for patients from Study 303 who

initiated a statin. Thirty-four percent of patients on OCA 25 milligram and 17 percent patients on placebo initiated a statin, which led to a decrease in LDL to baseline levels by month 12.

Now turning to hyperglycemia, rates for hyperglycemia adverse events were similar between OCA and placebo using a broad set of preferred terms. As shown here, the rate for clinically significant events of diabetic ketoacidosis were low and balanced, and no hyperosmolar event was reported. The serious cases of diabetes and diabetes inadequate control reflected patients with diabetes at baseline who were hospitalized for glycemic management.

Here we see the mean change in hemoglobin A1c for patients with baseline diabetes on the left, impaired glycemia at baseline in the middle, and normal glycemia at baseline on the right. After an early increase of 0.3 percent in hemoglobin A1c in patients with diabetes at baseline, as shown on the left panel, no clinically

significant difference was observed between the treatment groups over the 48-month follow-up period. In patients with impaired glucose control at baseline, in the middle, a mean increase in hemoglobin A1c of 0.1 percent was observed for the OCA 25-milligram group with no difference from placebo from month 18 and later time points.

As noted by FDA in its briefing document, the impact of this early transient treatment-related dysglycemia on the clinical course of patients is unknown. And finally, in patients with normal glucose control at baseline, on the far right, no difference was observed between the placebo and OCA groups.

We will now review data for cardiovascular events to inform any impact on cardiovascular outcomes. Here we see results for adjudicated MACE. A broad scope of triggers and all hospitalizations for potential cardiovascular events were reviewed by an independent cardiovascular committee. While the number of adjudicated events is small, a similar distribution

was observed between the placebo and OCA 25-milligram groups for core MACE, which included non-fatal MI, non-fatal stroke and cardiovascular death; 4-point MACE, which adds unstable angina; and 5-point MACE, which adds hospitalization for heart failure.

Now looking at MACE analyses stratified by 10-year atherosclerotic cardiovascular disease risk, as shown on the bottom panel, grades for MACE were higher in the higher risk strata as expected; however, there was no difference between the placebo and OCA groups.

Next, I will review renal events. Adjudicated acute kidney injury events were low overall and there was no clear signal for acute kidney injury. Given the background risk, labeling recommends monitoring of renal function.

I will now describe our overall recommendations for risk management, as well as our safety conclusions. Starting with our comprehensive risk management plan for hepatic safety, the first pillar is identifying the

appropriate patients for treatment. Patients with minimal fibrosis who are unlikely to benefit are excluded. Additionally, patients at higher risk for a hepatic safety event, as shown here, are contraindicated and, importantly, treatment with OCA will be restricted to gastroenterologists and hepatologists. We anticipate that 70 percent of the potential prescribers for NASH are the same GIs and hepatologists who are already known to us through our work in PBC.

The second pillar is rigorous education for both patients and prescribers. This will specify prompt interruption of OCA for any acute intercurrent illness or hospitalization; stopping rules for safety concerns or futility; and outreach through a specialty pharmacy.

The final pillar is to monitor and manage hepatic safety. Our proposed label recommends monitoring of liver tests at initiation of OCA at month 1 every 3 months for the first 18 months of treatment and every 6 months thereafter. I would now like to provide more detail about drug

interruption and stopping rules.

As shown on the left panel, our proposed label instructs prompt interruption of OCA for any acute intercurrent illness, hospitalization, signs and symptoms of hepatic impairment, or abnormal lab parameters, as noted here. This is common practice with numerous medications indicated for chronic use. On the right are stopping rules for permanent discontinuation of OCA based on safety as well as futility. OCA should be permanently discontinued for liver injury without alternate etiology, progression to cirrhosis, or clear evidence of worsening fibrosis.

We have three proofs of concept for this approach. First, our experience from the Study 303 2017 safety amendment, as discussed earlier; second, as Dr. Berrey mentioned, a separate study study, Study 304, was conducted in a more advanced population of more than 900 patients with compensated cirrhosis, and we saw no severe or irreversible hepatic safety event over the 18-month follow-up period; and third, when the PBC label was

updated in 2021 to contraindicate patients with more advanced cirrhosis, we saw the number of hepatic reports, including serious reports, decline. We are confident that the totality of these measures will help manage risk of hepatic safety events in the postmarket setting for NASH.

In terms of risk for gallstone-related events, the label contraindicates use of OCA in patients with symptomatic gallstone disease, as well as interruption of OCA during treatment in symptomatic gallstone-related events until managed, which is consistent with existing clinical guidelines. Given the comorbidities in this patient population, lipids, glycemic markers, and renal function should be managed for existing clinical guidelines.

We have also proposed additional measures, which have been successfully employed for PBC, which has more than 30,000 patient-years of exposure with OCA. These include prescribing by GI and hepatology practices who manage patients with chronic liver disease; education of these

prescribers; patient information and education; and finally, a specialty pharmacy network. In addition, we have also proposed enhanced pharmacovigilance activities for NASH, which include patient support programs, a website for safety information, and a patient registry, which will allow us to monitor safety of OCA in the postmarket setting. We look forward to collaborating with the FDA to continue to develop an effective and comprehensive risk mitigation plan.

In conclusion, OCA has a well-characterized safety profile based on large placebo - controlled, long-term exposure data. The profile is consistent with OCA's mechanism of action and background comorbidities in patients with NASH. Most of the observed events are known and commonly managed by gastroenterologists and hepatologists. Rigorous comprehensive assessments have shown that safety can be managed with existing practice guidelines. Thank you, and I will now turn the presentation to Dr. Arun Sanyal.

Applicant Presentation - Arun Sanyal

DR. SANYAL: Thank you.

Good morning. My name is Arun Sanyal. I'm a professor of medicine at VCU School of Medicine. Today, I would like to share my perspective, both as a clinician and as an investigator who has been treating and studying NASH for over two decades. I am being compensated for my time but have no financial interest in the outcome of today's meeting.

Let me start by speaking to the situation that I face in my clinic every day. I am seeing more and more patients with NASH present with clinically significant fibrosis. With only diet and lifestyle modifications and no approved therapies, they often progress to cirrhosis and eventually decompensate, necessitating evaluation for liver transplant. However, liver transplant is not an option for the majority of patients, underscoring the urgent need for therapeutics to prevent progression to cirrhosis and its associated complications.

Here is a typical patient example. This is a 55-year-old woman who I first saw in my clinic 10 years ago. She had a background history of diabetes, coronary artery disease, and heart failure. Despite multiple weight loss attempts, she had progressive increase in liver stiffness to about 14 kilopascals. We performed a liver biopsy that showed NASH with stage 3 fibrosis.

In the absence of approved therapies, I was left to wait and see how she would progress, knowing that she had a 25 percent likelihood of progressing to cirrhosis in 2 to 4 years. Unfortunately, two years later, almost on cue, she presented with thrombocytopenia, a further increase in liver stiffness to 25 kilopascals, and a decline in eGFR to 55. She had clearly progressed to cirrhosis, and given her comorbidities, would not be a great candidate for liver transplantation when she decompensates. Let's discuss what this means for the patient and also talked about missed opportunities for intervention.

As shown by Dr. Kowdley earlier, increasing

fibrosis stage is the strongest predictor of hepatic decompensation and all-cause mortality. Hepatic decompensation is the result of portal hypertension, which is linked to fibrosis burden. Now that my patient has cirrhosis, that is stage 4 fibrosis, she has a significantly higher risk of decompensation, and the risk of death has doubled even from when she had bridging F3 fibrosis. If an effective anti-fibrotic therapy had been available, I could have intervened earlier to reverse or halt the fibrosis progression to cirrhosis.

Let's review how OCA could have helped me accomplish this treatment goal. As shown on the left, OCA 25 milligrams doubled the likelihood of fibrosis reversal, using the primary regulatory endpoint analysis, where patients who missed the post-treatment biopsies were considered non-responders. Furthermore, when we look at patients who have both a baseline and month-18 biopsy available, as shown on the right, more than one-third of patients on OCA 25 milligrams had a one stage or greater improvement in fibrosis stage.

Just as importantly, fewer patients worsen fibrosis during the same time frame. And finally, as Dr. Capozza showed, in those patients who did not see a change in fibrosis stage, patients on OCA saw an improvement in non-invasive markers of liver injury and fibrosis compared to placebo.

I find these data compelling in their totality. Let's take a closer look at patients with stage 3 fibrosis who are arguably at the greatest risk of progression to cirrhosis. Nearly 40 percent of patients with stage 3 fibrosis experience a one stage or greater reversal of fibrosis, with a 22 percent placebo-corrected treatment effect. This is remarkable in a population that is one stage away from cirrhosis, and thus has the greatest unmet need.

Let me put this in clinical perspective. Progressive fibrosis leads to cirrhosis in NASH, as shown by the red line. The development of cirrhosis and eventual decompensation has a huge negative impact not only on the patient, but their caregivers and healthcare systems. My goal as a

hepatologist is to bend this fibrotic curve. The demonstration of fibrosis reversal by OCA provides proof that it indeed does bend this curve. Furthermore, the OCA-induced improvement in NITs, even in patients without a one-stage change in fibrosis, indicates that OCA stabilizes the underlying liver injury. It is then logical to expect that this, too, should translate into reduced fibrosis progression over the long term.

Having talked about the potential benefits of OCA, it is equally important to discuss the safe use and operationalization of this drug. Specifically, I would like to offer my perspective on some of the key issues raised by the FDA in their briefing document. Now, Dr. Loomba has already discussed patient selection, so I will focus on the remaining issues, starting with hepatotoxicity.

First, FDA's position is that frequent liver biochemistry testing can be challenging and will require lifelong monitoring. I would point out that NASH requires lifelong management regardless

of OCA. Furthermore, I see most patients with pre-cirrhotic fibrosis at 6-month intervals; however, if more frequent visits were needed, especially during the first few years of therapy, this would not be an issue. We routinely monitor their liver enzymes at every visit. This should easily allow us to identify asymptomatic elevations of liver chemistry.

The safety amendment provided guidance on monitoring and situations in which the drug must be held, such as when the liver chemistry criteria are met or during acute intercurrent illness. This resulted in a substantial reduction in liver-related safety events.

The FDA also noted that it is difficult to distinguish DILI from typical fluctuations in liver enzymes. While small fluctuations are common in patients with NASH, they rarely represent DILI. Clinically significant elevations in liver enzymes, bilirubin, and INR above the thresholds that Dr. Sawhney showed are more relevant and require discontinuation of all possibly offending drugs,

including OCA, until the etiology is determined. This is standard clinical practice and is a core competency of hepatologists and gastroenterologists.

Finally, liver biopsies are usually not required for the management of suspected DILI unless severe liver dysfunction persists, despite drug discontinuation. Together, these, with the multi-tiered monitoring approaches shown by Dr. Sawhney, should allow us to safely use OCA in appropriately selected patients.

Next, let us consider FDA concerns about monitoring for progression to cirrhosis. I respectfully disagree that a standard schedule is infeasible, as we routinely follow patients just as I noted. Assessment of progression towards cirrhosis is a core focus assessed at every visit for every chronic liver disease, and there are a variety of well-established tools for this process. Second, with respect to the ability of NITs to detect cirrhosis, NITs are used every day for this purpose and can be supplemented by selective use of

liver biopsy.

Finally, I agree that hepatology and gastroenterology subspecialty expertise will be required. Many new treatment paradigms require specific drug management strategies which have to be integrated into patient care and require new learnings. We have done this successfully before with education and training in similar scenarios that initially seemed challenging; for example, with testing for underlying hepatitis B and tuberculosis prior to initiating infliximab for IBD. We can certainly do this again.

Lastly, let me address the remaining three concerns. First, the majority of patients with NASH have multiple cardiometabolic comorbidities that are ideally managed in a multidisciplinary manner, requiring multiple medications for individual end-organ diseases as background therapy, regardless of OCA. The increase in LDL cholesterol can be abrogated safely with statins.

Second, patients with NASH already have an increased risk of gallstone disease, and we manage

this routinely every day. Those with symptomatic gallstones should have gallstone disease taken care of before initiating OCA therapy, and if symptomatic gallstones develop on therapy, the drug should be stopped and the patient considered for cholecystectomy, consistent with standard of care. Third, while patients do experience pruritus, it is generally mild and manageable. In my view, considering the range of adverse events I see every day while managing other chronic liver diseases, these adverse events are manageable.

In summary, we know the harm that will befall patients with increasing fibrosis, particularly with the development of cirrhosis. OCA has demonstrable anti-fibrotic benefit and is the first agent that can potentially prevent progression to cirrhosis, which could be life-saving for some. As with many new treatments, there are special monitoring considerations in order to minimize risks; however, these are well within the scope of routine GI hepatology practice and can be operationalized.

I would like to finish by sharing one final thought. Almost 30 years ago, when our clinics were filling up with patients with cirrhosis due to hepatitis C, interferon was approved as monotherapy with single-digit virologic response and a daunting side effect profile. This humble first step, however, led to progressive drug development for hepatitis C, culminating in a cure for virtually everyone.

Today, we stand on a similar critical threshold in time for our patients with NASH and clinically significant fibrosis for whom prevention of cirrhosis is literally a matter of life and death. OCA is the first agent that opens a window of opportunity to accomplish this, and we simply cannot wait any longer while outcomes data are being generated. It is time to put this in the hands of treating physicians so that we can make individualized risk- benefit assessments and decisions with our patients. Together, I believe these considerations provide a strong rationale for the accelerated approval of OCA now. Thank you,

and I will now turn the meeting back to the committee chair.

Clarifying Questions

DR. LEBWOHL: Thank you, Dr. Sanyal, and to all of those who participated in the applicant presentation.

We will now take clarifying questions for Intercept Pharmaceuticals. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again 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 your follow-up question with, "That's all for my questions," so we can move on to the next panel member.

I see Dr. Rakela has a question.

DR. RAKELA: Yes.

DR. LEBWOHL: If you could unmute.

DR. RAKELA: I have two questions. Have the investigators had the opportunity to demonstrate, with the measurements of hepatic with all the dynamic parameters, like wedged hepatic vein pressure did the decrease in one stage or more in fibrosis lead to a lower wedged hepatic vein pressure?

In follow-up to that, any EGD upper endoscopy demonstration that the size of varices changed that were present? Although that would be a criteria of exclusion, but if you have seen that in the clinical practice in the evaluation of these these patients?

DR. BERREY: Thank you, Dr. Rakela. That was not incorporated in this study in F2/F3 patients. We are accumulating clinical events, so any patient who did have progression of disease and was found to have varices, especially hospitalization for varices, would have been

captured as an event, but there were not routine measures to assess the new emergence of varices in this patient population. That's really focused more on our end-of-study accumulation of clinical events.

DR. LEBWOHL: Dr. Rakela, do you need any clarification or would that be it?

DR. RAKELA: I had a second question. Let me see. The second question is you have been showing that month 48, 48 months on treatment, that there's a significant drop in the ALT levels and other markers of [indiscernible] inflammatory changes in the patient. Have you had the opportunity or biopsies available that there is a change in the NAFLD score in those patients as well that you were not able to demonstrate earlier in 18-month biopsies, but in 48-month biopsies they're available.

DR. BERREY: Yes. We have been accumulating those month-48 biopsies; however, we were given strict instructions to remain focused on the month-18 interim analysis for this discussion today

because so many of the progression to cirrhosis clinical events we anticipate will be driven initially by the histologic progression to F4. So we have not begun looking at those month-48 biopsies, but as you point out, many of these patients who are now reaching year 4 are now undergoing those biopsies, so that is part of what we, again, would anticipate as part of our end-of-study analyses.

DR. RAKELA: Thank you.

DR. BERREY: Thank you.

DR. LEBWOHL: Dr. Czaja, please go ahead.

DR. CZAJA: Mark Czaja. Question for Dr. Capozza. I'd like to have some details on the histological results under the consensus method of the ITT old population, specifically what percentages were cases agreed upon by the two pathologists; what percentage had to go to the third pathologist; and what percentage had to go to the special committee?

DR. BERREY: Dr. Capozza?

DR. CAPOZZA: Thank you. In terms of the

number of cases that had to go on to a full panel, that was actually very small, in the single digits, less than 3 percent. The overwhelming majority of the cases in the consensus were agreed upon by the first two pathologists, and in only a small portion did they have to go on to the tiebreaker, and then, as I mentioned, on to the full panel review.

In terms of the agreement, we have done some analyses, and the overall agreement in the consensus approach, when we look at change in fibrosis stage, was approximately 56 percent, bordering on 60 percent, but that's the number that we can give you from the consensus read method.

DR. CZAJA: So that percentage applies to the two pathologists initially agreeing.

DR. CAPOZZA: Well, yes. It would apply to the two pathologists, although in that small percentage if you did go on to a full panel review, so that would be included in the near 60 percent agreement between them in terms of fibrosis shift.

DR. CZAJA: Thank you.

DR. LEBWOHL: Dr. Chang?

DR. CHANG: Thank you. Lin Chang. I had two questions. My first question was for Dr. Loomba on the slide, I think it was CC-38, about the sensitivity specificity of non-invasive tests. I know it's important to identify the proper patients for treatment and also to assess them over time.

I just wanted to know if you could comment on the fact that sensitivity is only 31 percent, although the specificity is 91 percent. Can you give some comments about the low sensitivity and using these non-invasive tests to identify the patients properly?

DR. LOOMBA: Thank you, Dr. Chang. We completely agree. This approach really identifies patients who are at highest risk for disease progression. So even among those who have histologic stage 2 or stage 3 fibrosis, this approach identifies the patients who have impending progression to cirrhosis; therefore, this would be the first group of patients who would be candidates for therapy. We agree there may be a much larger

and a much broader group of patients who could potentially benefit, but initially, utilizing such a conservative approach, we will only treat patients who would require this therapy and would have less likelihood of having earlier stages of fibrosis.

I would also like to point out that there are other consensus approaches that are available from Europe and other parts of the world, including the Baveno consensus, that may also allow us to identify patients who may have a sweet spot that is between 10 kilopascal to 15 kilopascal with a platelet count greater than 150. So this approach really identifies patients who have high specificity and have a low likelihood to have lower stages of disease.

DR. CHANG: Okay. Thank you.

My second question is for Dr. Sawhney, and I don't see the slide number based on the PDF that we have. But you identified these three main measures to interrupt drug treatment, but you didn't really state what's the guidance to restart the treatment.

Do you need to have improvement in all three areas and for some duration of time? I would imagine that would be an important aspect of clinical management.

DR. BERREY: Before Dr. Sawhney joins us, if I could just add, from the sponsor's perspective, following up on the question to Dr. Loomba, when we did look at that implementation of those proposed non-invasive test criteria, we've been able to identify a much smaller group in the U.S. of patients who have a diagnosis of NASH and who are currently under care under a hepatologist, or specialist, gastroenterologist practice. That number's around 700,000 patients.

So although we have recognized that the epidemiology nationwide is continuing to increase using this very specific, and as you point out, low sensitivity but high specificity, it does reduce the number of patients we would initially be targeting to around 700,000 in the U.S.

Dr. Sawhney?

DR. SAWHNEY: Yes. So you asked the

question about when to restart in case of -- if I could just have slide 1 up, please?

Just to clarify, I think your question is about the left-hand panel.

DR. CHANG: Right, yes.

DR. SAWHNEY: Correct. If a patient had any acute intercurrent illness, or signs of symptoms, or lab parameters, the instructions are that you interrupt drug; you assess and evaluate until those have resolved. And especially if you have increased lab parameters, the guidance is that you look for alternate etiologies, and if there is a reasonable alternate etiology, after resolution of that acute illness, or acute increase in the lab parameters, when there is resolution, then you can restart therapy. However, as indicated on the right side of the slide, if there is increase in those liver thresholds without alternate etiology, then the recommendation is to permanently discontinue therapy with OCA.

DR. CHANG: So there's no actual parameters on the duration and that there's normalization or

more details on the signs and symptoms. I just wanted to make sure that it was clear to physicians of when they could properly and safely restart treatment that's been interrupted.

DR. SAWHNEY: Right. So the proposed label will actually provide guidance on repeating those -- if a lab parameter was increased, he would repeat them depending on the level of increase, within 3 to 5 days, or if it was a less severe increase, within a week or 2 weeks. So the guidance is really based on you restart when there is complete resolution of any of those three parameters.

DR. CHANG: Thank you. I don't have any more questions.

DR. SAWHNEY: Thank you.

DR. LEBWOHL: Thank you.

Just as a reminder, panelists and sponsor, please state your name before speaking next. And also just keeping time, we only have about 10 minutes left for questions, so try to keep your questions and answers respectful of that.

Dr. Solga?

DR. SOLGA: It's Steve Solga. This is a question for Dr. Sanyal. Can he explain for me, please, the placebo effect seen during this trial? It appears that quite a number of participants regressed in their fibrosis stage 1 placebo.

I ask that because the narrative around this drug approval is one that NAFLD fatty liver is one of unrelenting progression -- this has come up over and over again during the presentations -- toward death, something like analogous to untreated hepatitis C or untreated cancer, but there's a lot of data in the universe that suggests that fatty liver is dynamic and can regress. In fact, the cover of CGH says this very thing. And Dr. Sanyal had a paper a year ago, which the sponsor's briefing packet mentioned, which was cited, I should say, in Hepatology May of '22, that demonstrated spontaneous regression apparently in the context of a clinical trial.

I'm wondering if these folks have been misclassified upon study entry, and that explains

the apparent regression or whether fatty liver natural history can indeed be bidirectional.

DR. SANYAL: Thank you, Dr. Solga. I think, first of all, we should acknowledge that the disease, particularly in its earlier stages, does wax and wane in severity, both in activity, as well as in fibrosis, so that's part of the story. But if you take a whole population as a whole, it is the integration of the progressions and the regressions that determine the overall trajectory. So when I said this is a disease that is progressive, that if you take the entire population over time, more and more people are progressing, as witnessed in our transplant waiting list.

Number two, in terms of your second question as to whether this is just biopsy variability and regression to the mean versus true waxing and waning, I suspect, and I can only hypothesize that the truth probably lies somewhere in the middle; that there is some natural waxing and waning of the disease, but there is no question that samples, biopsy size, pathology reading, and all of those

things do also impact variability in histological assessments. And that's why it is important to look at the placebo corrected response and not just at the response because that's the background noise that we have to account for in the tool that we're using to assess the histologic benefit. I hope that answers your question.

DR. SOLGA: Thank you.

DR. LEBWOHL: Dr. Heller?

DR. HELLER: Hi. Theo Heller; half a comment, then a question, and a question. I think we should be careful looking at fibrosis and all-cause mortality because this may be true and unrelated to implications that treating fibrosis will have some effect on that. It might just identify people who have rapid progressions in terms of the metabolic syndrome but not specifically for NASH. So the all-cause mortality I think is not quite as clear an issue.

My second comment to that question is looking at the decline in lipids and glucose, and given that this is a biological pathway, is there

tolerance? Do we know if the benefit is all upfront or if the benefit is sustained and continued? And aligned to that, with the ALT or AST being major things that we follow, I think non-invasive tests are very good. I agree with Dr. Loomba that this is a way to identify people who are most at risk, but what about NITs on therapy to identify progression? This is a question that's been raised; when patients develop cirrhosis it should be stopped.

The example of Dr. Sanyal is sort of a medical student level. Someone whose Fibroscan shoots up that much and platelets drop that much is easy, but most patients are more subtle, as we all know and as Dr. Solga implied. So my question is, have NITs been studied on therapy? Treatment will affect many of the components; for example, the lower ALT and AST but no change in fibrosis that we were shown in the talk. An alternative explanation for this discrepancy between NITs and biopsy would be that non-invasive tests don't always reflect disease progression because they're affected by

therapy itself. That's the end of my questions. Thank you.

DR. BERREY: Dr. Loomba?

DR. LOOMBA: Thank you, Dr. Heller. This is a really important question that every hepatologist and gastroenterologist faces in their clinical practice. I don't remember the last date when I did a liver biopsy to see if my patient has progressed to cirrhosis, so every hepatologist is using these tests in their clinical practice.

To that end, I would like to show slide BU-1264. This is in the latest 2023 AASLD NAFLD practice guidance, where a group of experts put together some clinical predictors or criteria that suggests a high specificity for a patient who may have cirrhosis or who may have progressed to cirrhosis. So these are available, such as FIB-4, ELF, VCTE, and MRE elastography to clinicians to see if their patient may have progressed to cirrhosis.

I would also like to show now slide BU-1494. Here, these are data to the left coming from

previously published randomized placebo-controlled trials in patients who had bridging fibrosis, and you can see that liver stiffness increased by 5 kilopascal, and a 20 percent increase predicts progression to cirrhosis in a patient who has stage 3 fibrosis; so a typical patient population that would be potentially treated if obeticholic acid were to be approved.

So you can pick by a 5 kilopascal rule. Now, you can say is that available to a practicing hepatologist? It is. If you look to the right, is the Baveno VII consensus, where the rule of 5 is already being practiced routinely in clinical practice. So if we think we target a patient population that's between 10 to 15 kilopascal, if there's a 5-kilopascal increase, that patient has progressed their disease and requires a reassessment, and potentially discontinuing therapy for a patient reaching 20 kilopascal on a FibroScan. So potentially with these, I think we may be able to monitor our patients who may be progressing.

I would also like to show slide, where we have --

DR. LEBWOHL: I'm sorry to interrupt, but we have a number of questions, and we're actually at the top of the hour. So what I'm going to ask is that we defer your next slide, and I'll ask the rest of the panel members, we're going to take five more minutes, short questions, short answers.

Dr. Coffey?

DR. LOOMBA: Thank you.

DR. COFFEY: Yes. Hi. Chris Coffey. My question is primarily for Dr. Capozza on CC-114. Just to get clarity, it was mentioned a couple of times that in addition to the primary endpoint showing benefit for improving fibrosis, that it also stabilized. But when I look at the graph on the right side, I don't see that; because if you combine the no change on the improved fibrosis, the differences for worsening are about the same. So it shifted those who, hypothetically under placebo, would not have improved but improved, but didn't necessarily lead to more stabilization. So I would

just ask for some clarity on that point that came up numerous times.

DR. CAPOZZA: Thank you. We do recognize that the word "stabilization" can mean different things, although we're suggesting that patients who have stabilized their disease, it's more of a lack of progression. So there is a small difference in the patients who have progressed by one stage, as shown on that table to the right where there is a shift in worsening in fibrosis, as you see going from right to left, with placebo at 23 percent and OCA at 17 percent.

In the middle, though, I think that's really where the question becomes this group of patients with no change in their histologic fibrosis stage at a month-18 biopsy, which direction are they headed in? And I think that is really where we tried to make the point that in this group of patients, there is evidence that patients on obeticholic acid are heading in the right direction, and those on placebo may not be heading in the right direction or at least are not changing

over time. So I think it's really about that group of patients in the middle and which direction they will head. And of course, ultimately, we need a third data point to see which way they go, and that would come in the month-48 biopsy.

DR. COFFEY: Thank you.

DR. LEBWOHL: Dr. Maher?

DR. MAHER: Jackie Maher, University of California San Francisco. I had a question for Dr. Sawhney.

Dr. Sawhney, you mentioned that in order to reduce any potential safety concerns regarding the medication, if it is approved, that you would restrict prescriptions to individuals who are under the care of gastroenterologists and hepatologists. I can see that that would be easy to operationalize for a disease such as PBC, but for a disease such as NAFLD, in which the patient population is quite large and there are a number of treating providers, I'm curious how you would operationalize that decision.

DR. SAWHNEY: Yes. That's a very important

question. As I showed earlier, the gastroenterologists and hepatologists that we anticipate will be the ones who take care of patients with NASH and would be potential users, prescribing OCA for NASH, we are familiar with them through our work with PBC and completely acknowledge that for NASH, which is a multidisciplinary team, we are very much committed to educating the NASH care team, which we recognize needs to be a multidisciplinary care team, including their primary care physicians, or especially those patients who have diabetes at baseline, working very closely with the endocrinologist or the primary care who might be managing their diabetes, as well as lipids, et cetera. So we strongly believe that we can, through appropriate education, educate the prescribers, as well as the patients on managing lipids and glycemic markers.

DR. MAHER: Thank you.

DR. LEBWOHL: Okay. I see that we do have more questions, but we are at time, so we will now

take a quick 10-minute break.

Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during this break. We will resume at 11:15 Eastern Time.

(Whereupon, at 11:05 a.m., a recess was taken, and meeting resumed at 11:15 a.m.)

DR. LEBWOHL: We will now proceed with the FDA presentations, starting with Dr. Rebecca Hager.

FDA Presentation - Rebecca Hager

DR. HAGER: Hello. My name is Dr. Rebecca Hager, and I'm a statistical team leader at the FDA. Today, I will discuss the regulatory framework and provide an overview of Study 303, including the key efficacy results from the interim analysis of surrogate endpoints. First, I will discuss the regulatory framework for today's discussion.

For a new drug to be approved for marketing in the United States, FDA must determine that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in

the product's labeling. The demonstration of effectiveness requires substantial evidence that the drug will have the effect it purports or is representative to have. Key for the discussion today is that the demonstration of safety requires showing that the benefits of the drug outweigh the risks.

It is important to understand the different types of outcomes and endpoints and how they relate to different regulatory pathways. A clinical outcome is an outcome that describes or reflects how an individual feels, functions, or survives. A clinical benefit is a positive therapeutic effect on this outcome that is clinically meaningful. The histologic measurements that we will be discussing today are not considered to be clinical outcomes.

A surrogate endpoint is a measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. A validated surrogate endpoint has been shown to predict a specific clinical benefit and can be used to support traditional approval. A surrogate endpoint

that is reasonably likely to predict clinical benefit has not reached the level of evidence needed to validate it. This type of endpoint can be used to support accelerated approval.

Currently, there are no validated surrogate endpoints for NASH. The reasonably likely surrogate endpoints that are discussed today were supported by epidemiologic rationale from the literature. As there are currently no approved drugs for NASH, we do not have data from interventional trials that can be used to understand the quantitative relationship between changes on the surrogate endpoint and changes in clinical outcomes.

Next, I will discuss different approval pathways. A traditional approval is based on a measurement of clinical benefit or an effect on a validated surrogate endpoint. Today, we are considering accelerated approval pathway, which is based on a drug's effect on a surrogate endpoint that is reasonably likely to predict a drug's clinical benefit. Drugs granted accelerated

approval must meet the same statutory standards for safety and effectiveness as those that are granted traditional approval.

Accelerated approval can provide patients with serious and life-threatening diseases access to new therapies sooner for conditions for which there is an unmet need for treatment. Because accelerated approval is based on the drug's effect on a surrogate endpoint, this accepts some additional uncertainty as a trade-off in providing earlier access to treatment. As a condition of the accelerated approval, FDA has required post-approval studies to verify and describe the drug's clinical benefit.

In summary, there are two different types of approvals, and we are considering accelerated approval today. We will discuss study results of surrogate endpoints that are reasonably likely to predict clinical benefit; therefore, there is less certainty that the observed treatment effect will translate into clinical benefit.

Now, I will discuss Study 303, which is the

primary basis of efficacy and safety that we are discussing today. As the applicant presented, Study 303 is an ongoing randomized, double-blind, placebo-controlled trial, which enrolled adult subjects with definite NASH. There was equal allocation to three treatment groups for OCA 25 milligrams, OCA 10 milligram, or matching placebo. Efficacy was evaluated in subjects with fibrosis stage 2 or stage 3, as defined by the NASH Clinical Research Network scoring system. There was a prespecified month-18 interim analysis of histological endpoints that was intended to support accelerated approval and is the focus of today's efficacy discussion.

This study is still ongoing to evaluate clinical outcomes, which are intended to support traditional approval; therefore, subjects from the interim analysis remain in the trial and additional subjects were enrolled. The month-48 and end-of-treatment biopsies are intended to evaluate progression to cirrhosis, which is a component of the clinical benefit endpoint. To maintain the

integrity of the ongoing trial, the endpoint assessing clinical benefit remains blinded.

As the applicant previously presented, this is the NASH CRN scoring system that was used to score histological assessments for inclusion in the study and for efficacy analyses. The month-18 interim analysis included two primary endpoints which were evaluated in subjects with fibrosis stage 2 or stage 3 at baseline. One primary endpoint is improvement of fibrosis and no worsening of NASH. The other primary endpoint is resolution of NASH and no worsening of fibrosis. These endpoints are considered by the agency to be surrogate endpoints that are reasonably likely to predict clinical benefit.

The final analysis of Study 303 will evaluate a clinical endpoint that is measured as the time to first occurrence of any of the listed adjudicated events, including death; MELD score greater than or equal to 15; liver transplant; hospitalization due to liver decompensation events; ascites; and histological progression to cirrhosis

according to the most recent version of the statistical analysis plan. This study is fully enrolled and ongoing to evaluate these outcomes. Once available, the final results that include these clinical outcomes could inform the benefit-risk assessment needed for a traditional approval.

The applicant prespecified a testing strategy to control the overall type 1 error rate when conducting multiple hypothesis tests for the month-18 interim analysis and the final analysis, the two different doses of OCA compared to placebo, and the two primary endpoints for the month-18 analysis. Details of this testing strategy are discussed in the FDA briefing package.

The the two month-18 primary endpoints were not co-primary endpoints, and demonstration of statistical significance on either endpoint was considered acceptable to support an accelerated approval. Because there was a complex strategy to account for multiple hypothesis tests, the p-values that are presented in the AC materials should not

be compared to a standard 0.05 threshold and the 95 percent confidence intervals cannot be used to determine statistical significance based on whether they rule out zero for a risk difference or 1 for an odds ratio.

We will present efficacy results for two different methods that were used for scoring the biopsy slides. The original NDA review focused on a central method in which a single pathologist's scores are used for each subject's efficacy assessment. The NDA resubmission focused on a consensus method in which at least two of three pathologists needed to agree on a score. The results, based on the consensus method, were included in the resubmission because FDA had concerns about the inter- and intra-reader concordance of the central method during the original NDA review. As you will see when we present the results, the method of reading the slides did not affect the overall efficacy conclusions.

The safety analysis population for this

study includes all randomized and treated subjects up to the data cutoff of December 31, 2021. There are two different efficacy analysis populations. The ITT old population was the prespecified efficacy analysis population for the month-18 interim analysis and included all fibrosis stage 2 or 3 subjects, according to the central read method, who were randomized by a specific time point and received at least one dose of investigational product. This data was the focus of the efficacy evaluation for the original NDA submission.

ITT histology is a second larger efficacy analysis population, which includes additional subjects who were expected to have the month-18 biopsy, according to protocol version 8 and earlier, but had this data collected after the cutoff for the prespecified month-18 interim analysis. Evaluations of all subjects in ITT old or all subjects in ITT histology maintain the full benefits of randomization in this blinded study, and we have confidence in the validity of

comparisons between treatment arms. Removing subjects from one of those analysis populations, based on post-treatment variables -- for example, those who did not complete the scheduled month-18 biopsy -- may lead to issues, including biased results.

When considering results of the efficacy analyses, statistical significance can only be discussed for the prespecified month-18 interim analysis of the ITT old population. ITT histology is a separate interim analysis that was not prespecified and not accounted for in the method to control the overall type 1 error rate; therefore, p-values and discussion of statistical significance are not applicable for ITT histology. Results are presented for ITT histology because of its larger sample size, which provides additional precision in the estimation of the treatment effect.

Now, I will discuss subject disposition and baseline histology characteristics. The briefing documents provide a summary of the subject demographics, and this table provides the

disposition of trial subjects in the safety population. The applicant presented some summaries for study discontinuation, and here we present summaries about study drug discontinuation. Per the protocol, subjects who discontinued study drug are encouraged to continue in the study until study termination. There was, overall, a high study drug discontinuation rate, with 40.5 percent of subjects discontinuing treatment in the OCA 25-milligram arm and 32.3 percent of subjects discontinuing treatment in the placebo arm. Additionally, there was a higher rate of treatment discontinuation due to adverse events in the OCA 25-milligram arm at 22.4 percent compared to the placebo arm at 12 percent.

This table presents baseline histology characteristics for the ITT histology efficacy analysis population. The first grouping of rows shows the baseline fibrosis stage as scored by the central method. Approximately 55 to 60 percent of subjects in ITT histology had stage 3 fibrosis at baseline according to the central method, with the

remainder having stage 2 fibrosis. When the slides for these same subjects were read by consensus method, some subjects were considered to not have fibrosis stage 2 or 3. FDA considers the consensus method a more accurate way to stage fibrosis, however, the central method may be closer to what is done when determining which patients to treat in clinical practice if a biopsy is required. This table shows that some patients chosen for treatment in practice may have stage 4 fibrosis, which is cirrhosis.

Next, I will present the efficacy results from the month-18 interim analysis of surrogate endpoints. Before I show the numeric results, here is an overview of the statistical conclusions from the month-18 interim analysis. First, the OCA 25-milligram arm demonstrated superiority to the placebo arm on one of the two primary endpoints, improvement of fibrosis and no worsening of NASH. The OCA 10-milligram arm failed to demonstrate superiority to the placebo arm on either of the two primary endpoints. Overall, the conclusions

regarding the treatment effect are consistent between each of the analyses using the two histology read methods and the two month-18 analysis populations. Lastly, I will reiterate that these month-18 primary endpoints are reasonably likely surrogate endpoints, so there is uncertainty about how the magnitude of changes observed on the surrogate endpoints may translate into meaningful changes in clinical outcomes.

Now, I will walk through the results for the month-18 primary endpoint of improvement of fibrosis and no worsening of NASH. To orient everyone to the table, I'm going to start by presenting the results from the ITT old population, which was the prespecified efficacy analysis population. Just over 300 subjects are in each treatment arm. The table shows two rows with results for the central method and the consensus method of reading the histological slides. The number and percentage of subjects who were responders on this endpoint are shown. Looking at the consensus read results, there was a

22.4 percent response rate in the OCA 25-milligram arm and a 9.6 percent response rate in the placebo arm.

Next, I have added columns to show the risk difference between each OCA dose arm compared to placebo. The risk difference is the percentage of responders in the OCA arm minus the percentage of responders in the placebo arm. Focusing on the results for the OCA 25-milligram arm compared to placebo, the point estimate of the risk difference was 11.1 percent by the central method and 12.8 percent by the consensus method. The asterisk in the tables denote the results that are statistically significant. The OCA 25-milligram arm demonstrated superiority to placebo for this endpoint, and the OCA 10-milligram arm failed to demonstrate superiority to placebo.

Next, I will go through the results for the ITT histology population. We can see the sample size for this population increases to just over 530 subjects per treatment arm. Looking at the percentage of responders, the results are generally

consistent with the results of the ITT old population. Lastly, I have added in the columns with the risk differences for the ITT histology population. Focusing on the comparison of the OCA 25-milligram arm to placebo, the risk difference in the ITT histology population is estimated to be 8.6 percent with a 95 percent confidence interval of 4.2 to 13 percent. Overall, evaluating this endpoint three different ways leads to point estimates of the risk difference for OCA 25-milligrams compared to placebo, ranging from 8.6 percent to 12.8 percent. As presented in the FDA briefing document, analyses evaluating subgroups of patients based on baseline factors such as baseline fibrosis stage resulted in generally consistent estimates of the risk difference for this primary endpoint.

Now, I will briefly cover the other month-18 primary endpoint, resolution of NASH and no worsening of fibrosis. For this month-18 primary endpoint, both OCA 25 milligrams and 10 milligrams failed to demonstrate superiority to placebo. I

will not go through the details of this table, but I will point out that the point estimates for the risk difference were in the range of 2.5 to 3.7 percent for both OCA dose arms when compared to placebo. When evaluating no worsening of fibrosis, regardless of resolution of NASH, the estimates for the risk difference were in the similar range as those presented here for the prespecified primary endpoint.

To revisit the summary of efficacy results, the OCA 25-milligram arm demonstrated superiority to placebo on one of the two month-18 primary endpoints, which was improvement of fibrosis and no worsening of NASH. The point estimates of the risk difference ranged from 8.6 percent to 12.8 percent. The OCA 25-milligram arm failed to demonstrate superiority to placebo on the other primary endpoint, resolution of NASH and no worsening of fibrosis. The OCA 10-milligram arm failed to demonstrate superiority to placebo on either of these two primary endpoints. Lastly, there is uncertainty in how the magnitude of change on a

surrogate endpoint may translate into meaningful changes on clinical outcomes. Clinical outcomes are still being assessed in this ongoing blinded trial with the intention to later support a traditional approval.

Dr. Paul Hayashi will now discuss drug-induced liver injury. Thank you.

FDA Presentation - Paul Hayashi

DR. HAYASHI: Thank you, Rebecca.

Hello. I'm Dr. Paul Hayashi. I'm the drug-induced liver injury team lead for DHN. I'll cover the predicted DILI fatality rate based on a lethal case associated with OCA; other cholestatic OCA-related cases in Study 303; and risk mitigation challenges.

I open with this slide because it goes directly to a key finding we wish to emphasize. FDA defines fatality here a death or liver transplant due to DILI. The bar graph provides the predicted DILI fatality rate per 100,000 for OCA and three other drugs. There's a dotted line near the bottom which marks a threshold of concern.

Since the early 2000s, the agency has used this threshold of greater than or equal to 3 per 100,000 to alert review divisions that there may be a DILI risk that threatens drug approvability. This threshold of concern was placed after several drugs were removed from the markets in the 1990s for DILI deaths, and three of those drugs are shown here: troglitazone, an oral anti-diabetes drug; ximelagatran, an oral anticoagulant; and bromfenac, a non-steroidal anti-inflammatory.

The predicted DILI fatality rates were determined retrospectively from premarket data after the drugs had shown unacceptable fatality rates postmarket -- hence, the threshold of concern -- which was based on these and other data analyzed at the time. Since this threshold has been put in place in the early 2000s, no drug has been removed from the U.S. market for fatal DILI, so the track record for this change has been good.

OCA's predicted fatality rate, which was set by the subject who required transplant, is 15- to 30-fold higher than the threshold and 6- to 13-fold

higher than the three drugs removed from the market. Of note, ximelagatran had a DILI fatality in its clinical trials which set the fatality rate shown. It was approved in 22 countries and removed from all 22 for fatal DILI. It never made it to the U.S. market.

The applicant made reference to Hy's law in hepatocellular DILI not applying to OCA cholestatic DILI, but this is irrelevant to the key point of this graph. The fundamental goal of DILI risk assessment is to prevent one primary outcome, death due to DILI, period, without stipulation on the DILI type. This is the fundamental goal because for the public, the healthcare system, the patient, the family, it will not matter which liver enzymes were leading that liver downhill.

UNOS does not use liver enzymes for transplant listing and enzymes are not part of the MELD score. In other words, a death due to cholestatic DILI carries the same weight as a death due to hepatocellular DILI. The agency sees no reason to have different fatality tolerances for

different types of DILI. So as we all assess OCA's risks and benefits, it's important to remember this context in which we deliberate, at least from a DILI perspective. This fatality rate also serves as an anchor point for our overall concerns about OCA liver injury; therefore much depends on this transplanted subject and we'll spend some time discussing him.

Subject 3 was a 63-year-old man with NASH and stage 2 fibrosis. He had no gallstone history. On day 1, he started OCA 25 milligrams. By day 129, he had the symptoms shown. On day 142, he self-discontinued OCA. On day 150, his total bilirubin was 26, alk-phos 399, and ALT 139. A liver biopsy suggested DILI versus bile duct obstruction. CT, MRI, and ultrasound showed a small dependent gallstone but otherwise unremarkable biliary system. The rash was pruritus related and felt associated with MRSA bacteremia.

Other evaluation testing for etiology of the liver failure did not reveal a cause, and he was listed for liver transplant with ascites and

hepatic encephalopathy. By day 164, bacteremia had resolved with negative blood cultures, and he was discharged to home. By day 164, he was discharged, and on day 175 with a MELD of 31 and total bilirubin 28.5. On day 187, he was readmitted and transplanted at a MELD of 39 and total bilirubin 28.9.

The differential for acute cholestatic liver injury with jaundice is not that long. Most cases are explained by bile duct obstruction, cholestasis of sepsis, DILI, and infiltrating diseases. Bile duct obstruction was ruled out by three imaging modalities. Ducts dilate in acute obstruction when the bilirubin rises to 15 or 20. It would be highly unusual to not have duct dilation. ERCP was not done even though the need to know about the bile duct is high for transplant evaluation, so presumably, the transplant team felt the ducts were clear by imaging. Moreover, transplant surgeons do a careful direct examination of the bile ducts of the biliary system before liver removal and implantation, and there was no mention of biliary

issues. So with bile duct obstruction being unlikely, DILI rose significantly on the differential based on pre-transplant liver histology.

What about cholestasis of sepsis? While this may have contributed to his illness early, his liver failure worsened even after the infection had resolved, and he was discharged with a MELD of 31. He was admitted 12 days later with a MELD of 39 and got transplanted the same day, suggesting he was called in and was not infected, so ongoing sepsis is highly unlikely, and cholestasis sepsis is not an indication for transplant. Infiltrating diseases of the liver were ruled out by biopsy, and he was not cirrhotic, so acute-on-chronic liver failure and NASH progression do not fit.

Lastly, transplant evaluations are exhausted, and no non-DILI diagnosis was found, so the FDA concluded that other diagnoses had become unlikely by the time of transplant, leaving DILI as the most plausible explanation. But which drug? There were only two contenders considered by the

sponsor's Hepatic Safety Adjudication Committee, or HSAC, and the FDA, but the FDA felt diclofenac was much less likely compared to OCA.

So why not diclofenac? When one is deciding between two drugs known to cause DILI, it comes down to two primary things, latency -- in other words, how long were patients on the drug before DILI occurs -- and the pattern of injury, cholestatic mixed hepatocellular. These two factors are essential in defining the signature for a particular DILI. OCA and diclofenac each have their own signature, and on both parameters, this case does not fit at all with diclofenac, and on both parameters it does fit with OCA.

The published graph shows the diclofenac experience of the U.S. Drug-Induced Liver Injury Network, or DILIN. Fifteen of the 16 cases occurred in less than 5 months from drug start and only one occurred in just over 6 months. In contrast, case 3 started diclofenac 11.6 months prior to DILI onset, making it a significant outlier on latency. The red color suggested all

the DILIN cases were hepatocellular. Case 3's injury was cholestatic.

Based on this case series and literature review done through the auspices of the National Library of Medicine, LiverTox concluded that the majority of cases present within 2 to 6 months, and the more severe cases tend to present earlier. The pattern of injury is almost exclusively hepatocellular, although cases presenting with mixed patterns have been reported. Case 3 was certainly severe, so anything of latency would be expected to be less than 5 months. No cholestatic cases were found in the literature by LiverTox. Indeed, if case 3 was fatal diclofenac liver injury, it would probably be reportable in the DILI's Team's opinion.

What about OCA? This published series of 8 cases of OCA liver injury in patients with PBC or PSC had a 210-day mean latency plus or minus 104. OCA latency was 150 days. All these acute injuries were cholestatic. Four patients needed transplant for acute-on-chronic liver failure. These data and

17 other reports to the FDA prompted the agency to restrict OCA from PBC patients with decompensated cirrhosis or with compensated cirrhosis and portal hypertension. So Case 3 fits well with OCA for both latency and injury pattern, while diclofenac is a remarkable outlier on both parameters.

With other non-DILI causes being unlikely and diclofenac's poor fit, the FDA concluded that this case was at least probable if not highly likely OCA hepatotoxicity, the same as our assessment in 2020. And as such, the DILI fatality rate was defined in this NDA just like it was for ximelagatran, which was shown in my first slide.

We also note that the sponsor's HSAC needed, quote, "considerable deliberations," end quote, as they debated between possible and probable. One reviewer wrote, quote, "Patient got both OCA and diclofenac and so have classified it as probable rather than definite. The patient clearly had DILI DILI." end quote.

So we surmise that they agreed at the higher end of possible while the FDA settled at a strong

probable. But still, was this case somehow spurious, a case of rare susceptibility never to be seen again, does it stand alone without similar cases? So we looked for non-fatal but jaundice DILI attributable to OCA. This is precisely what we do for a case of fatal hepatocellular DILI.

To start this search, we show a cholestatic scatter plot for 747-303. Post-baseline peak bilirubins are along the Y-axis and peak alk-phos levels along the X. OCA 25-milligram subjects are in blue, 10 milligrams in orange, and placebo in gray. There is a general shift in the active arms to the right and upper right compared to placebo, suggesting there is cholestasis and jaundice associated with OCA. The table counts for the right upper and lower quadrants confirmed there are more subjects with alk-phos twice normal with and without total bilirubin twice normal on OCA versus placebo. So there are data to suggest that OCA's associated with cholestasis, but is this imbalance truly due to DILI?

Next, we show the blinded assessments by the

HSAC of 361 liver injury events in 747-303. The HSAC reviewed each event and categorized them as highly likely, probable, possible, or unlikely DILI using the DILIN consensus method and blinded to study arm. On unblinding, there was an imbalance between 25 milligram and placebo arm, suggesting OCA was associated with the liver injuries.

Among 199 adjudicated events in patients who received OCA, 0.5 percent were judged as highly likely, 3.5 percent as probable, and 28.6 as possible DILI. In contrast, among patients who received placebo, none were judged as highly likely; only 0.6 and 6.8 percent were judged as probable or possible; and 92.6 percent were assessed as unlikely. But still, what was the clinical picture for these events? Were they like case 3?

Here, we show 12 cases of moderate-to-severe liver injury assessed as at least possible DILI by either the FDA or HSAC. Two to three FDA hepatologists were assigned each case and used the same DILIN scoring method as the HSAC. There are

several salient points on this table. First, the FDA and HSAC's consensus scores were similar. Second, the median latency was long, at 370 days, with a range of 28 to 912 days. Third, the R-value, which is the ratio of the ALT to alk-phos elevation suggest a cholestatic injury. An R-value of less than or equal to 2 is considered cholestatic.

Here, the median was 0.9. Indeed, only 2 of the 12 were not cholestatic. All but one subject was jaundiced and five had bilirubin levels over 10. In particular, the subject on line 2 had a bilirubin rise to nearly 20 without gallstone disease and was considered probable DILI by both the FDA and the HSAC. So there were other cases of cholestatic DILI with severe jaundice, suggesting that case 3 did not represent a spurious event.

Lastly, the four cases of gallstones as alternate diagnoses had the longest latencies, 461 to 912 days; yet all four were still considered possible DILI by the FDA or the HSAC. I ask you to remember these four because we'll come back to them

as we address risk mitigation, and we mitigate this risk.

We see three major challenges. I've mentioned the long latency, but we want to discuss the possible explanation for some of these long latencies. There are data suggesting that the frequency of liver enzyme testing would need to be more frequent than monthly, and the actions needed for elevation in liver tests may be complex.

To understand why the latencies may be long, we first show the data regarding a DILI dose response. Here again are the HSAC assessments of liver injuries in 303. We showed you the 25-milligram and placebo arms before, but here we added in the 10-milligram arm. There are rising percentages of probable and possible DILI from 10 milligrams to 25, suggesting an increased DILI risk with higher OCA exposure.

The second part of explaining the long latency involves gallstones. My colleague, Dr. Stewart, will show you that there was an increased risk of cholelithiasis and its

complications with OCA versus placebo. Here, we show a study suggesting that induction of fibrosis growth factor, or FGF-19, and increased cholesterol saturation index may explain the OCA-associated gallstones.

Twenty patients awaiting elective cholecystectomy for gallstones were randomized to 25 milligrams OCA or placebo for 3 weeks prior to surgery. Several tissues, serum, and bile samples were collected at the time of surgery. The cholesterol saturation index and gallbladder FGF-19 expression were increased with OCA compared to placebo. FGF-19 has been associated with gallbladder relaxation and mucin formation in the GI tract. All these factors would favor gallstone formation.

So what does this have to do with DILI? Here, we show the interaction of OCA liver injury pathways and how it may explain some of the long latencies. The OCA gallstone formation may take months to years. Over time, some will have biliary compromise, which will then lead to increased OCA

exposure in the liver. Why? Because biliary excretion is OCA's primary route of exit.

This rise in OCA exposure, even if intermittent, would then increase the risk of OCA DILI, thus explaining some of the long latencies. And if you recall, the four possible moderate-to-severe DILI cases with the longest latencies all had gallstones, with 3 of those 4 having documented biliary obstruction. Therefore, this pathophysiology is plausible, may explain the long latency, and would support the need for long-term surveillance. Of note, fibrosis progression may also increase hepatic OCA exposure and DILI risk.

There is one particular subject that may support this long latency interaction between gallstones and DILI risk. Subject 1 was not cirrhotic at baseline and had no gallstones history. She started OCA, and by day 444, she needed a laparoscopic cholecystectomy for new gallstones. Surgery was uneventful, but by day 461, she was jaundice and OCA was stopped. ERCP showed no leak, sludge was removed, and a

stent placed; however, her bilirubin continued to rise. Another ERCP 4 days later was normal. A serum OCA concentration happened to have been drawn that day. It was 3,950 nanograms per ml.

On the right, you see the mean Cmax OCA concentration by dose and fibrosis in the hepatic impairment study. Subject 1's OCA concentration is 1.8-fold higher than the maximum seen in the 8 subjects with F4 fibrosis, suggesting that the biliary obstruction may have led to increased OCA exposure and concurrent DILI that led to the increased bilirubin despite successful therapeutic ERCP. The HSAC and the FDA deemed this case as possible DILI.

The right panel also raises the concern that DILI risk will increase via increased OCA exposure for patients developing increasing fibrosis and cirrhosis. These data suggest that the intra-hepatic OCA levels also tend to increase with increasing fibrosis when given the 25-milligram dose, which, as I said, would increase the risk of DILI.

Moving on, how frequently would liver tests be needed? This is different from latency, which is the drug start to DILI onset. Here, we are trying to capture the pace of the DILI onset regardless of latency, so we show the interval between last prior liver tests and DILI onset in red font for the 5 subjects with at least possible DILI in the five highest peak bilirubin levels, shown in the far-right column. Arguably, these are the cases we would most want to capture early.

All five presented with jaundice and three had long intervals of 60 to 67 days, so not much help there. We just don't know the pace of injury in those cases. However, two had short intervals of 28 and 36 days between last stable labs and DILI onset, suggesting that testing would need to be done more frequently than monthly to capture these cases. Therefore, because OCA use for NASH is likely to go on for years, patients will need long-term surveillance with a high frequency of liver analyte checks.

In September 2017, Study 747-303's liver

safety protocol was tightened for DILI. The major changes are shown with a phone call every 2 weeks, labs every 6 weeks, and thresholds for repeat labs shown on the right. FDA is concerned about sustainability of such a plan over three or more years. There may be contact fatigue with a call every other week. The low threshold through repeat testing and complexity for the clinic staff may also take a toll on adherence. Even within the study, nearly 700 repeat labs that should have been done and verified were not. The protocol changes were tested only in a subset of 747-303, and effectiveness will be less in the larger postmarket population treated for years. We already discussed that rather than every 6 weeks, blood tests may need to be every 2 to 3 weeks, adding to the burden of surveillance.

The applicant's data suggested the DILI rate went down after these protocol changes based on study level analysis; however, there were still remarkable clinically serious DILI cases that occurred. You have seen this table of

moderate-to-severe liver injuries already, but the cases that occurred before October 1, 2017 are now in lighter gray font, while cases occurring after the protocol changes are in bold black font.

The 6 of the 12 occurred after the protocol changes. The reason the applicant counted only 3 subjects with moderate-to-severe DILI after the protocol changes is that they did not include the 10-milligram arm, which had an additional 3 cases. In fact, in line 2, the case in line 2 was in the 10-milligram arm and had a DILI more than a year after the protocol changes. Per peak bilirubin was 19.9, and as I said before, both the FDA and HSAC felt that this was probable OCA liver injury. So even though the incident rate by patient-years declined, we remain concerned that clinically serious DILI may occur under the mitigation plans that mirror the 2017 protocol changes.

So I end where I started with some history. There were two primary lessons learned from troglitazone, which was one of the drugs removed from the market for fatal DILI. These lessons make

us take pause because they ring familiar as we assess risk mitigation for OCA. Number one, monitoring and recommendations may not be well followed by physicians, even after warning letters are sent to all practicing physicians. Of note, the risk of troglitazone injuries span about 2 years, similar to OCA. Number 2, some cases of severe hepatotoxicity occur rapidly within less than a reasonable and practical recommended interval for monitoring, indicating that monitoring would provide, at best, only partial protection, even if recommendations were followed.

In sum, the DILI fatality rate for OCA 25 milligrams is well above that of drugs removed from the market or not approved because of fatal DILI. There are other cholestatic DILI cases with severe jaundice in 747-303 that suggests the fatal case was not spurious. FDA is concerned about adherence decay for risk mitigation over long surveillance periods, with frequent and multiple types of testing, frequent phone calls, and complex action plans in the larger community setting.

Now my colleague, Dr. Stewart, will speak about other safety issues. Thank you.

FDA Presentation - Charmaine Stewart

DR. STEWART: Good morning. My name is Charmaine Stewart, and I'm the medical reviewer in the Division of Hepatology and Nutrition. Dr. Hayashi just reviewed drug-induced liver injury. I'll be discussing other important safety concerns for Trial 747-303. The discussion will focus on analyses for OCA 25 milligrams, the to-be-marketed dose, as OCA 10 milligrams did not demonstrate efficacy. In this presentation, I'll define the safety population, adverse events of special interest, AESI, and will conclude with a summary of the agency's safety findings.

The safety population of 747-303 differed somewhat from the efficacy population and consisted of 1,968 subjects from the original submission and an additional 509 subjects from this submission, for a total of 2,477 subjects. All 2,477 subjects had histologically proven NASH and had received at least one dose of the study drug. 827 subjects

were randomized to OCA 25 milligrams while 825 subjects were randomized to placebo. 825 were randomized to OCA 10 milligrams. The current submission includes approximately 3 times as many person-years of exposure as the original submission. The focus of this review will be the OCA 25-milligram treatment arm and its comparison to placebo.

Analyses of incident adverse events outcomes, that is first events, were estimated using incident rates, IR, for within-arm estimates and incident rate differences, IRD, for comparing OCA to placebo. The incident rates of an adverse event of interest was calculated by dividing the number of subjects who experienced the events by the total number of person-years of follow-up. The incident rate difference was calculated by taking the difference between the incident rate for OCA 25-milligrams and the incident rate for placebo.

Analyses of safety outcomes are summarized on the basis of two follow-up windows. Analyses of treatment-emergent adverse events,

TEAEs -- dyslipidemia, dysglycemia, and pruritus -- utilized and on-treatment analysis follow-up window. The on-treatment analysis was defined as a follow-up window, including the time from randomization to the earliest of 30 days after treatment discontinuation or last contact date. Analyses of cholelithiasis with associated complications were conducted using an on-study follow-up window, which included time from randomization on to the last available contact date.

In this portion of the presentation, I will focus on four adverse events of special interests, AESIs, cholelithiasis, dyslipidemia, dysglycemia, and pruritus. I will now discuss cholelithiasis and its complications.

Cholelithiasis, although expected in this population, occurred more frequently in the OCA-treated group. Complications defined by the applicant included ascending cholangitis, acute cholecystitis, perforation, and others. For gallbladder disease and related complications,

subjects randomized to OCA 25 milligrams experienced 2.5 events per hundred person-years, which was twice as many as placebo subjects, resulting in an incident rate difference of 1.2 events per 10 person-years.

To manage these complications, some subjects underwent additional procedures such as multiple endoscopic retrograde cholangiopancreatography, ERCPs, an endoscopic procedure to evaluate bile ducts and pancreatic ducts. Finally, as shown in the last line, twice as many cholecystectomies were performed in the OCA-treated subjects compared to placebo-treated subjects.

In summary, for every thousand patients treated with OCA 25 milligrams for one year, we would expect to observe 12 additional gallbladder disease and related complications, six additional cases of severe gallbladder disease and related complications, and eight additional cholecystectomies than would have been observed on placebo. These numbers would double if OCA treatment duration was continued for two years.

We will now discuss dyslipidemia. LDL cholesterol was the focus of this discussion, as this was the primary lipid abnormality observed with OCA use. Baseline LDL cholesterol was similar across treatment groups, with a third of subjects having high LDL cholesterol values, defined as 130 milligram per deciliter or greater at baseline. Also at baseline, approximately half of the subjects were on lipid-modifying therapy, primarily statins.

Lipid assessments were conducted during the trial at prespecified time intervals: baseline, month 1, every 3 months of the first 18 months, and then every 6 months thereafter. Alerts were sent to the site investigators when a subject's LDL cholesterol increased by 15 percent or greater over the subject's baseline. More importantly, sustained increases in LDL cholesterol occurred in 488 subjects treated with OCA compared to 204 subjects on placebo, which constitutes a more than 2-fold increase in the OCA treatment arm, yielding an increased rate difference of

33 subjects per hundred person-years with sustained elevations in LDL cholesterol.

Reflective of the increased rate of LDL cholesterol elevations was a greater need for initiation and intensification of lipid-lowering therapy. All subjects not on statins at baseline, roughly 60 percent of subjects randomized to OCA 25 milligrams, required initiation of statin therapy, which was about twice as much as placebo subjects. In addition, 20 percent of OCA 25-milligram subjects that were on statins at baseline required either an increase in their statin dose or were switched to a statin of higher intensity such as rosuvastatin. This was almost twice as high as placebo subjects.

The graph shown here plots the mean LDL cholesterol over time for all three treatment groups. Means of the OCA 25-milligram treatment group is shown on the blue line and the placebo group means on the green line. At baseline, all three groups have similar mean LDL cholesterol. After 4 weeks, the earliest assessment of LDL

cholesterol on treatment, subjects randomized to OCA 25 milligrams had an increase of LDL cholesterol, on average, 24 milligrams per deciliter. In contrast, the subjects in the placebo-treated group had a slight decrease in LDL cholesterol.

Over time, LDL cholesterol in OCA-treated subjects declined, which was temporally associated with initiation of statin therapy; however, despite the prespecified approach for monitoring and initiation or intensification of statin therapy, the mean LDL cholesterol in the OCA-treated arm remained higher than placebo at month 18, an absolute mean difference of 10 milligram per deciliter and at month 48, an absolute difference of 6 milligram per deciliter.

In conclusion, subjects treated with OCA had higher sustained LDL cholesterol serum concentrations after initiation of OCA, which triggered initiation or intensification of lipid-modifying therapy from early statins. Despite additional lipid therapy, the mean LDL

cholesterol remained higher in the OCA-treated group as compared with the placebo group.

We will now turn our attention to dysglycemia. Dysglycemia is a common comorbidity in patients with NASH. Not surprisingly, more 4 out of 5 subjects had diabetes or pre-diabetes at the time of enrollment in 747-303. Enrollment criteria permitted inclusion of subjects with type 2 diabetes with hemoglobin A1c below 9.5 percent.

Dosages of diabetes medications were to be stable for 3 months prior to study day 1. Fasting plasma glucose and hemoglobin A1c were calculated at month 1, month 3, then every 3 months for 18 months, and every 6 months thereafter. Glucose elevations in type 2 diabetes were managed by individual site investigators according to the ADA guidelines. Safety monitoring included collecting adverse events related to hyperglycemia.

To assess potential OCA effects on glycemic parameters, FDA analyzed fasting plasma glucose and hemoglobin A1c during treatment by baseline

diabetes status. For subjects with normal glycemia at baseline, OCA was found to decrease the median time to incident pre-diabetes by approximately 9 months compared to placebo and 3 months for OCA subjects compared to 12 months for placebo subjects.

At 36 months, many in both treatment groups had progressed to pre-diabetes with 86 percent of OCA subjects and 79 percent of placebo subjects classified as pre-diabetic. For subjects categorized as pre-diabetic at baseline, at 3 months, 21 percent of OCA-treated subjects and 11 percent of placebo-treated subjects met the diagnostic criteria for type 2 diabetes. At 36 months, the observed imbalance persisted with 44 percent of OCA-treated subjects and 35 percent of placebo-treated subjects becoming diabetic.

Among subjects who had type 2 diabetes at the time of enrollment in the initial trial, OCA decreased the median time to clinically worsening of glycemic control by 2 months compared to placebo. At 36 months, the majority of both

treatment groups experienced glycemic deterioration, 88 percent of OCA subjects and 84 percent of placebo subjects.

In summary, OCA 25 milligram accelerated conversion to incident diabetes and pre-diabetes and hastened loss of glycemic control in diabetic subjects. The impact of OCA-related dysglycemia on the clinical course of NASH subjects is unknown because there is not a known cause of mechanism underlying the hypoglycemia.

Finally, I will review pruritus. The applicant prespecified the severity grading of pruritus, as well as the interventions to manage pruritus. Grade 1 was mild or localized pruritus and was managed with topical therapies. Grade 2 pruritus was more intense or widespread, intermittent with skin changes due to scratching. Grade 3 and higher grades of pruritus resulted in study drug discontinuation.

Pruritus was the most common adverse event. All grades of pruritus occurred more frequently in the OCA arm compared with placebo. The incident

rates of pruritus were 36.5 in OCA 25 milligrams and 10.2 in the placebo arm. The incident rate difference was 26.3 with a 95 percent confidence interval of 22.7 to 29.8. The incidence of severe pruritus, which required drug discontinuation, was 2.3 events per hundred person-years in the OCA 25-milligram arm. This was 20-fold higher than the placebo group.

The increased incidence and severity of pruritus due to OCA can be characterized by the higher rate of treatment discontinuations, treatment interruptions, and changes in dosing frequency, as well as the need for topical and systemic medications to manage pruritic symptoms in the OCA arm. As is shown in this table in the lower portion of the table, more than a third of subjects in the OCA 25-milligram arm who had been categorized as less severe, grade 2 or less pruritus, required additional medications to manage pruritic symptoms. In addition, although the protocol did not require drug discontinuation for grades 1 or 2 pruritus, 3 percent of subjects in

the OCA arm discontinued from the study, even when the severity of pruritus was not considered severe, that is grade 3.

In conclusion, OCA 25 milligram was associated with an increased risk of cholelithiasis, dyslipidemia, dysglycemia, and pruritus as compared with placebo treatment. Cholelithiasis was associated with increased morbidity, including an increased number of cholecystectomies, as well as an increase in the need for other interventions such as endoscopic retrograde cholangiopancreatography. Also, as previously discussed by Dr. Hayashi, cholelithiasis when associated with biliary duct obstruction may increase DILI risk.

OCA's effects on LDL cholesterol required initiation or intensification of statin therapy. OCA hastened the development of glucose intolerance, requiring earlier pharmacologic intervention to manage diabetes. More subjects taking OCA experienced treatment discontinuation and required additional therapies to manage

pruritus.

Thank you. At this time, my colleague, Dr. Mehta, will summarize the agency's presentation with an assessment of benefit-risk.

FDA Presentation - Ruby Mehta

DR. MEHTA: Thank you, Dr. Stewart.

To wrap up, I will provide a high-level summary of what we have learned from the original submission and what we have learned from this resubmission. In the original submission, efficacy was established for the surrogate endpoint of improvement of fibrosis and no worsening of NASH. Serious risks were identified from ongoing Trial 303, issues identified from 1,968 subjects with a total exposure of 2,395 person-years. Weighing these risks against modest treatment effect on a surrogate endpoint, the FDA initially concluded that the OCA was associated with an unfavorable benefit-risk profile.

In this resubmission, our assessment of efficacy has remained unchanged. In the assessment of risk, the larger safety database now includes

2,477 patients with almost 3-fold patient-years of exposure; thus providing a more precise estimate of the risks identified in the original submission. Our concerns regarding these safety risks also remain unchanged. Given these findings, FDA continues to believe that the benefit-risk profile of OCA 25 milligram remains concerning.

Revisiting the summary of efficacy that Dr. Hager presented earlier, the OCA 25-milligram arm demonstrated superiority to placebo on one of the two month-18 primary endpoints, which was improvement of fibrosis and no worsening of NASH. The estimated risk difference ranged from 8.6 percent to 12.8 percent. The OCA 25-milligram failed to demonstrate superiority to placebo on the other primary endpoint, resolution of NASH, and no worsening of fibrosis. The OCA 10-milligram arm failed to demonstrate superiority to placebo on either of the two endpoints.

To place in context a summary of the risks observed to date, if we treated a thousand patients with OCA 25 milligram for one year, that would

translate to approximately 2.4 additional DILI of moderate or greater severity and 11 additional patients with DILI of mild or greater severity, and to contextualize, a thousand patients treated for 2 years would approximately double these additional events. Similarly, about 280 events of pruritus were observed, and some of the patients had severe pruritus. This is a symptomatic patient-reported symptom, which is debilitating. About 200 additional patients with dyslipidemia, there will be additional cases of cholelithiasis and related complications, including cholecystectomy.

I will pause here for a moment to allow you to think if 6 to 8 million people are eligible to receive OCA and contextualize the safety concerns presented here.

(Pause.)

DR. MEHTA: I will now summarize factors important to the benefit-risk consideration of OCA 25 milligram and the clinical implications. There is modest efficacy of OCA 25 milligrams on the surrogate endpoint of one-stage improvement of

fibrosis with no worsening of NASH. There is uncertainty as to how these histopathologic responses may translate into clinical benefit for the patients because we do not have direct evidence to link these surrogates to clinical outcomes, and added uncertainty includes that OCA increases the incidence of dyslipidemia and hastens dysglycemia.

The primary driver for mortality in this population is related to cardiovascular events. Only a small subset of NASH population is expected to experience progression to cirrhosis, liver decompensation events, or liver transplant. The clinical benefit that is Trial 303 is still ongoing and collecting outcome data to demonstrate clinical benefit.

Moving on to the risk considerations, a clinical trial is the most optimistic setting to monitor and detect DILI. Even in this setting, DILI occurred in the phase 3 trial with serious consequences. The applicant's proposed frequency of laboratory assessment may not be sufficient to identify subjects who develop DILI, especially

given the long latency beyond one year. DILI was observed in the clinical trial subjects beyond year 1. If subjects are followed every 6 months after first year, it is possible that seriously DILI events are likely to be missed.

Cholelithiasis and its complications are associated with significant morbidity, need for hospitalizations, and additional procedures. Even after a cholecystectomy is performed, subjects are at risk of developing additional complications of bile duct obstruction, and as Dr. Hayashi noted, also increases the risk of DILI.

Dyslipidemia required initiation or intensification of statins in a greater number of OCA-treated subjects relative to placebo. OCA-treated subjects had more rapid progression to diabetes or pre-diabetes in normal glycemic subjects and acceleration of worsening of glycemic control in subjects for diabetes.

Pruritus can be a debilitating symptom with many patients requiring symptomatic treatment, or treatment interruption, or OCA discontinuation.

Additional medications required to manage dyslipidemia and pruritus can exacerbate the polypharmacy and potential for drug-drug interactions, as well as adverse effects associated with additional therapies. The substantial side effect profile of OCA, as demonstrated in the clinical trial, will require intensive management that goes beyond a single practicing gastroenterologist or hepatologist.

Moving on to treatment considerations, currently there are no biomarkers that can identify patients who progress to cirrhosis, especially if the patient is receiving OCA especially between stage 3 fibrosis and stage 4 fibrosis. Cirrhotic patients should not receive OCA because it lacks efficacy, and there is no reasonable expectation of benefit, and it only exposes the patient to OCA-associated risks.

Non-invasive tests, or NITs, can be used in the clinical settings, but they lack accuracy to distinguish between non-cirrhotic fibrosis and early cirrhosis; that is cirrhosis in the absence

of clinical signs, or symptoms, or radiological evidence. Therefore, it will be challenging to avoid treatment of cirrhotic patients in a clinical practice.

This is the conclusion of FDA's presentation. Thank you for your attention. I will now turn the meeting back to Dr. Lebwohl to proceed with clarifying questions.

Clarifying Questions

DR. LEBWOHL: Thank you, Dr. Mehta, and to all of the participants in the FDA presentations.

We will now take clarifying questions for FDA presenters. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again 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 the end of your follow-up question with, "That is all for my questions," so that we can move on to the next panel member. As a reminder, all these questions should be to the FDA presentation specifically.

We'll start with Dr. Lee.

DR. LEE: Brian Lee. I have two questions related to DILI for Dr. Hayashi. You presented the proposed mechanism for the cholestatic DILI, which was related to increased cholesterol saturation and bile lithogenicity, which seems like it's related to the gallstones but on a microscopic level. If it's not acute and spontaneous and it's a buildup, and NASH is chronic and suspected to require lifelong treatment, is the risk of this cholestatic DILI expected to be stable across time, based on this mechanism, or is the risk actually anticipated to be cumulative and increase over time?

Then my second question was you provided a historical perspective, so is there any precedent for other FDA-approved medications with such

rigorous lab surveillance recommendations; and you put up on your slide every 2 to 3 weeks.

DR. HAYASHI: Thanks for the question. First of all, I think maybe you're conflating the two, the gallstone problem that could cause bili obstruction and the actual DILI risk with OCA. We don't know exactly what's causing the DILI without the gallstone and bile duct obstruction. The point of that slide was that you can have an obstruction which would then increase the OCA exposure in the liver, and then you're moving into the realm where previously the patient was doing fine, but it's almost tantamount to a dose increase, and your cholestatic DILI would set in. But the mechanisms are not necessarily linked. We don't know that, and I didn't want to confuse you there.

Did that answer your first question? That means that it's not necessarily a constant risk. It would be more of an intermittent risks if you're talking about biliary obstruction, that may occur at any time.

DR. LEE: I see. So even based on the

latency and the liver biopsy result from the patient who underwent transplant, we expect that the risk is stable for this cholestatic DILI across time.

DR. HAYASHI: I guess so, because there were cases, even in the table of 12, that there wasn't a gallstone problem but the latency was quite long.

To answer your other question about can I think of a protocol or a maintenance program that would be every 2 to 3 weeks with action plan that goes on for 2 to 3 years, I cannot, and I don't know if any of my other colleagues can.

Sure. I have a colleague with a lot more experience here than myself coming to the podium.

DR. RACOOSIN: Good afternoon. I'm Dr. Judy Racoosin. I'm the deputy director for safety in the Division of Hepatology and Nutrition. I think what you're getting to is in the time since 2007, when the FDA Amendments Act of 2007 was passed and gave the authority to the agency to require risk mitigation, and risk evaluation and mitigation strategies, there have been a handful of drugs that

have been approved with these REMS programs that require liver testing. We can bring someone this afternoon to give you more detail on that but, in general, the drugs that have been approved with those kind of required LFT liver testing, it's no more frequent than monthly. They are drugs that are approved for much more narrow indications, and there's a lot of structure around these REMS in order to ensure that these things happen. But we can bring someone up this afternoon if there are more questions about that.

DR. LEE: Thank you. Those are all my questions.

DR. LEBWOHL: Dr. Coffey?

DR. COFFEY: Yes. Hi. Chris Coffey. My questions are related to slide 102. Specifically, more on the efficacy side for the primary fibrosis endpoint, there were two points made in the table. The second is clear to me that it's unclear what the benefit for this endpoint would be and certainly about what that implies to clinical benefit. But the first one where the point is made

to modest efficacy on surrogate endpoint, I'm not entirely clear I get the rationale for the statement of modest efficacy. So I wonder if the FDA could expand on why this is considered modest efficacy and what a more meaningful efficacy that might be expected would be.

DR. HAGER: This is Rebecca Hager, statistical team leader. From the numeric end, I'll start, and then my clinical colleague will comment further. As I presented, the point estimates on this endpoint range from 8.6 percent to 12.8 percent, and I'll let Dr. Mehta comment further.

DR. MEHTA: Thank you. Yes, it is modest efficacy; however, what we don't know is what would this one-stage reduction in fibrosis really mean in terms of the clinical benefit. Would that translate in less transplants or less decompensation? We don't know that because we don't have any clinical trial that has ever shown that one-stage reduction would really translate into a clinical outcome benefit.

DR. COFFEY: Can I follow up? I completely agree with that last statement. I guess my concern is, in the summary, "modest" implies somewhat suboptimal in terms of language, and to me, it seems like a fair assessment which would be to say efficacy on surrogate endpoint but uncertain about why it would lead to clinical benefit. So I'm more curious about why classify efficacy as modest as opposed to it was significant efficacy that may or may not translate to clinical benefit.

DR. ANANIA: Yes. This is Frank Anania, the director of the division. I think modest, we would anticipate that a robust or significant improvement would be more than what we're seeing at 10 or 11 percent. I think that's over placebo.

There was some discussion today also, Dr. Coffey, about there is some degree of resolution of fibrosis, even in the placebo cohorts, not only in this trial, but in the published literature. So taking those things into consideration, this benefit, based upon what we currently have from the data available to us,

indicates that this would be modest. Again, I think one of the issues that's come up here, as was mentioned by my statistical colleague, is that we don't have the clinical outcomes, and I would just remind you that we don't have clinical outcomes data for any of these because we don't have any treatments yet. I don't know if that answers your question.

DR. COFFEY: Yes.

DR. MEHTA: And I do want to add a little bit more, that out of 100 patients, about 11 to 12 patients would see improvement in fibrosis with OCA, so that's why we categorized it as modest.

DR. COFFEY: Thank you.

DR. LEBWOHL: Effect size or absolute risk difference. Thank you.

Next up is Dr. Chang.

DR. CHANG: Lin Chang. I had two questions. The first one is for Dr. Hager. On slide 40, there was a difference in the fibrosis ratings assessments by the old method and the consensus

method, where in the consensus method, 12 to 13 percent had stage 4. And I was wondering if you had efficacy and safety data excluding those patients who would not be in the indicator population of F2 or F3.

DR. HAGER: Could we please bring up slide -- hold on. We do have results. The applicant did submit to us results for just fibrosis stage 2 and stage 3 patients at baseline, as determined by the consensus method, so that would exclude those stage 4 patients.

DR. CHANG: Oh, you're saying that the data they presented already excluded the F4?

DR. HAGER: No, I'm sorry. I'm trying to find the results. They were very consistent if we just look at the stage 2 and stage 3 fibrosis stage patients at baseline by consensus.

Can we please bring up slide 152?

Once that slide comes up, if we just look at stage 2 and stage 3 patients at baseline by consensus, the risk difference is 12.7 percent, comparing OCA 25 milligrams to placebo, and the

second line has the other endpoint, which was resolution of NASH and no worsening of fibrosis, so 5.2 percent.

Did that address your question?

DR. CHANG: Yes. What about the safety though?

DR. MEHTA: So the safety analyzed the whole safety population. There was an increment in the adverse event as the fibrosis stage increased when we did the subgroup analysis by stage. Stage 1 patients had less severe or more serious adverse events as compared to stage 2, and then that further increased in the stage 3 population. We do have a slide. We could pull that up.

(Pause.)

DR. MEHTA: It would be slide 180 or 181.

Here we can see there was increasing adverse events as the patient's moved, as the fibrosis stages increased, whether it was pruritus, or gallbladder-related disease.

If you could move on to the next slide, please, 181, we see the same even with death

events, that there was an increase in events of death rate at stage 2 and 3 fibrosis compared to stage 1. The applicant does have in their briefing package a table, where they have shown this gradient across stage 1, stage 2, and stage 3, and there's an increasing adverse event by stage.

DR. CHANG: Yes, this is helpful. It's still hard to look at the group as a whole and compare the way the safety and efficacy data was collectively versus -- probably more for safety, it's a little hard to look at all these tables and to assess the safety aspect if you excluded the stage 4 patients. I don't know if that could be presented --

(Crosstalk.)

DR. MEHTA: The stage 4 patients --

DR. CHANG: -- a little more easily.

DR. MEHTA: I'm sorry, Dr. Chang. Stage 4 patients were not included in the study. In this study, there were stage 2 and 3 patients, predominantly 90 percent, and 10 percent stage 1 fibrosis patients were enrolled.

DR. CHANG: But the slide 40 shows that 12 to 13 percent had stage 4; is that right?

DR. HAGER: Right. This is Rebecca Hager, statistical team leader. So that was by consensus method, so some patients who were considered 2 or 3 by one rater were later considered stage 4 by consensus. The point of showing is that in practice that could very well be the case. Patients who maybe would have been stage 4 by a consensus method, which requires three pathologists, may be treated because in practice, even if a liver biopsy is required, it's very unlikely that it would go through that rigorous consensus method.

DR. CHANG: My second question is for Dr. Stewart. Since there's concern about gallstones, if somebody had at baseline gallstones, how did they do on treatment? Because I don't think that was excluded, right? That wasn't an exclusion criteria.

DR. MEHTA: We have not really looked at -- the patients with gallstones at baseline were

enrolled in the clinical trial. There were about -- I can't remember the exact number; the applicant could clarify, but there were about 20 to 30 percent patients who had gallstones at baseline, and then few patients developed gallstones during the clinical trial.

DR. CHANG: I was just trying to determine if somebody has gallstones at baseline, are they at more risk for adverse events, whether it's --

(Crosstalk.)

DR. MEHTA: We did not do that analysis.

DR. CHANG: Okay. Thank you. Those are all my questions.

DR. LEBWOHL: Next up will be Dr. Mannon.

DR. MANNON: I have two questions and a comment. My first question is, in preclinical models, rodent models, where OCA has been administered, there seems to have been a change in the gut microbiome and intestinal permeability that's favorable. So it's interesting to me to see that there is a dysglycemic as well as a dyslipidemic effect in many of the people who

received this, and also the placebo.

So I was just wondering, is there any data on changes in the microbiome or gut permeability in this study that could be correlated with at-risk events?

DR. ANANIA: That's a great question, Dr. Mannon. This is Frank Anania. So to start with, as you probably know, a lot of animal models that demonstrate effectiveness do not correlate necessarily with human subjects research, but to your point directly, there are no data that we have from the applicant about changes in the microbiota, if that's what you're asking, or permeability. And I don't know that that was obtained in their study that was reported in the basic science literature. I can't answer that for you.

DR. MANNON: Thanks, Frank. I appreciate in many ways the gap between animal models and human experimentation.

My second question is, given that the major outcomes here have been sort of non-response, and now having a new appreciation for some of the time

delay for the potential risk of OCA, would there be consideration of guidance for stopping this medication for just lack of response rather than waiting for, say, progression to fibrosis, where you could potentially mitigate risk overall? I just wondered if that was a consideration at all.

DR. MEHTA: At this point in time, we don't know that no progression of cirrhosis translates into a clinical benefit perspective. The data that we have reviewed so far internally for the 18 months, there was no significant difference between the placebo and the OCA 25 for no progression to cirrhosis, and Dr. Hager could elaborate a little bit more on that.

DR. HAGER: Yes. Just to clarify, if we bring up slide 154, it's no worsening of fibrosis, so we don't have the data on progression to cirrhosis yet; that is still blinded. So to get back to I think what your question was, we have the month-18 data on a surrogate endpoint, and we are not sure how that would translate into clinical benefit. So even if a subject did not show an

effect on fibrosis, we don't know what would happen in clinical benefit, and we also don't know the meaning if they do have an effect on fibrosis and what that would mean for clinical benefit.

On this slide, this is presenting the no worsening of fibrosis endpoint at month 18 based on the consensus results, so you can see for both ITT old and ITT histology, and this is like no worsening, and the risk differences are in the last column, 4.5 percent and 1.1 percent.

DR. MANNON: Thank you. My only comment would be the closest thing to the monitoring aspect of this would be inflammatory bowel disease, where we start people on Imuran or 6-MP, and monitoring their LFTs, and maybe amylase, and white blood cell count fairly frequently for the first 2 to 3 months, and then sequentially afterwards. And I would say that while it's very helpful, it is often challenging to make sure everybody's doing it on time, but thank you very much.

DR. LEBWOHL: Just keeping track of the time, I think we'll take just five more minutes

before we break, so I'll ask to limit the questions to the three remaining advisory committee members with their hands raised. We'll start with Dr. Assis.

DR. ASSIS: Hello. David Assis. I have a question for Dr. Mehta, based on slide number 6, if possible.

DR. MEHTA: Can you please pull up slide number 6?

Dr. Assis, please go ahead and speak your question.

DR. ASSIS: Sure. Yes. I just want to return a little bit briefly -- I apologize -- to the question raised by Dr. Coffey earlier, which is I understood from the comments made by the FDA that there was an underwhelming impression of the modest efficacy of the surrogate endpoint, but when I look at the draft 2018 guidance for industry, that seems to have been the roadmap for drug development. So maybe this is not easy to answer, but is there a sense now, a growing sense from the FDA or from others, that perhaps the surrogate endpoints that

are reasonably likely to predict clinical benefit are not stringent enough, and that could influence whether or not accelerated approval is appropriate or not versus more traditional approval; or once again, as Dr. Coffey also requested, is there a sense that the degree to which there was a meeting of endpoint number one was not sufficient?

I guess we're struggling a little bit with the 2018 guidance, and that's my question. Thank you.

DR. MEHTA: Thank you, Dr. Assis. We stand by our guidance. We do think that both these endpoints are surrogate endpoints that we think are reasonably likely to predict clinical benefit. The question over here that we are asking is that of the benefit and risk. The approval of a drug is contingent on a reasonable benefit-risk ratio. That is where the concern is, and we are not questioning the surrogate endpoint. We still think that these surrogate endpoints are acceptable for NASH drug approval.

DR. ASSIS: Thank you. No more questions.

DR. LEBWOHL: Dr. Wilson?

DR. WILSON: Thank you. Peter Wilson here. I had a question for Dr. Stewart, and it was related to slide 86. I think what I would be most interested in seeing is what happens with a higher dose of OCA and the top parts of the distribution on treatment with the OCA. We see a peak of a mean -- I guess it's a mean -- a little less than 140, but what about the higher levels? We may be seeing a relatively conservative estimate of the long-term rise, and the top quartile, for instance, might be considerably higher.

Then the follow-up on that is also related to some of these patients end up going on statins. It's a dysglycemic question. I'll ask two at the same time. The dysglycemic question is some patients go on statin, and that's going to adversely affect their lipids as seen in meta-analyses of multiple statin trials. So that may not be OCA; it may be statin effect. Those are my two questions. Thanks.

DR. MISRA: Hi. This is Dolly Misra. I'm

an endocrinologist, and I'm a clinical reviewer on the diabetes team in the Division of Diabetes, Lipid Disorders, and Obesity. I'll take your second question with regard to whether -- I think you said effect on lipids. But is your question that you're asking whether the initiation of statins had an adverse effect on the glycemia?

DR. WILSON: I would expect that if statins got added on to therapy, but you may have direct data from this trial.

DR. MISRA: Yes. Actually the data very clearly showed that within 1 to 3 months, we saw an acute abrupt rise in plasma glucose, and that change occurred greater in the OCA 25-milligram group than it did in the placebo. And as time went on, we did see that the difference between those two groups lessened, but actually as we had started off the discussion, is that this entire population, NASH, is at risk for dysglycemia. So the lessening that occurred during the trial was as much related to worsening of the placebo group as it was mitigation of the hyperglycemia.

So given the timing of the hyperglycemia that was noted, it doesn't appear that the statins had an effect there. As we followed it over time, I don't think that there was anything to suggest that when those statins were initiated, they had a significant impact.

DR. WILSON: Thank you.

DR. MISRA: Does that answer that you question?

DR. WILSON: Yes, that's very helpful.

DR. MISRA: Okay.

DR. CRAIG: Hi. This is Eileen Craig. I'm the acting team lead from the Division of Diabetes, Lipid Disorders, and Obesity, and I'll handle your question about the LDL levels. Certainly on this chart -- this is slide 86 -- is the total population. In the background package, there were also slides that looked at different populations, patients who were not on statins at baseline who did not initiate a statin during the course of the trial, patients that did initiate a statin, and in those patients who were on a statin at baseline who

either intensified their statin therapy.

This chart certainly has confidence intervals, but I think to get to your question, I think the best data that we have that, that we have a slide for, is slide 198, which looks at post-baseline LDL categorical increases from this study; so if we could pull up that slide.

DR. MEHTA: Can you please pull up slide 198?

DR. CRAIG: So that slide, while we're waiting for that to be pulled up, will just show the different categories of subjects that had an LDL greater than 100, greater than 130, and greater than 190 milligrams per deciliter across the three treatment groups of OCA 10, OCA 25, and placebo. And as you would expect, the OCA 25 has a higher number and percentage of patients who are at increased thresholds, certainly at 190 and 130. So hopefully that gives you some information to answer your question.

DR. WILSON: Yes. That's a concern. That's what we might have guessed -- I might have

guessed -- is that they're going to need more than statin, probably. They're going to need double lipid therapy, statin plus something else.

DR. CRAIG: We agree. That is a concern.

DR. LEBWOHL: We'll move on to our final question by Dr. Rakela.

DR. RAKELA: Yes. This is Jorge Rakela. I have a question for Dr. Hayashi or Dr. Anania. Any data on hepatic OCA concentration among patients with DILI that you would allow to study if there's any relationship between the hepatic concentration and the severity of the clinical presentation, and that indirectly provides some insight into the mechanism, direct, idiosyncratic, or indirect?

DR. HAYASHI: That's a great question. We didn't have intra-hepatic concentration of OCA levels, at least not provided to us, I don't think; at least not given to us by the applicant, but it's an important question. In the diagram I had, there was an arrow going to DILI and then back to the liver, suggesting that once the DILI starts, we do have some concerns that maybe it will stall the

clearance of the OCA of the liver because you've created now cholestasis. So there is this concern I have that once the DILI begins, it may make it harder for the liver to clear that OCA out. But I take your point, Dr. Rakela. It's a good question.

I don't know. Frank, do you have anything to offer about that?

DR. RAKELA: Thank you.

DR. MEHTA: I just wanted to add that although we don't have the PK data in another population, that's the PBC population, it seemed that even at the lower dose, the 5-milligram dose, patients with Child-Pugh B and Child-Pugh C, or even Child-Pugh A, with portal hypertension started having a lot of decompensation events or DILI; so that sort of goes into the concept that probably the intra-hepatic exposures when they're higher, the liver does not tolerate that very well.

DR. RAKELA: Thank you.

DR. LEBWOHL: Thank you to all the questioners and answerers.

We will now break for lunch. We will

convene in 33 minutes; that's 1:30 p.m. Eastern Time. Panel members, please remember there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to reconvene around 1:20 p.m., 10 minutes before we start up again, to ensure that you're connected before we reconvene at 1:30. See you then. Thank you.

(Whereupon, at 12:58 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 argument to advise the committee of any financial relationship that you may have with the applicant, its product, and if known, its direct competitors. 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. Thank you for your cooperation.

Speaker number 1, please unmute and turn on your webcam. Will speaker number 1 begin and

introduce yourself? Please state your name and any organization you're representing, for the record. You have four minutes.

DR. ABRAMS: Hi. This is speaker number 1. Can you hear me?

DR. LEBWOHL: Yes.

DR. ABRAMS: Thank you.

Good afternoon. I'm Dr. Michael Abrams from Public Citizens Health Research Group. I have no financial conflicts of interest on this matter.

Non-alcoholic steatohepatitis with fibrosis, or NASH, as we've heard this morning, impacts millions of people in the U.S. each year and marks liver disease that over many years can lead to transplantation or death. There are presently no FDA-approved pharmacologic treatments for this illness. Diet and exercise, induced weight loss, and bariatric surgery are both used to treat NASH, but they have challenges, of course.

There are currently several pharmaceutical interventions in development for NASH. Today you are discussing transient obeticholic acid, or OCA,

a synthetic form of bile acid that is slightly different from the native substance that it aims to mimic. A single randomized, placebo-controlled trial, that is trial number 303, which you heard about this morning, was initiated in 2015 to test daily 10- or 25-milligram doses of OCA versus placebo as a treatment for NASH. That trial has since randomized 931 subjects into three equal groups, and followed them for 18 months for interim analysis to evaluate two prespecified surrogate outcomes for the explicit purpose of seeking accelerated approval on OCA.

Those analyses, plus supplemental analyses with more statistical models and subjects, and sometimes longer time horizons, have demonstrated only one small therapeutic effect so far, an improvement in fibrosis that was observed in 23 percent of the 25-milligram patients and 12 percent of the placebo patients. No differences with placebo was seen with the 10-milligram OCA dose, and neither does demonstrated efficacy in actually resolving NASH, the other prespecified

outcome. These findings were generally similar with the addition of more subjects and alternative histological grading.

Equally important, hundreds of observations from the post hoc and main interim 18-months randomized trial demonstrated many adverse effects of OCA. Focusing here on the 25-milligram dose, we've heard that serious adverse events, for example, occurred in 10.2 percent of subjects taking the drug and 7.5 percent of those on placebo.

Treatment interruption due to pruritus occurred in 20 percent versus just 2 percent of subjects, respectively. Probable or possible drug-induced liver disease was identified in 32.1 percent versus just 7.4 percent, respectively, requiring liver transplantation, as we heard, in at least one case where OCA was used.

Gallbladder disease, bad cholesterol increases, worst blood sugar control, and more cancer and kidney injury all were evident with the OCA use versus placebo. Moreover, if OCA were to

be approved to treat NASH, it would plausibly dramatically increase the need for liver biopsies, or at least liver assays, on an ongoing basis, and the use of other drugs such as statins and corticosteroids, which have their own adverse effects.

Accordingly, the FDA's summary review has concluded that the clinical efficacy of OCA remains unknown, and that wider use of the drug will require unrealistic metabolic monitoring and expose patients to numerous drug-induced and other iatrogenic risks. The FDA further concludes that the existing data thus, quote, "cannot justify OCA use in NASH subjects with stage 2 or 3 fibrosis," close quote. We agree with that assessment, and thus we encourage you, the committee, to vote today against approval of obeticholic acid as a treatment for NASH. Thank you very much.

DR. LEBWOHL: Speaker number 2, please unmute and turn on your camera. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are

representing, for the record. You have four minutes.

MR. ESKRIDGE: This is Wayne Eskridge. I am the founder and CEO of the Fatty Liver Foundation. As a foundation, we get contributions from a lot of people, and that includes Intercept. I'm not personally paid by them, but they have contributed to our programs over the years.

Just to get you acquainted, that's me and my wife before I was identified, and I'm a typical guy, a typical American guy. I gained a pound or two a year for 50 years, and I ended up pretty big. Now, I honestly don't remember ever having to lift my belly to tighten my belt, but clearly I did. I had gallbladder surgery in 2010, and you can see that my liver looked pretty ugly at that time, and that of course started me on my liver journey, but I'm a classical NASH patient.

A couple of waypoints along the way, I had a biopsy in 2010. You can see I had steatosis at that time. You can see chicken wire F2 in that slide. The 2015 slide is stage 4 cirrhosis. I've

got bridging cirrhosis. I am a fast progressor, but the thing that makes me unusual is that I'm a near perfect patient because over the next year and a half, I lost 30 percent of my weight. I stabilized my disease. I have tracked it with FibroScan and MRE, and various other tests, and I am now, in fact, a high stage 2 fibrosis score.

The thing, from a patient perspective, that I think we all have to understand is the vast, vast numbers of people that we're facing. This is fairly old data, but if you look at just the increase of hospital admissions as a result of NAFLD-NASH, you can see that we're going to overwhelm the medical industry at some point in the not-too-distant future. And the reasons, of course, the young lady there with a sandwich, those are our habits. We bring this on ourselves very often with the way we've structured our disease or our food systems.

The young lady there in the corner, you might think that that I just think she's a cutie, but we see this happening to younger and younger

people all the time, and it's also significant that we have lean NASH, which she's an example of. There's a significant number of people who have NASH who really don't fit the overweight, obese model.

DR. LEBWOHL: Speaker number 2, we're now at time. If you could just wrap up your remarks in the next one to two sentences.

MR. ESKRIDGE: Oh my.

I really wanted to get to this. What I want to say is we're developing a lot of tests. There are a lot of coming things that are available to us. I've used all of these. These are my personal measurements over the years. There's talk of requiring biopsy for this treatment, and I think that that ignores the fact that science is advancing so fast, and we're getting better and better testing equipment every year.

DR. LEBWOHL: Thank you, speaker number 2. I'm afraid we're going to have to move on to speaker number 3.

Please unmute and turn on your camera. Will

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

MR. BETEL: My name is Michael Betel, and I am the president and founder of the Fatty liver Alliance. I have no financial disclosures to state. Our charitable organization is dedicated to raising awareness about NAFLD and NASH, and advocating for access to approve treatments and care. As an NAFLD patient myself, a parent of an NASH patient, and over 25 years in the pharmaceutical industry, focused on liver health, I bring both a professional and deeply personal perspective to this committee.

Physicians are accountable and responsible for patient care. Patients have the right to be informed about the risks and benefits of treatments. Informed patients working alongside their physicians and caregivers are capable of making critical decisions about their treatment paths. The arrival of new treatments like

obeticholic acid is a significant milestone for NASH patients and their families.

While many might view a 22 percent primary treatment endpoint success rate as underperforming, I reflect back on the early days of FDA-approved interferon monotherapy for hepatitis C and its low response rate of between 15 and 25 percent, and how it was a building block towards a cure that we have today. Adverse events from treatment like pruritus and elevated LDLs will be manageable and can be resolved; however, we recognize, based upon the data, that OCA has caused drug-induced liver injury.

It is our recommendation that for many patients, there is a serious and unmet need for treatment, and that treatment may have side effects of concern. The conditions of approval for OCA should include limiting its use to centers of excellence where there's a high level of confidence that only the dedicated patients and subgroup populations will receive the treatment and where they can be carefully monitored by specialists.

With regard to liver biopsies, we randomly surveyed U.S. NASH-treating physicians at the DDW conference just over a week ago, and 90 percent indicated that they felt non-invasive tests in combination with other diagnostics were an acceptable alternative to a liver biopsy outside clinical trials. This is another opportunity to empower physicians and patients to choose what they believe is best for the patient's liver health.

The choice to treat should belong to physicians and patients together. They will have access to all the available data, including risks and benefits to treatments, enabling them to make the best decisions for their health. An informed patient is an empowered patient, one who can actively participate in their healthcare outcomes.

My daughter Allison [ph] faced her own difficult decisions when managing her NASH. She chose a challenging path, undergoing gastric bypass surgery, losing half her body weight, eliminating her NASH, but is now dealing with subsequent surgeries and health issues. It wasn't an easy

journey, but it was her decision, and she made her choice based on her options at the time.

With the advent of new treatments like OCA, patients have more choices. Yes, these treatments may have side effects. Yes, controls will need to be in place to ensure patient safety, but they do offer patients and their families hope. They offer patients another way to take control of their disease and potentially improve their liver health and quality of life. Thank you to the GI Drug Advisory Committee for giving me the opportunity to share my thoughts today.

DR. LEBWOHL: Speaker number 4, please unmute and turn on your webcam. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you are representing, for the record. You have four minutes.

MR. VILLIOTTI: Yes. My name is Tony Villiotti. I'm a liver transplant recipient resulting from NASH cirrhosis and liver cancer, and the founder of NASH kNOWledge, a patient and

advocacy nonprofit. I'm speaking today as a patient and not representing NASH kNOWledge. I do want to disclose, though, that NASH kNOWledge has received grants from Intercept but will not benefit in any way from this meeting.

NASH patients have very limited options in battling the disease. Lifestyle change is usually seen as the best option, but it is most effective in the early stages of liver disease. This option is not often effective for those with F2 or F3, as liver diseases is typically asymptomatic and not diagnosed until it has reached a stage where it is too late for lifestyle change to be helpful.

In addition, studies have shown that lifestyle change goals are seldom achieved, and it does not always work. In my case, I lost 15 percent of my body weight, but my liver disease continued to advance. This leaves a patient to watch their disease to progress to the point where they need a transplant. That's what happened to me.

A transplant is in no way an ideal outcome

for patients. First, not everyone who needs a transplant will get one. Second, a transplant brings its own set of issues. Post-transplant and anti-rejection medications are harder on the body. Since beginning those medications, I have lost about 70 percent of my kidney function and my type 2 diabetes has worsened to the point where I take as many as 4 insulin shots a day, and studies have shown that my experience is not unique.

The lack of a medical solution for NASH is a serious and urgent unmet need and robs patients of a viable option. Patients cannot put their disease on pause while drugs are being studied. Absent a medical solution, patients will continue to see their disease advance and suffer adverse health consequences. Many will die. A 2021 study by Dr. Sanyal and others projected that 18,000 people with F3 will die annually and another 15,000 annual deaths will occur from patients who progress from F3 to F4. To put that in perspective, that means that 30 patients will die during the course of this meeting.

Stopping disease progression or achieving a one-stage fibrosis improvement is very important to patients. This results in patients viewing risk far differently than the FDA staff. The staff views safety risks in an absolute sense, while patients view it in relative terms. OCA does not introduce risk into a patient's life; risk is already there. Patients are living with the risk of deteriorating health, and even death, from liver disease. In a patient's eyes, the side effects of OCA are viewed as a risk that is acceptable when linked with a drug that offers potentially life-saving benefits. There is no benefit associated with maintaining the status quo, which is no drugs. The choice between [indiscernible] cases is an easy one for most patients.

No drug is going to be a magic pill that brings NASH to a halt. NASH is not a one-size-fits-all disease. Different solutions will be a fit for different people. OCA may not be a solution for everyone, but will be a solution for many people, and is an important first step in

providing a medical solution to those advanced liver disease.

I know there were some concerns about potential side effects for OCA. We all see TV commercials where a sales pitch for a drug is followed by a list of possible scary side effects. The choice is left to the patient in consultation with their doctor to weigh the risks and rewards of that drug. I implore you to give NASH patients that same choice.

I strongly support the approval of OCA. Please do not let the search for a perfect solution stop the approval of a good solution. NASH and the patients deserve the right to decide, along with their doctors, whether OCA might help them. I would also add that a liver biopsy should not be a precursor to receive OCA, as the current state of NITs provides sufficient guidance. I want to thank you for this opportunity to share my views.

DR. LEBWOHL: Speaker number 5, please unmute and turn on your camera. Will speaker number 5 begin and introduce yourself? Please

state your name and any organization you are representing, for the record. You have three minutes.

MS. CRYER: Thank you. My name is Donna Cryer. I am the founder and CEO of the Global Liver Institute. I have served as a member of the American Association for the Study of Liver Disease NASH Task Force, and have been a guidelines reviewer for both AASLD and AIDS. I have no financial conflicts of interest; however, the Global Liver Institute, as a convener of the 80-member NASH Council since 2017, does have industry partners alongside major cardiovascular, endocrinology, obesity, and hepatology organizations, both patient and medical, as well as minority-serving organizations.

I have also been in your seat twice as a voting member of FDA ADCOMs, including the initial advisory committee for OCA, and have followed the data closely. I thank you for your time and attention, and your questions. I'll speak for the rest of my brief comments particularly about the

externally-led, patient-focused drug development meeting that GLI conducted with the community and consequent discussions. First, we must recognize how many patients die every day due to NASH; how many have died since the CRL; and how many will die before an outcomes trial is complete. Death is not a manageable side effect.

OCA has not only met the FDA agreed-upon endpoint, but the expectation for side effect or efficacy of the patient community. For this first drug for the treatment of NASH, this is the beginning of an era, should you allow it; not the apotheosis. We look forward to drugs with many mechanisms of action to address the heterogeneity that we see with NASH patients. As the previous speaker testified, we deserve the right to choose.

As for these side effects, I have experienced each of the side effects that have been discussed today before my descent into end-stage liver disease and transplantation: pruritus; elevated LDL; dysregulation of my glucose; cholestatic disease; and gallbladder removal.

These are all manageable.

Fourth, the patient community is aligned with the identification of appropriate patients for this particular compound, and this anti-fibrotic compound is important, so I would ask that you vote yes, that the benefits do outweigh the risks, as the patient community has deemed. I would also ask that you vote yes, that we should meet this serious unmet medical need today. Thank you.

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

MR. DIMMIG: Thank you, committee members, for your attention to my testimony today. I'm Bruce Dimmig. I was compensated for being a patient representative of a NASH panel for Pfizer, Bayer, and Salix. I'm speaking on behalf of myself. I'm before you today to relate why approving OCA for the treatment of F2-F3 fibrosis

associated with NASH is so critical to myself and all liver patients.

I've been dealing with my liver disease for over 11 years now. Without any prior weight or diet issues, I was unaware that I had anything wrong until early 2012. That year alone, I averaged a blood test every 2 weeks, imagings once a month, and three procedures that included two liver biopsies. Through these, I was diagnosed with liver disease. Since those biopsies, I've had two more. Out of the four, one was too fragmented to diagnose from, which led to another one, and the one that I had when I had my gallbladder out in 2019 showed no fibrosis, which turned out to be a sampling error. That points to the need to rely more on non-invasive tests to diagnose NASH.

Only three years later, I was finally diagnosed with NRH, nodular regenerative hyperplasia, which is a very rare disease affecting approximately 5,000 in the U.S., and NASH, which led me before you today because for many of the years of my journey I was told that there are no

drugs available to treat any of my conditions, only some of the symptoms. It hasn't been until the last few years that patients were told that there were any drugs being investigated, and now that OCA is to this stage, there is an urgent need to approve this and give patients an actual treatment option.

At one point during my journey, I progressed from F1 to F2 to F3 fibrosis in just a year and a half, and if this medication had been available then, my fibrosis may not have progressed to the point it has and could have forestalled or prevented my disease from becoming what it is today. When one is told that there isn't anything that can be done to treat their condition, it can have a detrimental effect on their mental health, which translates through the stress and efforts to manage their diseases, to actual physical impacts that can lead them to get sicker as a result. Therefore, if the medication is taken by the targeted population, and even if there are possible side effects to this medication, it should be a

decision that is arrived at between the doctor and the patient, as some help or hope is better than no help or hope, and in my case, my lipids are well controlled with medications.

There are serious unmet needs, and without treatments, one disease can get worse, meaning that patients generally have to endure many more tests, procedures, and imagings that could reasonably be avoided if there was a treatment available to halt or even help reverse progression of the disease. This burden is also borne by the medical profession, as there are consequently more visits to offices, hospitals, freestanding facilities, and pharmacies.

Dreaded outcomes of not treating liver disease early enough can be liver cancer, and/or transplantation, and/or death. These are very expensive to deal with, and the cost is paid by the health insurance industry, the patient, and/or the public. The hidden costs are the time and/or income that patients and their families lose when they go to the doctor for test, imagings, and

procedures. This can result in a drop in their productivity and can affect the efficiency of their place of work. This is assuming that their disease hasn't rendered them disabled and unable to work like myself since 2012 due to my hepatic encephalopathy.

If this issue of treatments of liver disease isn't addressed now, it will get exponentially worse in the near future, as it is estimated there are between 80 to 100 million people in the United States that have fatty liver, and it is further estimated that 25 percent of those will progress to NASH, putting a major strain on the healthcare industry and the economy as a whole. I urge you to vote yes, and thank you for your time and consideration today. Thank you.

DR. LEBWOHL: Speaker number 7, please unmute and turn on your webcam. Will speaker number 7 begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have four minutes.

MS. MADISON: Hello. My name is Gina Villiotti Madison, and I want to thank you for the time here today. I'm coming here today as a family member of a patient; however, I am also the executive director of NASH kNOWledge, and as NASH kNOWledge, we do receive grants from pharmaceuticals such as Intercept, but I have no personal or professional/financial interest in the outcome of this meeting, and have not received any funding personally or professionally for this meeting in particular. The funding that we receive is purely for the work that we do to raise awareness out in the community.

I am going to be speaking from a personal standpoint today on the effect that my Dad's liver disease journey and NASH journey has caused; however, it's hard to not bring the personal aspect into the work we do professionally, as well. I can speak really clearly that the lack of a medication and having a medication such as OCA available would strongly improve not just the quality of life for patients themselves and their caregivers, but for a

family as a whole.

As a daughter of somebody who had NASH, it was just so troubling for our entire family to watch my father's health just continue to deteriorate. My dad has five grandchildren, and two of them are my children. And my son, really, the simplicity of a child, I think he just said it best one day. He said, "I just don't understand when Pop was so sick, he wasn't getting medicine, and now that he has had his transplant, he has a box full of medications that he has to take every day."

That simplicity from a child and just that confusion of my pop is going through, and watching his health deteriorate and him get sicker and sicker, and knowing that there was no medication that he could take, and either transplant or death was going to be his only option. And once he finally got that life-saving transplant and you think we're walking in the clear -- yes, my dad's health has improved drastically from a transplant, which should not be the option for NASH patients.

It should not be a transplant. But now this young child, he's seeing my dad needing to take lots of these medications just so he feels healthy, and sees that he's still not at full health.

So I really, really believe strongly -- I'm here strongly in belief that OCA should be approved; that we need medication for NASH; that this really should be a decision that's taken upon the patient and their provider together to really weigh what are the risks and what are the benefits because we want our patient to be here to be able to make those decisions. If we don't have a medication available, we're seeing more and more people die from NASH.

As I mentioned, it's hard to not take my personal and professional and combine them together, but we go out into the community, and we are at tables, and we are talking to people one on one, and I can't even tell you how many people have come up to us and told us that they have had family members who have had fatty liver disease that progressed to NASH, to cirrhosis, and

they have died because of lack of medication.

So I just really, strongly am encouraging you to really understand and think about that patient view. Patients across the board should be able to make those decisions for themselves and really be able to make the decision if the risks of a medication and if the side effects of a medication outweigh the benefits that that medication would cause. There truly is an unmet need in the community. We see it more, and we're seeing the cases of NASH rise every day, and people are dying while we're waiting for a medication to get approved.

So I just want to thank you so much for your time today, and for letting me bring that family perspective because this truly is a disease that affects the entire family, and medications, and OCA in particular, would just give better outcomes to family units as a whole. So thank you for the time. I appreciate it.

DR. LEBWOHL: Speaker number 8, please unmute and turn on your webcam. Will speaker

number 8 begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have four minutes.

BETH: Hi. My name is Beth. I am 62 years old. I live in New York City. I am here representing myself. I'm not being paid to be here, although, full disclosure, I was paid in the past, the last time being 2018, by Intercept as a consultant at various educational programs.

I was diagnosed with NASH stage 2 in the fall of 2017, and over the course of the next year, I was able to change my lifestyle, my eating habits, and my liver is healing and the damage has been and is reversed. However, I feel, because of personal experience, both my mother and my brother died from NASH -- my mother in '94 and my brother in 2014, so when I was diagnosed with it -- and I also believe that I was lucky to have had a primary care physician who was on the ball because I had absolutely no symptoms, and no one had ever mentioned this to me at all. I was motivated

because I knew you could die from it.

Also, living in New York City, I have access to good doctors and to good food, but I know how hard it is for people to change. I think that if a drug had been available to both my mother and my brother, they may still both be alive today, and I know that also people in other parts of the country don't have the doctors that I have, and don't have the access to the food that I have.

So that's why I would urge you to approve it because if it gives anybody a leg-up or buys anybody some time to make the more critical change -- and also, I don't know other people's situations. In my case -- I don't understand the science -- I'm a success story. I do know that I have to keep on it. I am monitored all the time, and I have to stay on top of it. I don't know what might happen. My mother was 67 when she died, my brother wasn't even 60, and I'm 62, so I don't know what the future holds for me, but thank you for listening. I trust you to make the right decision.

DR. LEBWOHL: Speaker number 9, please

unmute and turn on your camera. Will speaker number 9 begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have four minutes.

MS. VILLIOTTI: Hi. I'm Betsy Villiotti, and I'm the vice president of NASH kNOWledge, and, yes, we have received a grant from Intercept, and my daughter and my husband has told you the rest. But I'm here today to give the caregiver's perspective.

I was my husband's caregiver, and I accompanied him to all his doctors' appointments, and I had to find liver-friendly recipes, and at first Tony seemed to have no symptoms. He was often tired and confused, but I thought this was just due to to his dehydration and his age, of course; then overnight, everything seemed to change for us.

I was out of the house for about an hour and a half. When I came home, Tony was trying to walk through a wall. He didn't know who I was, he

didn't know who he was, he didn't know where he was. I thought he was dehydrated. I tried to get him a glass of water. He very angrily pushed my hand away, he was rude and disrespectful, and Tony had never been like that in our nearly 40 years of marriage.

Once I finally got him to the hospital, the doctor said that I was lucky I got home when I did because I could have found Tony in a coma or worse. Immediately, I quit my job, and from that day on, I never knew what Tony was going to show up, the one I married or the one being held captive by this horrid disease.

Tony became confused. He was angry, he was throwing things, he was depressed, a totally different person, dependent on me for everything, and unable to control his emotions. One day he's planning a trip for vacation after transplant. The next day, I walk in, tears rolling down his cheeks, and he's writing his obituary. I became Tony's nurse, his mental health provider, his medical liaison, his chauffeur. I was unemployed, sole

manager of the household, very stressed, exhausted, and sleep-deprived, and because of the stress, I also started to develop my own health issues.

I run a support group for NAFLD and NASH patients, and this disease is now affecting a younger population. Many are in their 30s, 40s, and 50s. One person, when he could no longer work because of the disease, had to sell his home and move into an apartment that was affordable on his wife's income. Some have school-age children, and when their disease had progressed to the point that they lost their job, they needed someone to move in with them to be their caregiver, to run the household, and take care of the children. But imagine, being a child and not knowing if your loving parent's going to show up or the one held hostage by their liver disease.

As my daughter stated, this disease does not affect one person; it affects the entire family. Tony was lucky to receive a life-saving transplant. That's not always the case for everyone. As my daughter said, when we're out in the community at

health fairs, we're always approached by people telling us stories of losing a loved one to NASH that progressed to cirrhosis. Some who have passed away were in their late 30s and early 40s. We talk to hundreds and hundreds of people, and we hear the same story over and over. They had never even heard of NASH until they were diagnosed at stage F2 or F3, and then they progressed on to cirrhosis.

Some are now on the transplant list, others have liver cancer that spread, so they're no longer eligible for a transplant, and sadly, many have died. But I just wonder, how many more people need to lose a loved one while this very serious unmet need continues? I am respectfully requesting you to please approve the medication OCA, and thank you for your time.

DR. LEBWOHL: Speaker number 10, please unmute and turn on your webcam. Will speaker number 10 introduce yourself and state your name and any organization you're representing for the record? You have four minutes.

MR. FRANK: Hi. My name is David Frank. I

have no financial relationship with Intercept Pharmaceuticals. I am representing myself and a website that I run called NASH AWARE to help raise awareness for NASH.

Six weeks. That's how quickly Mom went from being diagnosed with NASH to leaving us forever; just enough time for the survival instincts to kick in; enough time for a family not accustomed to failure to execute a plan of attack; to prepare for a transplant; to bring Mom home for a time, and we thought a crash diet change and carefully administered medicine would provide a life boat to recovery; to learn a modest amount about bilirubin levels, and cirrhosis, and MELD scores, and begin to hope that she could beat it.

My name is David Frank, and in October 2014, my mother Geraldine passed away after a very brief and completely unexpected battle with late-stage NASH. She was only 62 years old, and had shown no symptoms until just weeks before being diagnosed. Like most people, my family and I had never even heard of the disease that took her from us.

They call NASH the silent killer, and in Mom's case it was certainly true. She was never diagnosed with any form of liver disease at all before NASH. We had noticed some yellowing of her eyes and convinced her to go to the doctor about a month earlier, but it took time to get an appointment with a specialist who checked her into a hospital upon the visit. She stayed there for a few days of testing, and then was released pending the results of a liver biopsy.

My family was concerned but optimistic, based on the lack of other symptoms. Mom seemed totally fine. Of course, I now know that simply being overweight is one of the most crucial indicators of NASH. A few days later, I received a frantic call in the early hours of the morning from my dad. Something was wrong with Mom. Luckily, I was only a few blocks away and raced over to find her in a dazed and confused state, aimlessly walking in circles and incoherent, a condition I later learned was due to her liver failing and not being able to cleanse dangerous toxins from her

[indiscernible]. She was rushed to a local hospital, where the initial diagnosis was not good. The liver biopsy returned later that night and confirmed the initial suspicions. Mom had late-stage NASH that had progressed to severe cirrhosis. There was no treatment. She needed a liver transplant to live.

For a long time afterwards, I struggled with grief, guilt, and a complete feeling of helplessness, so I started looking for things to do to help others. I researched NASH and other liver diseases and learned as much as I could. I found out that over 90 million Americans are afflicted with non-alcoholic fatty liver disease, and that more than 20 million of them may have already progressed to NASH, most without even knowing it. I read about NASH becoming the leading cause for adults being placed on liver transplant lists, surpassing hepatitis C. I discovered that, globally, nearly a quarter of the entire population of the planet might have some form of NAFLD.

These numbers are simply staggering. Now

combine those daunting figures with the one-two punch of a NASH diagnosis and remedies. Abysmal early detection rates due to a lack of efficient non-invasive diagnostic methods and a total lack of any viable treatments for patients that progress to NASH. Like Mom, when you finally figure out that you have a problem, there is nothing you can do about it, except hope to be lucky enough to get a transplant.

I ultimately decided that I couldn't really read and learn about the disease that took my mom; I had to do something. I started out volunteering with the great folks at the American Liver Foundation, and now serve on their board of directors. I also founded NASHAWARE.com to help raise awareness and educate others, and have been tracking the progress of promising pharmaceutical treatments for years.

As a patient advocate, I cannot understate the importance of having an approved treatment for NASH. In my many conversations with NASH patients, one of the most daunting psychological issues is

that there is no treatment at all, leading to hopelessness and despair. There are GPs that are mostly unaware of the specifics of NAFLD-NASH disease progression and unable to provide support or guidance on how to manage it. They wait months to get appointments with the hepatologists, only to be told that there are no treatments and any trial spots are full. If they're at late stage, they then wait for a liver transplant that may never come.

When considering whether or not to approve this drug before the committee today, as well as any other future treatments that may come before it, the severe disease burden that NASH has on the nation must be considered. When combined with recent advancements in early diagnostics, pharmaceutical treatment will be life rafts for the enormous population of aging adults impacted by liver disease. Thank you for allowing me time to tell my story today.

DR. LEBWOHL: Speaker number 11, please unmute and turn on your camera. Will speaker

number 11 begin and introduce yourself? Please state your name and any organization you are representing, for the record. You have four minutes.

DR. POCKROS: Good afternoon. My name is Paul Pockros. I was an investigator in the phase 3 REGENERATE NASH trial, whose data you looked at today, and I was also an investigator in the POISE trial using OCA in primary biliary cholangitis. I was also a paid participant in a mock advisory board meeting that Intercept held in preparation for this meeting.

I've been a clinician and a transplant hepatologist most of that time for 38 years at Scripps Clinic, and therefore I've seen many, many, many hundreds or thousands of patients with end-stage liver disease during my practice. The prior epidemic we had was with hepatitis C, and the period we're in right now reminds me of when the first drugs were approved in 2011 for hepatitis C.

The critical drug at that time was called telaprevir. It was an NS3 protease inhibitor, and

we had to give it in combination with interferon ribavirin. It was a very toxic drug, it was difficult to give, it required careful monitoring, and it was far from perfect therapy. Actually, we stopped using it two years later when better drugs were approved, and now we have fairly easy oral therapy for hepatitis C.

Despite that, I treated over 100 patients successfully with telaprevir during that time, and I follow a number of them right now, and I know that some of them would not be alive had I not treated them when I did, so I see an analogy with NASH in 2023. I follow a large number of patients with advanced fibrosis with NASH, and we have no approved therapies for them. Those that are diabetic may be put on semaglutide, and that's off-label therapy for NASH because it's based on phase 2 data, and we certainly have a lot more data with OCA than we have with semaglutide. It doesn't look like semaglutide reverses fibrosis.

OCA is clearly not a perfect drug. It's got toxicities and probably will be replaced by more

effective, less toxic drugs for NASH, eventually, or when they're approved. However, OCA does reverse fibrosis, and we need to start treating patients now, I believe, rather than in a few years; therefore, I urge the committee to approve OCA for NASH. Thank you.

DR. LEBWOHL: Speaker number 12, please unmute and turn on your webcam. Will speaker number 12 please introduce yourself? State your name and any organization you are representing, for the record. You have four minutes.

DR. ABDELMALEK: Hello. My name is Dr. Manal Abdelmalek. I currently am representing myself. I'm a director of hepatobiliary diseases at the Mayo Clinic in Rochester, and the opinions I share are not that of my primary institution. I'm not paid by Intercept to be here today, nor do I have any conflict of interest.

But by way of introduction, I've been in the space of non-alcoholic fatty liver disease for 28 years, caring for patients with this condition at the time of first reporting that this does

progress to cirrhosis. And over the past 28 years, I have invested broadly in the clinical trials landscape, and as a seasoned trialist, I have participated with the NASH CRN for 17 years of my career and was a leading investigator both on the FLINT study, the REGENERATE study, and the REVERSE-IT trial, and am well-versed in the side effects and management of OCA. I'm also a certified transplant hepatologist, and all the stories you heard today from our patients and patient advocacy groups are very real and very tangible.

Over the years, there is not one day of clinic that I don't see, now, multiple patients with NASH-related cirrhosis. Every week I have to experience telling a patient that they don't qualify for transplant, refer a patient to hospice or palliative care, or advocate for a transplant listing, or be managing focal liver cancers at tumor board meetings. The epidemic of complications from cirrhosis and need for a transplant is escalating, and the existing

therapies with diet and exercise are not effective for patients with advanced liver disease.

We've talked about many concerns that the FDA has in managing OCA in real practice, but I could tell you as a hepatologist, cholestatic DILI is something we manage. In fact, it occurs with many drugs that are currently on the market, including ciprofloxacin, antibiotics, erythromycin, azathioprine, and even recently approved drugs such as imatinib for cancer.

Now, one could argue that NAFLD and NASH are not cancer; however, when patients reach the terminal stages of their disease, their morbidity and mortality are potentially no different than cancer. They're looking at death, transplantation, or downstream medications to treat liver transplantation that do have side effects. And furthermore, when we do advocate for their transplantation, we have to do new and novel things like consider sleeve gastrectomies or bariatric surgery at the time of transplantation. This is not miniscule. So I would advocate that in the

hands of hepatologists, we can manage, monitor, and treat cholestatic liver injury from an armamentarium of drugs.

There was also concern raised about gallstones. Yes, patients with NAFLD and NASH and diabetes have gallstones, about 20 percent in fact. What didn't get mentioned is what happens after bariatric surgery. The incidence of new gallstones after bariatric surgery is approximately 20 percent and, in fact, this occurs because of bile acid recirculation to the liver, and patients do develop gallstones.

The need for a laparoscopic cholecystectomy after a Roux-en-Y gastric bypass approaches about 20 to 30 percent at 1 to 2 years. These are manageable sequelae and, in fact, the incidence of post-bariatric surgery, gallstones, and need for a laparoscopic cholecystectomy exceeds that of what you saw today with obeticholic acid nearly 10-fold.

We've also talked about the dyslipidemia. I happen to be on the writing group for the American Association for the Study of Liver Disease

guidances, and I think now we can broadly say that all patients with NAFLD and NASH metabolic syndrome who are risk for cardiovascular outcomes should be broadly put on a statin therapy without concern for use unless other side effects occurred. So I think we have mitigation strategies in place that will help us manage dyslipidemia accordingly.

DR. LEBWOHL: As we're at time, I'll just ask you to wrap up your remarks in the next one sentence.

DR. ABDELMALEK: Sure.

Pruritus was very manageable in the overwhelming majority of my patients with topical therapies, and the new incident diabetes that we see, actually, if challenged with oral glucose tolerance tests can be uncovered in the majority of patients with NAFLD and NASH. These are all manageable, and as was eloquently put, death is not manageable, and we need to curtail this huge epidemic that we're seeing, and OCA is one way to offset this rapidly rising curve. Thank you.

DR. LEBWOHL: As speaker number 13 has

withdrawn, we'll move on to speaker number 14. Please unmute and turn on your camera. Will speaker number 14 begin and introduce yourself? Please state your name and any organization you are representing, for the record. You have four minutes.

MS. MARTINEZ: Hi. My name is Kimberly Martinez. I am Hispanic. I'm 7 years post-liver transplant due to NASH. I was diagnosed at age 51. I'm speaking as a patient. My first point I'd like to make is Hispanic Americans are disproportionately diagnosed with fatty liver. My dad died of cirrhosis in 1998. My sister died of cirrhosis February 2020. In May of 2013, my older brother, Paul, had been on dialysis less than a year. I decided to be his living kidney donor. In May of 2013, I made lifestyle changes and ate healthier. I joined the YMCA, and in 7 months, I had lost 96 pounds.

December of that year, 7 months later, I woke up sick. I stayed in bed all day. When my brother came to check on me, soon afterwards I

vomited up a large amount of blood. I landed in the ER, where that night I met a lot of people in a short amount of time. I was emergently bounded, admitted, and told by my doctor I had end-stage cirrhosis. In his estimation, I had 2 years to live. I was shocked.

Living with NASH, NASH has many symptoms that lessens quality of life for patients. Fatigue was omnipresent, making it tough to be there for my family. I would have insomnia at night, and as soon as the day began, I would run and go to sleep. My eyes were jaundiced. I suffered with ascites in my abdomen and around my lungs. My liver had trouble making clotting factors, so I bled easily. I had bruises. I was cold all the time, even in August, a bone-chilling cold that constantly [indiscernible] on me. I had malnutrition, and I suffered muscle wasting.

All of this affected family [indiscernible] and work obligations. There are many doctor visits and hospital stays. NASH can destroy lives and does destroy lives and families. The average age

of a NASH diagnosis is between 40 and 59, the prime earning years, the years where families are still caring for children, and in many cases, elders.

Why am I in favor of approval of OCA? NASH is fast becoming the number one reason for liver transplants. Fatty liver disease progresses to NASH many times with little to no obvious symptoms. Many primary care doctors don't take fatty liver as seriously as they should. Without a drug therapy to treat fatty liver, doctors have a hands-off approach of advising lifestyle changes and losing weight, with no follow-up with anyone that could help patients want to make the necessary lifestyle changes.

A drug therapy along with lifestyle changes will be a vast improvement from what is available now. OCA should be approved to begin to meet the serious unmet needs of more than 80 million Americans with fatty liver. It's a tool that can be safely utilized for fatty liver patients under the scrutiny and care of the patients and the doctors.

Having an effective drug therapy for fatty liver and NASH will help keep more liver disease patients from ending up needing a transplant like me, or dying too young like many NASH patients I personally know. It will lower the numbers of NASH patients on the transplant list, not only freeing up and donating livers for patients in need, but making it possible to have more living donors from the ranks of the patients that will be successfully treated at earlier stages of NASH like me.

Please don't let the perfect be the enemy of the good. With proper guidelines, the drug therapy OCA can be the first shot across the bow of this deadly disease, NASH. Thank you for your time.

Clarifying Questions (continued)

DR. LEBWOHL: The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. I would like to thank all of those participants in this open public hearing who've contributed such value to this hearing, and I hope that you understand our efforts to stick to time and

appreciate your cooperation with that.

Before we move on to the charge to the committee, the applicant has requested additional time to clarify some additional items that were raised. For that purpose, we will give the applicant five minutes to present, starting now.

DR. BERREY: Thank you, Dr. Lebwohl.

We appreciate the opportunity to clarify a few questions that arose following the FDA's presentation. First, we wanted to clarify that we as the sponsor can and will monitor which physicians and control which physicians are able to prescribe OCA for NASH if we are to receive accelerated approval. We've shown our ability to do this through PBC, which although is a rare condition, we can control the physicians and make sure that these are at centers of excellence and these are hepatologists, and specialists, and gastroenterologists. We have already identified those patients and looked at the numbers of subjects who are under their care who could be identified using the non-invasive test strategy

that we delineated earlier, and that number of subjects is no more than 700,000.

So again, because of the known hepatic safety that we are very, very concerned about, we want to make sure that the appropriate patients are being identified and the appropriate physicians are being identified to work with those patients, and that that is administered safely.

I want to then turn to Dr. Tom Capozza and our external physicians who can walk quickly through how the patients that were identified as potential drug-induced liver injury could have been mitigated through our planned hepatic safety mitigation strategy.

Dr. Capozza?

DR. CAPOZZA: Thank you. If I could have slide 1, please?

As a reminder, during our presentation, we proposed a sequential, non-invasive test algorithm that would identify patients. In addition to that algorithm, we included several upper boundary labs, including platelets, albumin, and direct bilirubin.

So using that as a framework for identification of patients, we see that in the group of three that had early onset of lab abnormalities from table 12, two out of the three of those patients clearly had evidence of cirrhosis with probable portal hypertension at baseline, and those two patients would not be within the target population. They would be off label, and thus would not receive OCA in the community. The other patient, as you see, did have excursions early that resolved with discontinuation of the investigational product.

If I could have slide 2 now?

The second group of patients are those that had excursions in the 1 month to 1 year time frame. As you see on the top line in pink, that is the liver transplant case. I would note that there were more than diclofenac as confounders, including allopurinol and amlodipine. Several other patients looked to have baseline cirrhosis if we used an NIT algorithm, which also would be contraindicated in terms of therapy. And that other patient actually was not NASH; it was probably alcohol-induced

steatohepatitis.

If I could go to the last slide, please, slide 3, with the greater than 1 year, we see that there are two more patients that had evidence of cirrhosis that would have had their drug either not initiated or stopped once that was identified. So we do believe that using a non-invasive algorithm, we can clearly identify patients that have high risk and either not initiate therapy or immediately interrupt therapy, which when done will mitigate the injury and is reversible.

DR. SAWHNEY: So earlier there was a question about risk of gallstones-related complications in patients who had gallstones at baseline. If I could have slide 2 up, please?

Here we see that the relative risk for those patients who had gallstones at baseline was actually no different than people who did not have gallstones or gallstones status not known at baseline. Thank you.

DR. McGUIRE: Hi. Good afternoon. I'm Dr. Darren McGuire, professor of medicine,

University of Texas, Southwestern Medical Center in Dallas. I'm a general cardiologist, and I've spent the last 25 years doing cardiovascular clinical outcomes trials in diabetes, lipids, and obesity. I want to just follow up a little bit on Dr. Wilson's last comment about the treatment implications of the rise in LDL cholesterol.

If I can have slide 3, please? You saw this slide in the core presentation. I think two really important take-home messages here is the slide on the right represents the patients in 303 who were initiated on statin therapy during the study. And I'll remind you, as is in the FDA briefing document, the median time to initiation is 177 days or roughly 6 months, so patients didn't immediately come under statin.

What you can see in this, unlike the overall population that got back toward baseline at month 18 with initiation of statin, that accelerates the resolution to get back to baseline at month 12. The panel on the left is the most reassuring data that I've seen in this presentation

with regard to LDL cholesterol. This was a randomized prospective trial of three different doses of OCA and placebo who were treated for 4 weeks, and then everyone independent of LDL cholesterol was initiated on 10 milligrams of atorvastatin, including the placebo group.

What you can see is there's an immediate drop, resolution of the excess LDL cholesterol, and in fact, an excursion below baseline to a very small, somewhere around 10 milligram per deciliter, contrast with placebo that occurs within 8 weeks and is sustained out to 16 weeks. This is just 10 milligrams of atorvastatin. We would use 40 milligrams at a minimum and probably 80 milligrams for most patients with NASH and comorbidities for cardiovascular risk. Thank you.

DR. LEBWOHL: And with that, it's time. Thank you for these clarifications.

We will now proceed with the charge to the committee from Dr. Frank Anania.

Charge to the Committee - Frank Anania

DR. ANANIA: [Missing audio] -- division

director of the Division of Hepatology and Nutrition, and on behalf of all of my colleagues here at the Food and Drug Administration, I would like to offer my sincere thanks to all of the participants, the study participants in 303, the applicant and all of its speakers, and the passionate hearing that we heard from the American people today. Most of all, I want to thank the advisory committee. We appreciate your service, and we know how much time it took to get here today and how much work you did in preparation.

As AC members, you have been selected by the FDA to advise us with your best scientific expertise, and you were selected based upon that expertise and your stature in the field. We will review once again the topics that will be laid before you in this final segment of the agenda in which you will discuss several questions that I think are important following today's discussion. There will be two voting questions. One is a yes/no question and the other is a choice, a multiple choice question.

Before I turn the meeting over to you as a committee, I want to make a few comments about advisory committees. Just as a reminder to the committee, the applicant, and the public listening today that advice is exactly that, and it is non-binding to the agency, and any regulatory action taken on this product will be at the discretion of the Food and Drug Administration.

Now, there are a number of things in which the applicant and the agency concur, and I want to go over those first so that we can put the benefit-risk into context. To begin with, we agree with the applicant and with the patients who spoke passionately today that NASH is clearly an unmet medical need, and that specific pharmacotherapy, as yet, has not been approved in the United States. We also agree with the applicant that there are somewhere between 6 and 8 million Americans that will be eligible for this potential treatment should it be approved.

We also concur with the applicant that, in general, as I think everyone saw, the efficacy

statistical analyses are relatively the same by the applicant and the agency; however, there are a couple of things to keep in mind about this. NASH is a chronic illness, and therapy will be at least for several years, if not lifelong. It is like the conditions in which it travels: type 2 diabetes mellitus; hypertension; hypercholesterolemia; polycystic ovarian syndrome; and the like. We cannot be sure that the treatment will be for lifelong.

Another question that has come up about the progression of fibrosis, in the AASLD guidance for caring for patients that was recently updated, the guidance notes that the rate of fibrosis progression and hepatic decompensation varies from individual and depends not only on fibrosis baseline severity, but also on other factors, including genetic, individual, and environmental, as well as other comorbidities that the patients may have. Now, we recognize the spectrum of non-alcoholic fatty liver disease, including NASH, is common, and while some patients do progress with

cirrhosis, NASH disease progression is as, I indicated, invariable and can be slow. We are not yet sure who progresses faster compared to others. In some cases, the progression to cirrhosis can take years.

I remind also that the spectrum of disease, except for those that are cirrhotic, the number one cause of death is related to cardiovascular disease and the development of non-hepatic malignancy. I also point out that in all MELD trials, cardiovascular outcomes such as in this trial are limited by the number of subjects enrolled and the scope of the trial.

Now, the proposed indication is written here, and you heard it today, that the applicant wants to apply for approval under the accelerated pathway to use 25 milligrams of OCA to treat adult patients with pre-cirrhotic NASH. Just a point of clarification about the FDA guidance that was published in 2018, the guidance denotes that treatment indication is for patients who have F2 and F3 fibrosis; that is to say, patients with NASH

in the absence of fibrosis, stage 0, or minimal fibrosis, F1, we do not concur should be treated.

I also want to point out another issue that was brought up today, and that is that the dose of the drug 25 milligrams is two-and-a-half times the dose that has been prescribed for the drug that was approved for primary biliary cholangitis. As has also been pointed out, the disease for which this drug has been approved affects about 225,000 Americans. The treatment indication for this condition, NASH, would be somewhere between 6 and 8 million Americans.

Now, Dr. Mehta reviewed the initial complete response that we made when the applicant submitted its application in late 2019. As you heard today, OCA 25 milligrams met one of the two surrogate endpoints likely to predict clinical benefit; that a one-stage reduction in fibrosis and no worsening of NASH and that treatment difference was 11.1 percent. However, OCA 25 milligrams did not meet the second endpoint, NASH resolution and no worsening of fibrosis, and as we heard before from

both the applicant and the agency, the 10-milligram dose did not meet statistical significance on either surrogate endpoint.

Now, at the time the initial application was reviewed, key safety concerns were demonstrated, as we show here today. And I'm not going to go through all these; you've heard about them. Following review of this revised application in December 2022, the conclusion of the review team at that time felt that safety was a major serious concern, and this slide summarizes what was relayed to the applicant in their CR letter that was sent in June of 2020.

Now, in comparing the findings, what is the issue for the charge today to the advisory committee? You heard a lot about benefit-risk on behalf of my colleagues who spoke to you from the agency. Benefit-risk is what we need to assess to consider approval of any agent. The original submission, as we heard today, showed efficacy that we reviewed for you and the applicant reviewed, and that serious risks were identified at that time;

and at that time, the agency concluded that there was an unfavorable benefit-risk assessment.

In terms of the resubmission, the efficacy, in general, has not changed in large measure from the original submission; however, as was stated both by the applicant and the agency, there was more safety data to allow us to do more investigations and analyses, and you can see at the last line of this slide I made, the larger safety database provided us with significant patient exposure compared to the initial application.

Now, Dr. Mehta presented this slide to you, and I'm not going to go through all of the details, but I want to make a few points about it as I close the day and turn the meeting over to the chair and to all of you. This summarizes some of the key adverse events that the agency considers considerable, and the calculations are for you to review.

Now, because the initial application, in terms of benefit-risk, was assessed to have modest benefit -- because it was a surrogate endpoint, and

compared to all of the safety issues, the FDA in its complete response letter of June 2020 recommended to the applicant to withhold resubmitting their application until they completed the ongoing Trial 303, which would yield clinical outcomes data related to benefit -- the applicant chose to resubmit this application without these clinical outcomes data. The FDA's ability to assess clinical benefit compared to risk, therefore, is unchanged from the initial submission.

I would also like to point out that since there are no drugs approved for this indication on the accelerated approval pathway, the surrogate endpoints have not been verified yet as having clinical benefit. This resubmission included the added person-years of safety information from the ongoing Trial 303, so the additional time and additional events provide more clearly the clinical risks that have been outlined for you today in the population to be treated. Therefore, while the efficacy data have remained unchanged, and we don't

dispute those, the safety data in this resubmission provide more certainty, and not less, on the safety risks associated with OCA 25 milligrams.

This slide was shown you by my colleague, Dr. Hayashi, today. The most concerning safety signal is DILI. OCA has a DILI fatality rate that he pointed out to you is far above other programs for which the drugs were removed from the marketplace. Now, the members of the review team have had considerable deliberations on DILI risks and are concerned that this risk in clinical practice would be difficult to mitigate and manage in the nearly 6 to 8 million people that could be potentially eligible for this drug; importantly, as stated, that the drug would be taken for a prolonged period, perhaps a prolonged time.

I also want to make a comment about the NIT data. To our knowledge, the use of NITs, or any risk mitigation strategy, based upon the law enacted by Congress in 2007, would be difficult to take care of in 8 million patients, and would put a great strain on the healthcare system and the

providers, not to mention that the adherence, as Dr. Hayashi indicated, would be far more difficult as treatment period ensued.

So about the benefit-risk, we are certainly concerned that the OCA risk has been magnified here because of the report by the applicant that the risk to NASH patients with compensated cirrhosis may be higher because they demonstrated no efficacy in one-stage reversal of stage 4 fibrosis to stage 3, so there is no benefit to a compensated cirrhotic to take this medication. The applicant also acknowledges that once a patient becomes cirrhotic, therefore, the patient should be withdrawn, and this is in line with the safety labeling change on the drug at 10 milligrams for PBC.

Now, respectfully, let's talk a minute about the non-invasive testing. While the agency has come to recognize that non-invasive testing is a good tool to identify patients who have NAFLD that may have NASH, and they could be eligible for treatment, we do not concur, respectfully, with the

applicant that these tests are ready for prime time use because the data are not available. And I would add to the committee, and to those listening today, that this is the reason why we have not yet accepted NITs to gauge efficacy in market applications.

The data are not available yet; they're preliminary. In fact, the guidances that were quoted by the applicant from the AGA, the AASLD, and other societies indicates, primarily, utility of non-invasive testing for screening patients in primary care settings, to send them, therefore, to hepatologists and gastroenterologists. Therefore, with the additional data that we have been provided in this resubmission, and considering the entire OCA development program for NASH, the FDA remains concerned about the overall benefit-risk of the agent.

I would like to turn the meeting over to Dr. Lebwohl and to the advisory committee. We are anxious to hear your thoughts, and we want to thank you very much for your attention. I will not read

the questions again. I think they have been reviewed for you, and for the sake of time, and I turn the meeting back over to the chair. Thank you very much for your attention.

Questions to the Committee and Discussion

DR. LEBWOHL: 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'd like to remind the 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'll pause for any questions or comments concerning its wording. We'll proceed with our first question, which is a discussion question.

Discuss the strength of the available efficacy data on the histopathologic endpoint, a surrogate endpoint that is reasonably likely to predict clinical benefit, in NASH patients with

stage 2 or 3 fibrosis treated with OCA 25 milligrams.

Before we get into discussion, I would like to know if there are any questions about the specific wording of the question.

(No response.)

DR. LEBWOHL: If there are no questions or comments concerning the wording of the question, we'll now open the question to discussion. I encourage panel members to use the raise-hand function. As a reminder, this discussion really is only for panel members, voting and non-voting. If there are specific questions directed at FDA or the applicant, we may ask them to respond, but this really is for the panel members themselves. So feel free to start using that function, and we'll start on discussion question number 1.

(No response.)

DR. LEBWOHL: If there are no hands raised quite yet, why don't I kick things off?

One thing that I noted was that when moving from smaller sample sizes to larger sample sizes,

and also from the initial histopathologic grading system to the consensus grading system, it appears that the effect size is shrinking somewhat. It's settling at not quite 10 percent in terms of the difference between OCA 25 milligrams and placebo. Actually, when comparing that to phase 2 data, the effect size back then was larger yet. So I'm wondering why even before this is let out into the world, we're seeing shrinking efficacy; just a comment out there.

Dr. Solga, I see that you have your hand raised. I don't know if that's a response to this question or if you have --

DR. SOLGA: Yes, it's similar. Steve Solga. I thought I'd just jump in to start conversation. I'm actually pretty positive about the efficacy data for stage 2 to stage 3 fibrosis, but in NASH. And I don't think the NASH part has been discussed so much. We heard presentations about the utility of non-invasive testing to identify F2s and F3s, but not whether it's NASH versus not NASH. We recognize there is an enormous number of people

with fatty liver who may be at F2 or F3, but they're not at super high risk of progressing because they don't have NASH. We don't have a NIT for NASH that we have confidence in.

So one of my concerns on potential approval is that, yes, it may be efficacy for fibrosis in the highest risk patients, NASH patients, but very rapidly, I think who's going to get treated with this would be a bunch of people with fatty liver who do have the fibrosis, but may not actually are more likely to progress to NASH [indiscernible]. And that's not something that was really discussed in the conversations this morning or I haven't heard it. I'm done.

DR. LEBWOHL: Dr. Floyd?

DR. FLOYD: Hi. This is James Floyd. I just wanted to comment that I agree with the FDA's characterization of evidence of modest benefit that's quite uncertain because in contrast with things like lowering blood pressure or treating LDLC, where treatment effects on these surrogates have reliably reproduced and translated into

treatment effects on clinical outcomes, we actually have no idea. We might hope or expect that it will, but we don't. And that's no one's fault, but it does factor into the great amount of uncertainty about the treatment effects on clinical outcomes, which the sponsor and the FDA are doing this the right way. Those events are accruing, and we will have an answer at some point.

This isn't a situation where it's impossible to collect those data for logistic or operational reasons. We will have those data. Just like in the early days of the HIV epidemic, we investigated various surrogates but we also collected clinical outcomes data, and when those data came out, they verified suppressing viral load as a validated surrogate. So I think that evidence will come, but at this point in time, this is a very uncertain efficacy assessment, and I agree with FDA.

DR. LEBWOHL: Thank you.

Yes, I'm reminded of this quote often attributed to Adam Cifu from Chicago. "A surrogate endpoint is something a patient didn't care about

until a doctor told him about it." Right? There are certain well validated surrogate outcomes. This one has a good amount of observational data behind it, but in terms of as a target of a treatment, we're not there. So while we have an effect size, how to interpret that effect size, in light of uncertainty regarding its connection with the ultimate outcomes, including the primary endpoints of this trial, we have to use our best judgment.

Dr. Lee?

DR. LEE: Just to comment that this is a surrogate. Surrogates are not events, and in this case, I think we're really at risk of conflating what we've seen from observational studies. So I think that the clinical benefit from fibrosis is really related to we know that fibrosis is associated with clinical events. We know that in natural history studies, or weight loss, or bariatric surgeries, that reduction in fibrosis reduces events, but those studies, those mechanisms, affect different pathways.

For example, bariatric surgery or weight loss, they improve the lipid profile, they improve the diabetic profile, and that mediates the mechanism for the event. Actually, in this case, we're actually going in the opposite direction for some of these pathways, so I think that needs to be considered when we're trying to speculate as to what the surrogate means in terms of clinical benefit.

DR. LEBWOHL: Dr. Assis?

DR. ASSIS: David Assis. I agree with the FDA's assessment of a modest effect as seen in this surrogate endpoint. I think an additional concern that I have, which I think was highlighted earlier, is that even if this is correct as an efficacy, which I don't doubt as far as reduction of the surrogate endpoint, I do worry that in real practice, with the potential approval, that only a minority of patients would truly undergo the histologic assessment upon which this was based. I think the NITs are a very promising tool, and I think, as was just mentioned in the preceding talk,

are used for screening and for categorization. But as a measure of response to therapy, there is some concern that in the real world, the histologic assessment, pre and post, will just not be done. And if it is done on 8 or 9 million people, there is a risk of some morbidity from that alone. Thank you.

DR. LEBWOHL: Theo Heller?

DR. HELLER: [Inaudible].

DR. LEBWOHL: I'm afraid we might be having trouble hearing you.

DR. HELLER: [Inaudible].

DR. LEBWOHL: Maybe if we can have AV work with Dr. Heller, we can circle back to him.

Dr. Czaja?

DR. CZAJA: Mark Czaja. I'd also like to express some concerns as similar to the others about the surrogate endpoint and the importance of the efficacy achieved in that. NASH is not just fibrosis, as we've talked about. It's other factors as well and other components as well. In fact, fibrosis is really a secondary effect to

hepatocyte injury, and cell death, and the inflammation that occurs in this disease.

So although I think the applicant has done a good job in addressing the surrogate given to them, we have to consider the possibility that this surrogate is not a good one. Several others things have been mentioned, the questions. I think Dr. Jorge Rakela mentioned the fact you may reduce fibrosis but have no effect on portal hypertension, and therefore, reducing fibrosis will have no clinical effect on the patient. We may eliminate fibrosis but, again, liver injury and inflammation continue to go on, and for that reason, the patient develops liver failure and, again, eliminating fibrosis has no important effect. A patient may die from their cardiovascular disease, obviously, as well and, again, we wouldn't expect a reduction in fibrosis to affect that.

I'd like to highlight what one of the other advisors mentioned. I was bothered by the fact that the applicant three or four times in the application compared this treatment to bariatric

surgery. And in bariatric surgery, in many of the studies, it was greater than an 85 percent resolution of NASH as well as an effect on fibrosis. So I think it's really unfair to compare that and say, well, we eliminated fibrosis in bariatric surgery, and that had a clinical outcome that was beneficial; therefore, this is a similar situation. I think the situation to just have an effect on fibrosis is very different. Thank you.

DR. LEBWOHL: Thank you.

If I could actually ask a question to the sponsor, and if we have the ability to call up slides, CC-59 I believe is the slide that would be relevant to this question. This touches on efficacy to some degree. This was not the primary histologic endpoint, but it was another endpoint, basically ignoring steatohepatitis, looking just at fibrosis, showing that those who got OCA 25 milligram had a higher proportion of individuals who had improved fibrosis and 17.6 percent had a worsened fibrosis stage.

I guess my question is, among those who

started at F3, what proportion of OCA 25-milligram patients worsened by one stage, i.e., F4, and, really, for safety purposes and futility purposes should stop the drug?

DR. BERREY: In those patients who were F3 at baseline, about 15 percent worsened while on OCA 25. So a majority of these patients had slightly greater percentage than F2 at baseline.

We do have the opportunity to address other ways to assess NASH, and specifically steatohepatitis that was the original primary endpoint in the FLINT study, as I think was referenced earlier. We did look at steatohepatitis not using the current guidance, as I think has been addressed. There are still new data that are emerging in the field of NASH about the overall importance of fibrosis, which I think has now been very strongly associated with those outcomes, but that the overall damage is initiated by steatohepatitis. So we do have global assessments of steatohepatitis that I think I could ask Dr. Sanyal to speak to, both from the FLINT phase 2

study and on this study as well.

Dr. Sanyal?

DR. LEBWOHL: Thank you. I think for now we'll continue the discussion among advisory members --

DR. BERREY: Okay.

DR. LEBWOHL: -- but if any advisory panel members have questions specifically for the applicant, by all means, we'll ask you to reply.

I see that Dr. Hunsberger from FDA requested to clarify a comment.

DR. HUNSBERGER: Actually -- Dr. Hunsberger -- I'm from the NIH and part of the advisory committee. I'm not from FDA --

DR. LEBWOHL: Forgive me.

DR. HUNSBERGER: -- just to clarify.

I, too, am worried about the translation of a surrogate endpoint to the clinical benefit. We've seen it in many different situations where it just doesn't translate and, typically, you would need a much bigger effect on a surrogate to see

anything on a clinical endpoint. Then I'm also worried about in the real world, where you wouldn't have this close monitoring likely, that your benefit would be reduced and we wouldn't even know it.

Then finally, what I would really like to see, that slide C-59, if you would do a combined endpoint of either worsening or having one of those bad safety events, that could easily wipe out any benefit that you saw if you're saying that all you want to do is slow progression. If you do a combined thing of safety and no progression, I think you would wipe out everything. So I agree with the FDA that using a surrogate endpoint is probably not strong enough data. Thank you.

DR. LEBWOHL: Dr. Coffey?

DR. COFFEY: Yes. Hi. Chris Coffey. I just wanted to make a comment on the last discussion. I agree if you put the risk-benefit ratio in this, but as written, we're just looking at the available efficacy data. I did want to make a point that I don't think the surrogate endpoint

in and of itself, if there was no risk concern, is as negative as the conversation has went. If there were no safety concerns, I think given the data that we've seen for efficacy, this would be acceptable. I mean, there's an FDA guidance document that supports this as a surrogate to be used for this purpose.

So I did want to just come back to that, where I think -- and some of this may get to the wording of the question that maybe we should have clarified. But if you just look at the available efficacy data by itself, I think it's pretty promising. It's when you get into the risk-benefit discussion that it becomes a bit more complicated. Thank you.

DR. LEBWOHL: Dr. Rakela?

DR. RAKELA: I think, as described, it's modest, but it's progress. We can say it's 8 percent to 10 percent of improvement that we have compared to the control group. What really worries me, not only on one side, is whether this improvement will translate in the improvement of

better clinical outcomes, as was outlined by Dr. Anania and the FDA group, but also the concern I have is about DILI in these patients.

Even with the close monitoring that has been suggested that will impact heavily in the practice of several groups because of the frequency of tests that have to be done, they may still occur. I would like to know more about what is the mechanism of this cholestatic DILI these patients have. That's why I was asking the question about concentration of OCA in the liver because it seems to be a correlation with the dose that we use, that this would be more serious in those with higher dose versus lower dose. So that would point towards a direct toxic effect versus idiosyncratic, which will be unexpected, probably immune-mediated, et cetera. We don't know.

That is the concern I have, and the fact that that is happening in these patients, you only need one patient in your practice to occur, and your enthusiasm will fade away very quickly. You can rescue the patient with transplantation as was

done with the cases we discussed, and the presentation by the applicant was very well done in terms of showing that some of these serious DILI have been prevented by the monitoring that has been suggested.

So on one hand, I think it's fair to say that there is progress in what we had before these studies. We call it modest, 8 to 10 percent, and that progress has a price which has to do with DILI, and DILI can be very severe, and I would need to know more about it, how unpredictable it is and how real is the situation the side effects would be prevented by a mediated policy as suggested. My enthusiasm is tempered by that in terms of the occurrence of DILI.

Then I would say maybe waiting, as suggested, until we get the longer follow-up in Study 303 would be wise. We'll learn more, and how much of this impact of fibrosis will translate into better clinical outcomes. Also, we'll know more about DILI, hepatotoxicity, and drug-induced liver injury in this case.

DR. LEBWOHL: Thank you, Dr. Rakela.

I suggest we expand our discussion of DILI in the next discussion question shortly. But while we're focusing on efficacy, I appreciate that it's sort of a two-sided coin because our assessment of efficacy does depend on how concerned we are about toxicity. Let's continue this discussion of question 1.

Dr. Lee?

DR. LEE: Just a brief comment, that I do think it's really important to assess risks when we're thinking about this question because in the end, the clinical benefit will be measured by reduction in liver-related events and all-cause mortality. And if we're seeing in this population that the majority of deaths will be from cardiovascular disease, cancer events, and liver-related events, then if the main risks and safety signals have been DILI and worsening cardiometabolic profile, I think we have to consider those risks in this question.

DR. LEBWOHL: Yes, point taken.

Fortunately, the primary endpoint of the trial will shed more light while we're still driving in this heavy fog. I look forward to more comments.

Dr. Mannon?

DR. MANNON: I think a propos that last comment, for me one of the big shadows over this conversation in my judgment is the mortality data that was presented by FDA. So my question is, those deaths, were they all within the context of phase 4 data? What was the dosing of the OCA? Were these in the context of other trials? How many of these were with off-label use? Those kinds of things. I'm just trying to see how that risk would relate to the trial we're talking about now.

DR. LEBWOHL: Thanks, Dr. Mannon.

If FDA would like to respond to that question about overall mortality and just the raw numbers even, if not percentages, just raise your hand, and I'll recognize you.

Dr. Maher?

DR. MEHTA: This is Ruby from the FDA. The data on deaths that has been presented in the

briefing document, those patients in the 303 trial, they were dosed with OCA 25 milligram. In the Japanese trial, there were no deaths. In the FLINT trial, there were 2 deaths, again OCA 25-milligram dose. So all the trials, we had OCA 25-milligram dose.

Could you please pull up slide 190? Thank you. This is not the phase 4 program, Dr. Mannon. This is the phase 3 program, the data from the phase 3 trial. The phase 4 trial is still ongoing.

DR. LEBWOHL: Would the sponsor like to address specifically Dr. Mannon's question about overall mortality?

DR. BERREY: I believe we understand the question is the overall mortality in Study 303, which was presented as 8 patients in placebo, 9 patients in OCA 10, and 10 patients in OCA 25. But I'm not sure that that was the question or whether this was specifically regarding either -- I apologize. I don't understand if the question was overall deaths, in which we saw no evidence for excess cardiovascular deaths, or if it was specific

for hepatic concerns.

DR. MEHTA: This is Ruby again from the FDA. Slide 190. The difference in deaths that we had at our end is we included all the patients on-study. That's the analysis we used. There were 17 deaths in the OCA 25-milligram treated patients across the whole program, which included the phase 3 trial, the FLINT trial, and 747-309. If you were to look at only the 303 trial, there were 14 deaths in patients dosed with OCA 25 milligram compared to placebo, and there were 10 deaths in that arm. Again, the cause of death, it was difficult to ascertain, except that there were two patients who died because of acute-on-liver failure in the whole program, and then one patient from Trial 303 who died because of ACLF.

DR. LEBWOHL: Now that that's been clarified, thank you, by the agency.

Would the sponsor like to respond to these specific data?

DR. BERREY: Yes. A majority, if not all, of the deaths that have been reported are in

patients who were either, in retrospect, considered cirrhotic; in particular those patients from 209, which did enroll patients who had more advanced cirrhosis, or in Study 303, when we've looked at the non-invasive tests or at the month-18 biopsies, where it was very clear that those patients had evidence of cirrhosis, either on biopsy or at baseline non-invasive tests. And when we looked specifically at those non-invasive tests, we actually found that they were more sensitive in detecting those patients with cirrhosis, who we have recommended be contraindicated both for lack of efficacy and for a potential increase.

Once we get to DILI, I would love the opportunity, if we could, to have Dr. Paul Watkins address some of the mechanistic questions that were raised. It may be more appropriate in the next question.

DR. LEBWOHL: Yes, perhaps during the second discussion if a panel member wants to ask specifically about that. Thank you.

Dr. Maher, you've been very patient.

DR. MAHER: Thank you. Jackie Maher, San Francisco. I'm trying very hard to keep my focus on the question at hand, which is really the strength of the available efficacy data in the absence of a consideration of toxicity. I think in that context, we have to acknowledge that the applicant has actually met the appropriate criteria by the FDA; that they have achieved a statistically significant improvement in fibrosis without a worsening of NASH in this patient population.

I think where it becomes much more nuanced is how strong is this data. It has met statistical significance, but is that degree of statistical significance, which we've averaged at about 10 percent, enough to translate into biological efficacy over a longer term? I for one struggle to determine whether this degree of improvement is going to be sufficient to predict an overall clinical benefit over a longer period of time. I would love to hear whether the statisticians have a comment about this or whether other clinicians would like to comment on that as well. Thank you.

DR. LEBWOHL: Thank you.

Dr. Chang?

DR. CHANG: Lin Chang, UCLA. I agree with what Dr. Coffey said and Dr. Maher was alluding to. This endpoint was prespecified. It was in the guidance. The sponsor addressed this endpoint in the trial, and they did meet the endpoint. So just based on meeting the efficacy data that was described and required by the FDA was met.

Now, the question about predicting clinical benefit, I think the issue probably is this is a large group of individuals and there's a lot of complexity. There's a lot of comorbidity, there are other medications, and I think what's going to happen is that the efficacy, based on this histopathologic endpoint, will predict clinical benefit in a subset of individuals. I don't know who that subset is, but it likely will be a certain subset, but it will probably be very complex on who and all the factors that are involved in it, and that's, I think, the problem of trying to determine the clinical outcome and also how you're going to

use it in clinical practice because we don't know that information. But I think it's definitely promising, and I am sure that there will be some patients with clinical benefit. So that's just what I want to say about the efficacy data question.

DR. LEBWOHL: Thank you.

I see there are three more hands raised, and after that I will attempt to summarize the group's feelings about this efficacy question before moving on to the next discussion question.

Dr. Czaja?

DR. CZAJA: Mark Czaja. I'd also like to agree with Dr. Maher. I'm concerned with the degree of effect in terms of it only being 10 percent. I'm also bothered by the fact that I think we have to consider what that 10 percent is based on, and that is liver biopsy. Certainly a liver biopsy is a gold standard. I think the applicant has done a tremendous job in performing Study 303, it's a beautifully performed study, but we have to take into account the fact that a liver

biopsy is a very random test. It's a very big organ and it's a very small piece, and there's going to be a lot of artifacts. For instance, someone had asked why did some of the NASH patients improve who were not treated or were on placebo. Maybe they didn't improve, but it was simply an artifact, again, of two different biopsies from two parts of the liver which showed different levels of disease.

The second part of the problem with the liver biopsies is the interpretation of them. It's not easy. I think we saw that in two instances; one with the consensus reevaluation of the histology. A number of biopsies changed. Suddenly there were some F0s in there and some F4s, so clearly disagreements, mistakes, and whatever had been made in the initial assessment. And even in the consensus evaluation, 50 percent of the time, the two pathologists did not agree on the stage of the fibrosis.

So my point is not only is the number numerically low, but I think we also have to

consider that there could be inherent artifacts to the total reliance on a liver biopsy. Hopefully they balance out in the two groups, but we have no way of knowing that. Thank you.

DR. LEBWOHL: Dr. Heller?

DR. HELLER: Let's see if the second time is a charm. Can you hear me?

DR. LEBWOHL: Yes, loud and clear.

DR. HELLER: Okay. Great.

Three things. I think the applicant did meet the endpoint that was laid out by the FDA; I agree with that. The second thing is that I think a comparison to hepatitis C and the leaders [indiscernible] of hepatitis C is not fair because those 5 percent that Dr. Hufnagel cured are not the same as the 11.1 percent here. These patients have not been cured. I think it's an important distinction that leads straight into the last point.

What worries me is sustainability. Even if we accept everything being reliable in this very well-executed study, do we know that this will be

maintained over time? And if we look at bariatric surgery, to use the analogy in a different way, people gain weight again over time, so again, I worry about the long term sustainability and I worry about the lack of validation of NITs as a measure of disease progression on therapy. I understand Baveno; I was there. I understand the fact that you can make an arbitrary [indiscernible] cutoff of 5 increase, but I don't know where the evidence is for that on treatment. So I'd like to see data that would kind of show that this is sustained, particularly as patients are not being cured.

DR. LEBWOHL: Thank you, Dr. Heller.

Dr. Solga?

DR. SOLGA: Hi. It's Steve Solga. I agree with the concerns raised by many of us on the committee, but I do think it's reasonable to return to one of the sponsor's talking points from this morning. There were a lot of issues that did not meet the endpoint, but they did not worsen. Sometimes stability in a disease process is

meaningful victory in its own right. And in no uncertain terms, it appears that people were more likely to progress in F4 when they were on placebo than when they were on treatment; therefore, I think the efficacy signal is present, and it's something bigger than 10 percent.

DR. LEBWOHL: Thank you, Dr. Solga.

So if I can attempt to summarize, it sounds like there's broad consensus among this advisory group that this histologic endpoint as a surrogate endpoint is acceptable, as FDA had previously outlined and, indeed, the sponsor met it. They did meet statistical significance. Actually, if you look beyond their prespecified analyses and you look in other ways -- non-invasive biomarkers and non-worsening or stability as a desirable outcome -- they made it there, too.

At the same time, there's a broad sense here that this efficacy data is problematic and can't be looked at in a vacuum in light of looming safety concerns. There remains uncertainty about how and to what degree this efficacy data will translate

into clinically important outcomes. There remains uncertainty regarding pathophysiology even. They did not meet the other primary endpoint relating to a resolution or diminution of steatohepatitis, and what are the long-term implications of that?

Will it be, as was asked, a subset of individuals who will ultimately respond well? And the flip side of that is will we one day identify a subset of individuals for whom this drug should not be given because of safety concerns? There's also a concern about reliance on the biopsy because of its patchy nature and differences in inter-rater scoring and the fact that it does not correlate perfectly with these clinically important outcomes. So in light of these looming safety concerns, our enthusiasm for the efficacy data is tempered.

With that, I suggest we move on to question 2. I'll ask that we project that question, and I'll read it aloud, first asking if there are any questions about the specific wording of that question, that discussion question.

While we're waiting for it to be projected,

I'm going to go ahead and read this question.

Question 2. Discussion. Based on the data presented concerning cholestatic drug-induced liver injury, DILI, in OCA 25-milligram treated patients, discuss: A) whether periodic liver enzyme monitoring could adequately mitigate the risk of DILI; B) the frequency of such monitoring; and C) what stopping criteria should be developed to aid clinicians' decisions to discontinue treatment.

Before we go and open it to discussion, are there any questions specifically about the wording of the question?

(No response.)

DR. LEBWOHL: If there are none, we will now open the question to discussion. As was the case for question 1, this is open for any panel member. Please use the raise-hand function and feel free to kick off discussion. If you have specific questions for either FDA or the sponsor, please address it to them, and in that case they'd be permitted to respond.

So feel free to raise your hands and ask

questions about any and all of these items related to monitoring for safety.

I see Dr. Rakela has his hand raised.

DR. RAKELA: Yes. I may be out of order in what I'm going to say, but the point made regarding the previous point that we discussed, the previous question, is that there is a segment of patients that do not progress, and that would be also aligned with a good response. That was the implication of the discussion we had.

Do we have a comparison of the proportion of patients who are stabilized and do not progress in the treatment group versus the control group. I don't recall to have seen that, if that data is there. It was hanging from the previous discussion that I am asking now.

DR. LEBWOHL: I'm not sure if the sponsor or agency has an answer to that question.

DR. RAKELA: The point was made by the applicant.

DR. LEBWOHL: Would the sponsor like to address this question?

DR. RAKELA: The applicant, yes.

DR. BERREY: Yes. Sorry. We were waiting to make sure we were on. Yes, I think we did review that. Dr. Capozza reviewed that in his presentation on the proportion of subjects who showed no change on histology, and then he was able to show through the non-invasive tests that those patients who were on OCA 25 versus those on placebo had changes in FiberScan and in ALT.

If we could have those slides, I'll have Dr. Capozza review those data for you.

DR. CAPOZZA: Thank you. If I could have the slide from my core presentation on no change in fibrosis with the ALT and AST reductions. I think the question at hand is that patients who had no evidence of change in their fibrosis stage after 18 months, within that group, when we looked at other markers like liver stiffness and ALT, we do see reductions in liver stiffness in the OCA 25-milligram group despite having no change on histology after 18 months, and as well on the right, you see that we see reductions in ALT on

OCA 25, again, in patients with no change, and in both cases, to a greater degree than on placebo, which suggests that these patients are experiencing some improvements, whether that be through liver stiffness or hepatocellular injury, and that over time with a another data point, we would expect that these patients could actually achieve a fibrosis benefit.

DR. LEBWOHL: Thank you.

DR. RAKELA: Yes. The question that I have, can you speculate why that's not reflecting an improvement of NASH and NAFLD activity score?

DR. BERREY: Yes. Dr. Sanyal will address that question for you, please.

DR. SANYAL: Could I have slide 1, please?

This goes to actually how the pathologists evaluate NASH. In the NASH Clinical Research Network, which has a dedicated committee of pathologists with arguably the most experienced NASH pathologists in the United States, we do not evaluate NASH in the way the FDA specifies.

The FDA definition requires NASH resolution

to have a ballooning score of zero. In a landmark study by Brunt, where they had a number of pathologists evaluate a bunch of biopsies, they identified about several hundred or I think thousands of cells that they called ballooned, but there was only one cell that all of them agreed on, so there's tremendous variability. So the presence of NASH is really determined by an overall global assessment of the histology.

Now, if you look at this slide, on the left are the data from FLINT. This is reviewed by the NASH CRN, done completely independent of Intercept, and you see a significant improvement in NASH resolution. It's defined differently. In Study 303, in the original assessment by histology, you see when the pathologists looked at it in the same way, which is a global assessment, there was a significant improvement in OCA 25 milligrams; then we look on the right on the consensus method, and we also asked them to give a global assessment, and then once again there is a significant improvement. You can see 23 -- I can't read it. Is it 23 or 25?

DR. RAKELA: Twenty-five.

DR. SANYAL: Yes, I'm getting old; I can't see very well anymore. But anyway, you can see they're virtually on top of each other.

So we've been saying that there was no NASH [indiscernible], and we sort of blew off that it has no effect on disease activity. That is actually incorrect. It is scientifically and factually incorrect.

DR. LEBWOHL: Thank you, Dr. Sanyal; though it does seem the placebo is catching up. In every subsequent trial, the placebo response rates for NASH is also increasing.

Dr. Floyd?

DR. RAKELA: Thank you.

DR. FLOYD: Yes. I'll just comment on the question. I'm not a hepatologist. I'm a general internist and drug safety scientist, and I have some familiarity with REMS programs. And I'll just say that I'm not convinced, based on what I saw from the trial and what I know about DILI -- the long latency, the variability of

presentation -- that any kind of practicable monitoring could actually mitigate this risk.

I'll save my comments for what I think of the safety signals for the later questions, but if the FDA is even considering an approval with monitoring, I think you have to look at elements to assure safe use, and that's an aspect of REMS that probably some advisors aren't familiar with. But I think anything that's kind of voluntary and not monitored closely is going to be wildly unsuccessful. Even with a registry with verification of monitoring, I still am doubtful that you would prevent all the DILI that could occur, but I just need to bring that up as a consideration. Thank you.

DR. LEBWOHL: Thank you, Dr. Floyd.

Dr. Assis?

DR. ASSIS: Yes. Hi. David Assis. Just building on the question by Dr. Rakela, as well as what was just mentioned, both for safety but also monitoring for improvement, the applicant brought up some data a few minutes ago on transient

elastography.

Can I just ask a question about the end-of-study analyses? It's been referred to a few times that there's more data to come. I have the addendum here or the appendix to some of the data from the trial design for REGENERATE. Is it correct that transient elastography will only be measured in a small subset of patients who complete this study? And if so, that would, unfortunately, represent a missed opportunity to look at the correlation between improvement, lack of improvement, or progression of transient elastography in some of the events that we're looking to avoid when it comes to safety, but also benefit. I have a question for the applicant in that regard.

DR. LEBWOHL: The sponsor has that information. They can respond.

DR. BERREY: We do have that information. We are conducting transient elastography of FibroScan at every site, at which it is available, so we do have that. As we shared, many of the

patients who had been identified as having liver injury were identified -- and we went back and looked at those baseline assessments -- as having more advanced disease by TE.

If I could have slide 1, I can show you those data. These are blinded data, not by treatment group but by looking at baseline non-invasive tests. So as we said, we have been collecting those data. The study was begun in 2015, late 2015, early 2016, so quite a while ago, and we have been adding those assessments as more has been learned about the non-invasive tests, as Dr. Loomba walked through. But you can see on the bottom right-hand corner, transient elastography was successful in identifying those patients who were at increased risk. And even more importantly, the combination of FIB-4, ELF, and TE, two of these three non-invasive tests, so that we have at least two for every patient, were able to identify those patients who were identified in table 12 of the FDA's briefing book as having significant liver events.

To round that out, for our patient risk mitigation, number one would be identification of the most appropriate patients by use of non-invasive tests, which as you can see here and in the DILI cases that we reviewed, would have eliminated 11 of the 12 cases.

DR. ASSIS: Thank you. And just to clarify, some materials out there suggest it's not in every patient. Is transient elastography being checked in every patient at the end of the study?

DR. BERREY: It's in every patient at which they have FibroScan, yes; so a majority of patients have TE.

DR. ASSIS: Thank you.

DR. LEBWOHL: I see FDA has a response to this question as well.

DR. MEHTA: We have a response to the prior question asked by Dr. Rakela. If you could please pull up slide number 155, please, from the FDA slide deck?

DR. HAGER: Rebecca Hager, statistical team leader. Just to orient to the slide, we have

results for some additional histology data. This is in the ITT histology population using the consensus method. Just to direct you to the table, look at the second half of results for steatosis, lobular inflammation, and hepatocellular ballooning, and if you look at the last column, that has the risk differences for OCA 25 milligrams compared to placebo, and I'll hand it over to Dr. Mehta to discuss those.

DR. LEBWOHL: Dr. Mehta, before you go ahead, I just want to remind the panel we're really supposed to be focusing on toxicity and safety monitoring, but I understand that you were asked this question. So why don't you wrap this up, and then we'll pivot back to that.

DR. MEHTA: Sure. We just wanted to state here that the difference in NAS score seems to be coming predominantly from steatosis. Lobular information and hepatocellular ballooning, this difference is very small. Thank you.

DR. LEBWOHL: Thank you.

If I could ask for the AV folks to call up

slide 55 from the FDA deck. This really comes to the heart of the question about DILI. This was that bar graph that was shown first by Dr. Hayashi, and then Dr. Anania, and it's very striking, and it was shown early on. No one will accuse you of burying the lede.

These are extraordinary differences, but after mulling this over and thinking about this dramatic gulf between OCA 25 and these other drugs, I came to remember that for these other drugs, they were being tested in people without pre-existing liver disease, and OCA specifically is being given to people who are at high risk for the hepatic decompensation and have chronic liver disease.

I guess what I would ask FDA to comment on here is now that we're looking at a drug specifically for this indication, where the target population is more likely to develop any kind of liver injury and decompensation to begin with, should we be comparing this drug to drugs that were not used in that kind of population, and should the threshold perhaps be different when considering

DILI?

DR. HAYASHI: This is Dr. Hayashi. Yes, that's an interesting point. You're asking us to basically have a different fatality tolerance for different baseline diseases. My answer would be, I would have great reservations about that.

When those three drugs were pulled from the market or had problems postmarket, there was a fair amount of fanfare, and I don't think it mattered that, oh, they were diabetes patients or, oh, they were NASH patients. I think the point is when you get these DILI fatalities happening postmarket, I think the underlying disease becomes, I think, less important, is my opinion, and I think the agency would have a hard time adjusting fatality tolerance by different diseases across the board. It's more about risk and benefit. If there's great, great benefit, then the tolerance can be thought about, but not so much the underlying disease, no, would be my answer. Thanks.

I don't know if Ruby has something.

DR. MEHTA: Yes. This is Ruby Mehta again.

I do want to add that in a clinical trial, we had the placebo arm and the treatment arm, so we identified the differences at a population level first, and then we honed down and did a qualitative assessment, and we were able to identify these elevations or these fluctuations are not -- even the mild DILI were not just elevations. Moderate to severe is a different story.

So it would be problematic if OCA was approved because the physicians would have a difficult time to distinguish between the fluctuations versus who is the patient who's progressing. And this is the very reason we want the AC committee to opine, and we're seeking our advice on the cholestatic DILI and the risks associated, and in the postmarketing period can we identify this.

DR. LEBWOHL: Thank you.

Dr. Lee?

DR. LEE: Brian Lee. To just try and focus on the question, the first one was whether periodic liver enzyme monitoring can mitigate the risk of

DILI, and I think the sponsor has shown pretty compelling data that once they increased the frequency of monitoring and had very strict stopping rules, that they were able to significantly reduce the DILI events; and that when they were to catch early events, withdrawal of the drug did lead to improvement in the cholestatic DILI. So I think the answer is yes. Dr. Hayashi proposed that 2 to 3 weeks monitoring would be a proposal. I think that frequency would be very challenging in the postmarketing world, especially if we think that most patients will be on this drug for years, really.

Another stopping rule that's important is progression to cirrhosis or F4 disease. I think the sponsor has really intimated that non-invasive testing would be the most reasonable approach from the feasibility standpoint, but I think that it may be early is what I would say. I don't think that there's sufficient data to support longitudinal use of NITs, particularly on an intervention that is expected to affect both fibrosis and hepatitis, the

discrimination of F3 versus F4.

The sponsor did show themselves that the sensitivity is very low, so you could have many negative results and actually miss cases of progression to cirrhosis. I think that there would need to be some type of different stopping -- monitoring for cirrhosis, if that were the case.

DR. LEBWOHL: Thank you.

Dr. Wilson?

DR. WILSON: Yes. Peter Wilson here. I had the same question Benjamin Lebwohl had about what is the fair comparator, so I'm wearing my epidemiology hat. In Arun Sanyal's New England Journal article, which was sent to us in advanced materials, his figure 2, death from any cause and hepatic decompensation events, you can start to get some sort of feeling for the event rates. I don't think there's a way to pull this up, but those of us who had the advanced materials, it's about hepatic decompensation at 4 years.

For the F3 level, it's about 1 in 100. For

the F0 to 2, it's about 1 in 400, and then from death from any cause, F3, it's about the similar number of cases, but we don't know what they died from, and F0 to 2, it's 11 cases -- F0 to 2, it's 14 cases.

So it's not easy to get there, but these numbers are much higher for patients with 0 to 2 and F 3, who you would think would represent the people who were in the trial. And this was the paper that was the prospective study of outcomes in adults with NAFLD, based on 1700 adults. Many of us had this sent out to us ahead of time.

So they're much higher, exactly as you said, Dr. Lebwohl. They're much higher, and I think we have to think about 0 to 2 and level 3 patients is not the same as the free living person, for instance, who might have been put on troglitazone for diabetes management.

DR. LEBWOHL: Thank you.

Dr. Floyd?

DR. FLOYD: I wanted to build on the comment that you made, Chair, because I think it's an

important one, and I've struggled with the same thing. In a vacuum, if this weren't a therapeutic for liver disease patients, one or two DILI fatalities would be a non-starter. We wouldn't be discussing this in an advisory committee. And honestly, I can't think of a time that FDA has approved a drug in the last 20 years where there's been even a single fatal DILI case. The difference is that these are patients at high risk of cirrhosis and decompensated events.

One thing I learned many years ago, actually, from John Senior when reviewing DILI cases for diabetes drugs is that it's very, very hard to do causality assessments. I've tried to do them, FDA has done them in this study, the sponsor has, but there's still uncertainty, and the best tool we have is randomization and actually counting events. I don't think we can actually weigh the magnitude, the absolute magnitude, of the DILI risk until we look at the potential benefits in terms of clinical events. Are we seeing reductions in hospitalizations, variceal bleeds, ascites

requiring therapeutic paracentesis? And until we have counts of that, I don't see how we can weigh this really uncertain estimate of DILI events, which are quite serious and can be fatal or lead to a transplant, and right now, I think we have to be conservative.

I mean, if you're talking about millions of people with NASH who could go on this drug, 1 in a thousand could get severe DILI. I mean, you're talking about a new epidemic of liver disease as an adverse effect of a drug. I'm even a little surprised at seeing this at an advisory committee, but just thinking about how to weigh this drug versus others with liver signals, I don't see how we can do that until we see benefits in terms of tangible clinical events.

If you're preventing 10 cases of ascites and variceal bleeds for every hundred patients on this drug, and you have one DILI per thousand patients, sure, we can weigh that and say the benefits clearly outweigh the risks, but with histologic evidence as the evidence of benefit, I don't see

how you can do it. Thank you.

DR. LEBWOHL: Thank you, Dr. Floyd.

Ms. Hugick?

MS. HUGICK: Yes. Thank you. We're talking about risk and monitoring, and I think something that came up from Dr. Sawhney this morning was related to the enhanced pharmacovigilance proposals and the risk management, and the piece that we haven't talked about today -- I'm the consumer representative, so I feel like I need to represent the voice of the patient -- is that piece of it. The faster things can be identified, the sooner that we can stop it.

The patient plays a role in that. I just want to keep that on people's minds. We didn't really talk at all about what that looks like for this, but I do think that whether it's a website or a patient assistance program, having those things in place so that if 6 to 8 million people start taking this drug -- and we don't really know; there's so much uncertainty. I just wanted to put that out there so that we're thinking about it.

Thank you.

DR. LEBWOHL: We'll take two more comments. First there will be Dr. Assis, and then will be Jennifer Schwartzott.

DR. ASSIS: David Assis from Yale. Specifically to the questions asked here, I do have concerns that periodic liver enzyme monitoring could adequately mitigate the risk of DILI, the latency, and I think we've known from PBC studies that there can be an effect of bile acid retention that I think can be very difficult to predict. I think we don't have enough data on the frequency of monitoring, and I think we also didn't hear enough -- because there just is no data -- about what type of stopping criteria regimen to come up with, so I think those are concerns.

To the point about these patients having pre-existing disease, as a hepatologist, if a patient has stage 2 fibrosis with NAFLD, that's very different from being on the verge of a liver transplant. So I think our risk tolerance needs to be adjusted for the severity of what we're talking

about, and that I think has to be important. We saw some events which did not occur in placebo, so that's another effect that needs to be kept in mind. Thank you.

DR. LEBWOHL: Ms. Schwartzott?

MS. SCHWARTZOTT: Hi. Jennifer Schwartzott, and I'm the patient representative. I'm coming at it from a totally different perspective because I am the patient. I represent patients, and I was really impressed with those that spoke earlier.

I'm really struggling. I'm not a renegade, I'm not a major risk taker, so I'm struggling between the benefit and risk assessment. But it struck me when you put up the slide, slide 55, that predicts the DILI fatality rates. They're concerning for sure, very concerning. But what are the predicted fatality rates for people who were not treated for NASH, who were not treated for the fibrosis? They've got to be way higher.

I'm lucky that I'm not in this predicament right now, but I could become that. So for me, I would rather have the risk of a DILI reaction and

adverse reaction, knowing that all the things that we have discussed could happen to me, versus dying from untreated liver disease. And when it comes right down to it, I have most of those things that are the adverse events, and I live a perfectly wonderful life with quality of life, with diabetes, and with cardiovascular disease. I have mitochondrial disease that affects your entire body, so every organ system is affected, which is what also likely causes the NASH. So I can live with those factors. I can live with all those adverse events, but you can't live if you're dead. So I'm really struggling with the benefit and risk, but I think we really need to think about that.

I also do think if I did take the drug myself, I would want very close monitoring. I would want them to find out if this is not the drug for me. And if I had to stop it, at least I tried; it would be something trying. And hopefully we'll get more medications soon that will be a better option, but at least this is an option. So I wanted to make sure that I stated this because, to

me, the benefit outweighs the risk.

DR. LEBWOHL: Thank you --

MS. SCHWARTZOTT: Thank you.

DR. LEBWOHL: -- for your perspective.

If I can attempt to summarize the panel's impressions, and I would say that it's far from unanimity, my attempt would say that the monitoring program that was set up does appear to mitigate, in part, risk of DILI, and has been associated with reduction in events, but does not entirely eliminate the concern that the panel has about safety. Particularly with regard to the question of frequency of monitoring, there's concern that what's suggested by the sponsor might not be adequate, particularly in light of the fact that DILI may occur a long way out from drug initiation and cholestatic liver injury may occur pretty rapidly after even one normal spot check of liver enzymes and bilirubin.

With regard to the question of what would be a tolerable risk of DILI, the agency's approach is that DILI is DILI, and fatal DILI is something that

is really a showstopper. There was some feeling among the advisory committee that perhaps in a drug for chronic liver disease, where those not exposed to drugs are also at risk for severe liver-related outcomes, maybe that should be a different consideration. At the same time, ultimately there was concern that given how common NASH is and the burden of disease, unleashing a medication that has a non-trivial risk of DILI, including even fatal DILI, could have public health implications. There's uncertainty about whether non-invasive monitoring will be adequate to identify those who progress to F4 to cirrhosis in whom efficacy would no longer be applicable and in whom there would be substantial safety concerns.

That would be my overall summary of this discussion question. What I would suggest now --

DR. BERREY: Dr. Lebwohl, apologies. This is Michelle Berrey from the sponsor. Given that so much of the assumptions around DILI have been based on the assumptions that this is a classic small molecule DILI and, unfortunately, because we didn't

receive the FDA's slides until about 20 minutes before the presentations began this morning, we didn't have an opportunity for Dr. Paul Watkins to address what we do understand about liver injury related to this molecule, and we would appreciate a short opportunity for Dr. Watkins -- five minutes, please -- to just explain --

DR. LEBWOHL: I would suggest that before the break, we give Dr. Watkins two minutes now to present, and then we'll take a 10-minute break.

If, Dr. Watkins, you are available and you are able to present on that short time scale, I would appreciate it.

DR. WATKINS: I am. Paul Watkins. I'm a clinically trained hepatologist professor at University of North Carolina, with a very long-standing interest in mechanisms of drug-induced, liver injury, and I direct the Institute for Drug Safety Sciences there, which has been dedicated on finding mechanisms and understanding how they can predict a liver safety liability of new drug candidates and how to manage

that liability when it exists.

It's been brought up, is this an idiosyncratic toxicity? That's what the DILIN Network has been doing for 20 years, and I have chaired, or co-chaired, the steering committee, and also chaired the genetics committee since the inception. And what we've learned is that idiosyncratic DILI, which is usually small molecules but not entirely, generally involves an adaptive immune attack on the liver; that is cytotoxic T cells honing in to hepatocytes and killing them, or cholangiocytes and killing them. These attend to occur after months on treatment, and once you initiate the immune attack, removing the drug doesn't necessarily make the injury go away. And, in fact, about 20 percent of patients with idiosyncratic DILI still have evidence of ongoing liver injury at 6 months.

The value of monitoring, you cannot predict which patients are going to get there, although genetic risk factors are slowly being defined, and actually the value of liver chemistry monitoring

has never been really adequately figured out in that case. OCA is different. OCA is lipophilic bile acid, and as a class, it's known to be directly toxic. So even in phase 1 human volunteer studies, they saw to increase the dose. They saw toxicity. It is eliminated in bile so that it is possible to identify patients' susceptibility factors. So obviously a stone in the biliary tree will prevent the elimination of OCA, and if you continue to take the medicine, it will go up.

If you have cirrhosis progressed on to global liver dysfunction, the values would go up, and also functional obstruction; in other words, situations in which bile production is reduced; and staph sepsis was probably part of the mechanism for the patient that needed the transplant.

The point is, it's not an idiosyncratic toxicity. Removing the drug at the earliest detection of a problem and allowing the liver exposure to go down below the threshold limit is a rational plan for monitoring. Thank you.

DR. LEBWOHL: Thank you, Dr. Watkins.

What I suggest we do now is that we take a 10-minute break. Panel members, please remember there should be no chatting or discussion of the meeting topic with anyone during the break. We will resume at 4:05 Eastern Time.

DR. SEO: Dr. Lebwohl, this is Jessica speaking, the DFO. I think we might want to just verbally ask the FDA if they would like an opportunity to respond before the break.

DR. LEBWOHL: So if we've not yet gone on break, and if FDA is interested, is the FDA interested in providing a 60-second response to Dr. Watkins?

DR. HAYASHI: Sure. Thank you.

Yes, I think the point's well taken. A lot of DILIs are partially idiosyncratic and partially dose related, and this one maybe has a fair factor of dose related. But I think it only strengthens the concern about the OCA concentration exposure going up. You cannot predict a bile duct obstruction with a stone. You cannot predict a patient occasionally passing a stone or sludge.

You may never even know it. They may have some dull pain, but during that time, the OCA exposure in the liver will probably go up, and therefore your DILI risk will go up.

So I take Dr. Watkins' point, but in a way, it only strengthens our concern that over a long period of time, bile duct obstruction can happen without any notice, and then DILI will happen right on that. Thank you.

DR. LEBWOHL: Thank you, Dr. Hayashi.

And now as promised, we'll take that break. We'll convene at 4:05 Eastern Time.

(Whereupon, at 3:56 p.m., a recess was taken, and meeting resumed at 4:05 p.m.)

DR. LEBWOHL: We will now move on to the next question, which is a voting question. Dr. Jessica Seo will provide the instructions for the voting.

DR. SEO: Hello, Dr. Lebwohl. Thank you.

Before we begin the vote, I just wanted to relay a request from the sponsor to have another minute for a final statement. Again, up to you, at

your discretion as the chair. I just received this, so did not have a chance to relay it to you until this moment, so sorry to put you on the spot.

DR. LEBWOHL: Why don't we give the sponsor 60 seconds? No more.

DR. SEO: Okay.

DR. BERREY: Thank you very much.

So very quickly, I just wanted to reiterate that we're willing to limit the population to optimize benefit-risk to those patients who are at highest risk for progression to cirrhosis, and they're happy to work with the agency to continue the stringent monitoring that we've shown we can implement successfully in PBC.

As has been acknowledged, we have met twice the endpoint specified in FDA's guidance for accelerated approval for products like NASH, and would carry forward to outcomes should we be granted accelerated approval. We've also stated publicly, in the absence of accelerated approval, it is not clear how continuing the study to outcomes would be economically feasible for this

small company. Thank you.

DR. LEBWOHL: Thank you.

And now back to Dr. Seo.

DR. SEO: Thank you, Dr. Lebwohl.

This is Jessica Seo, DFO speaking. Questions 3 and 4 are voting questions. Voting members will use the Zoom platform to submit their vote for this meeting. If you are not a voting member, you will be moved to a breakout room while we conduct the vote. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, we will announce that voting will begin. A voting window will appear where you can submit your vote. There will be no discussion during the voting session.

You should select the radio button that is the round circular button in the window that corresponds to your vote. Please note that once you click the submit button, you will not be able to change your vote. Once all voting members have selected their vote, I will announce that the vote

is closed. Please note, there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the list, and each voting member will state their name and their vote into the record. You should also address any subparts of the voting question, which includes the rationale for your vote.

Are there any questions about the voting process before we begin?

(No response.)

DR. SEO: Alright. I don't see any hands. Since there are no questions, I will hand it back to Dr. Lebwohl, and we can begin.

DR. LEBWOHL: As there are no further questions, we'll now begin voting on question 3. I'll read the vote question, and then I'll ask if there are any questions about the wording.

Given the available efficacy and safety

data, do the benefits of OCA 25 milligrams outweigh the risks in NASH patients with stage 2 or 3 fibrosis?

Are there any questions from the panel members about the wording of the question?

Dr. Coffey?

DR. COFFEY: Yes. My question is with the last part, the stage 2 or 3 fibrosis, and kind of getting clarity specifically for the risk aspect of it because one of the key points in the FDA presentation was that there may be difficulties in ensuring that only stage 2 or 3 individuals are identified to get this.

I'm just seeking clarity on when it says with stage 2 or 3 fibrosis, is that definitive stage 2 or 3 fibrosis or stage 2 or 3 fibrosis as it would be implemented here?

DR. LEBWOHL: Would the agency like to respond?

DR. ANANIA: Yes. This is Dr. Anania responding to you. Patients with stage 3 or 2 fibrosis, Dr. Coffey, will be as they have

presented today.

DR. COFFEY: Okay. Thank you.

DR. LEBWOHL: Dr. Chang?

DR. CHANG: It's not really about the wording, but I have to say it's a little challenging to vote on this when if it does move forward, we don't know what the safety monitoring aspect is and if what would be decided would be something that would be acceptable to the committee. I'm just having trouble with that because we don't know, if it goes through, what will happen.

Do you know what I mean? If there was a very good mitigation strategy that people felt comfortable with for the safety of the patients, then it may be a different tendency to vote versus not at all knowing what would happen.

DR. LEBWOHL: Would the agency like to respond?

DR. ANANIA: Yes. Thank you for the question. You have the option of abstaining from the vote, first of all, yes, no, or abstain.

Secondly, the question is written with both issues in mind. That's why you are here; that there's a benefit-risk assessment. So we are asking you as an expert to vote on the data that has been presented in both the efficacy data and the safety data, and answer the question yes or no, but again, you can abstain if you'd like.

DR. LEBWOHL: Thank you.

If there are no further questions or comments concerning the wording of the question, we will now begin the voting on question 3.

DR. SEO: We will now move non-voting participants to the breakout room.

(Voting.)

DR. SEO: The voting has closed and is now complete. The voting results will be displayed. There were 2 yeses, 12, noes, and 2 abstentions.

Dr. Lebwohl?

DR. LEBWOHL: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also concisely include the

rationale for your vote.

We'll start with Ms. Hugick.

MS. HUGICK: Joy McVey Hugick. I abstained. I don't take lightly the serious unmet medical need, especially after hearing from so many passionate patients and family members this morning, and being one myself. But at the same time, I feel there's too much uncertainty as it relates to safety concerns and lack of clarity when it comes to monitoring should this drug get approved, so I had to abstain.

DR. LEBWOHL: Dr. Maher?

DR. MAHER: Jackie Maher. I voted no for a couple of reasons. Although I acknowledge that the applicant has met the primary endpoint for efficacy and I would like to be very optimistic that this will translate ultimately into clinical benefits, I remain concerned that a drug such as this will be able to be restricted to prescription by only experts who are willing to take the necessary steps that are required to mitigate risk, and I also am concerned that the high prevalence of biliary

disease in this population is going to raise the bar, the potential for risk of drug-induced liver injury, which can be both sudden and severe. Thank you.

DR. LEBWOHL: Dr. Coffey?

DR. COFFEY: I voted no. Although the efficacy data looked promising, I think the risk-benefit ratio and the challenges to mitigating the risks are just too substantial, and without the clinical data, it's very difficult to put that in full context. Thank you.

DR. LEBWOHL: This is Benjamin Lebwohl. I voted no. This pivotal phase 3 study has a primary endpoint of death and other important outcomes, including a high MELD score, liver transplant, and decompensation. Right now, we're seeing numerically more deaths in the OCA 25 milligram than placebo. We have a promising outcome with regard to a surrogate endpoint. The degree to which that promising surrogate endpoint will ultimately yield benefits in terms of the primary endpoint of the study remains marred and

uncertainty. Particularly regarding the concerns relating to DILI, at this point I do not believe that the benefits outweigh the risks. We're keeping in mind that this is a surrogate endpoint among people who are asymptomatic at baseline. This is a serious disease; however, the bar needs to be quite high when considering the effect.

Next is Dr. Floyd.

DR. FLOYD: I voted no. For this drug, we have clear evidence of safety risks, including for very serious safety concerns with DILI, but we have only evidence for potential efficacy on the surrogate, and it's impossible, in my mind, to ensure a good risk-benefit profile based on this surrogate endpoint data, and we need to see the full clinical outcomes. Thank you.

DR. LEBWOHL: Dr. Mannon?

DR. MANNON: I voted no, and for many of the same reasons. I was very unimpressed with the efficacy signal, and coupled with some of the doubts about measures and how to mitigate risks, and coupled with the background potential DILI

fatality, I just didn't think it was ready for prime time yet.

DR. LEBWOHL: Dr. Czaja?

DR. CZAJA: Mark Czaja. I voted no. Although I think the applicant met their endpoint, I was concerned about the minority of patients that were possibly affected by the drug. I was concerned about the inadequacies of the surrogate in that it may not reflect clinical outcome, and I was convinced that there was good evidence of the number of side effects. I'm concerned how those will be managed once this drug is released to the general population. In particular, I was concerned about a lot of the side effects that we didn't talk about that much, ones related to the metabolic syndrome, particularly the effects on lipids and glucose. Thank you.

DR. LEBWOHL: Ms. Schwartzott?

MS. SCHWARTZOTT: I voted yes. This is Jennifer Schwartzott. As a patient and a patient representative of my community, I want this option to be available, even if under limited use. I do

have concerns. OCA is definitely not perfect. There are many uncertainties. There are risks. But even as a non-risk taker, the inherent risk of the disease itself is way scarier to me than the risk of the adverse events. So that was my thinking on that. I do feel that the company has been very responsible so far, and I encourage them to continue to do that and to limit the availability. Thank you.

DR. LEBWOHL: Dr. Wilson?

DR. WILSON: Yes. My video won't come on, so no video. Peter Wilson here. I voted no. I had concerns about the fibrosis, the DILI, the gallbladder outcomes. I wasn't so concerned about lipids and the glycemic, but I think that would involve increased care by experts in lipids and glycemic control, especially endocrinology, and that may be an unanticipated extra need for such patients.

DR. LEBWOHL: Dr. Assis?

DR. ASSIS: David Assis. I voted no largely for the reasons already stated. As a hepatologist

who takes care of patients with NAFLD, it is a complex issue, and it's painful to not have therapies for patients. But given the question as it was stated, I think that the potential risks outweigh the potential benefits. The company, I should just add, did a laudable job in the studies thus far and did meet the endpoints, but I think if you were to upscale this much beyond what was done in PBC, there is a potential for risk, and that risk concerns me too much. Thank you.

DR. LEBWOHL: Dr. Solga?

DR. SOLGA: I don't embrace these drugs readily. I'm a very slow prescriber by nature. When I read the FDA briefing packet, I figured there was no way I would vote yes on this. I guess I was just feeling oppositional today or something. At some point during the day, I felt like I flipped a bit, in part because of the lack of options.

The analogy to troglitazone, the thing is there are many, many ways to manage diabetes, and there are many instances in the world. There isn't another way to manage this issue, and I think in

liver clinic, a lot of what we do is just really manage the anxiety. Folks come in and they're very super wound up.

When I manage fatty liver, I tell people to encourage healthy lifestyles, go for a walk, and I try to reduce their concern over this. Many of them have done their very, very best. In a small minority of patients, this drug might help, and they would sign up for the liver monitoring, and it would get done.

I guess I feel ultimately what flipped me into the yes vote [indiscernible] is feeling like individual patient agency is more important to me now than it used to be, and maybe that's COVID residue, so empowering folks to have potential options. But I do share the rest of the panel's concerns.

DR. LEBWOHL: Dr. Chang?

DR. CHANG: I was struggling through this one, but just looking at safety and efficacy, I did feel that they met their endpoint that was prespecified, and listening to the patients and

recognizing there aren't options, as was mentioned earlier, that you can have progression and death from this disease. But I felt that the efficacy outweighed the safety probably in a select group of patients, but other patients, it was reversed. So that's why I struggled because I do think that efficacy could outweigh safety in some patients. The problem is, as someone mentioned before, there's uncertainty. I just struggled. That's why I gave it an abstain.

DR. LEBWOHL: Dr. Lee?

DR. LEE: Brian Lee. I voted no. I thought that the sponsor addressed the high unmet need and did meet their clinical endpoint. I still do think that the surrogate is an important surrogate, but I thought that the magnitude of what they demonstrated was unimpressive, and I'm concerned that the predicted effect on clinical events would be attenuated. I was especially concerned about the risk and how they would translate to a postmarketing world with less monitoring and longer follow-up, and I thought that the risk mitigation

strategies seemed impractical and inadequate in this postmarketing world.

DR. LEBWOHL: Dr. Heller?

DR. HELLER: I voted no. I agree with a lot of what has been said. I agree that the applicant met the criteria for efficacy. Modest or not, they met it. My concerns are also to all the risks mentioned. The fact that they're asking for accelerated approval, this is not whether or not we approve. The option of continuing with the study is still there. Whether they do or not is up to them or their finances. I think in a controlled setting of a clinical trial, we'll get definitive answers to a lot of the questions we're asking, and we would not get it easily any other way.

DR. LEBWOHL: Dr. Rakela?

(No response.)

DR. LEBWOHL: Dr. Rakela, you're muted.

DR. RAKELA: I voted no, although the applicant fulfilled in the trial one of the criterion endpoints of efficacy. But I will eagerly await the clinical outcome data and also a

better definition of the incidence mechanism and clinical outcome of DILI associated with OCA.

DR. LEBWOHL: Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger. I voted no for many of the reasons everyone else did it. Given the safety concerns, the surrogate endpoint isn't quite strong enough to be able to outweigh the safety concerns, so I think we have to get the clinical efficacy data to be able to understand how to use the drug, and what populations it might benefit, and how you would actually monitor and select patients. So I think without that clinical efficacy data, you don't know how to use this drug or who it might benefit. That's all. Thank you.

DR. LEBWOHL: Thank you.

So to summarize, if I may, the majority did vote no. The panel expressed laudatory words for the sponsor and acknowledged that they did meet their primary endpoint. At the same time, those voting in the majority noted that there remained some uncertainty about the meaning, ultimately, of the surrogate endpoint and how it will translate to

clinical outcomes, particularly in light of some safety concerns that have come up.

The minority of voters who voted yes or abstain noted that it would be helpful to have options in this area, particularly for subgroups who may benefit, and particularly in light of the great unmet need in this disease area. The broad consensus is that we do eagerly await the full outcome data from the ongoing trial.

So with that, we will now move to question 4, also a voting question. I'll ask for it to be displayed.

DR. SEO: Dr. Lebwohl, I apologize for interrupting. This is Jessica speaking, DFO. Just really quickly, I was informed before, when I read the vote totals into the record that the audio had partially cut off my statement. So just to ensure the public is aware, the vote totals are as follows. There were 2 yeses, 12 noes, and 2 abstentions to question number 3.

Thank you, Dr. Lebwohl, and we can wait for question 4 to be brought up for display as

Dr. Lebwohl has requested. Thank you.

DR. LEBWOHL: Thank you.

Yes, if we can now display question 4, and I will read the question. After I read it, I'll ask if any panel members have any particular questions or comments about the wording of the question. I'll start reading question 4.

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

Are there any questions or comments from the panel about the wording of this question? Please use the raise-hand function.

(No response.)

DR. LEBWOHL: If there are no further questions or comments concerning the wording of the question, we'll now begin voting on question 4.

DR. SEO: We will now move non-voting participants to the breakout room.

(Voting.)

DR. SEO: Voting has closed and is now complete. The voting results will be displayed. There was 1 vote for A; 15 votes for B; and zero abstentions.

Dr. Lebwohl?

DR. LEBWOHL: Thank you.

We will now go down the list and have everyone who voted state their name and vote in the record. You may also concisely include the rationale for your vote. We'll start with Dr. Floyd.

DR. FLOYD: This is James Floyd. I voted no for the reasons I stated earlier. Thank you.

DR. LEBWOHL: Dr. --

DR. FLOYD: No. I voted for B. Sorry.

Thank you.

DR. LEBWOHL: Just to clarify.

Ms. Hugick?

MS. HUGICK: Yes. This is Joy McVey Hugick, consumer representative. I voted to defer approval. Again, the unmet need and the lack of options weigh heavily on me. At the same time, it's just too hard to predict clinical benefit with the surrogate endpoint at this point. I do want to state that I hope the sponsor will continue on and have the resources to bring this to the traditional approval process because I do think once we have more data, we'll be able to lessen that uncertainty and hopefully make a better decision in this committee.

DR. LEBWOHL: Dr. Assis?

DR. ASSIS: David Assis. I voted to defer approval for the traditional approval process. I think we've struggled with this question and the burden and the risks all day, but I think this also illustrates precisely the value of traditional approval processes for points in which we have this

uncertainty, and I think this makes a strong case for traditional methodology for a situation like this. Thank you.

DR. LEBWOHL: This is Benjamin Lebwohl. I, too, voted to defer approval. One comment that really stuck with me from the open public hearing was that we need a medication for NASH, and I agree. The unmet need is real and growing, but given the real possibility of the primary endpoint, a clinically important endpoint, from this trial may not be met, the known safety signals that we're seeing, including effects on lipids, gallstones, possibly glycemic effects, the DILI issue, and in light of the relatively modest effect size of the surrogate outcome, I'm concerned that acting now may lead to a reversal down the road, which will not benefit the millions of Americans who are looking for our guidance in identifying safe and effective therapies. Perhaps OCA might turn out to be such a therapy, but I advise to wait.

Dr. Maher?

DR. MAHER: Jackie Maher. I also voted B.

Dr. Lebwohl stated it very eloquently. I have made my choice for many of the same reasons, so I will yield to the the next voter.

DR. LEBWOHL: Dr. Lee?

DR. LEE: Brian Lee. I voted B. Really, I'm just concerned about potential harm. I think it's best to be prudent in this scenario.

DR. LEBWOHL: Dr. Coffey?

DR. COFFEY: Chris Coffey. I voted B as well, much for the same of the previous. I think given the risk-benefit observed here, the clinical outcome data will be critical in making a more educated decision. Thank you.

DR. LEBWOHL: Dr. Mannon?

DR. MANNON: I voted B as well, again, for many of the reasons already stated, and I'm hoping maybe they can roll in lack of progression, as well as with reverse of some of the fibrosis and things.

DR. LEBWOHL: Dr. Rakela?

DR. RAKELA: I think you, Dr. Lebwohl, said it very clearly. I endorse that statement.

DR. LEBWOHL: Ms. Schwartzott?

MS. SCHWARTZOTT: I am the only one that voted for A, but I am the patient representative, so I come from a different perspective. This did really weigh on me, though. I could not make up my mind back and forth, but I kept thinking about the patients who are waiting for this, who are in trouble now, and how long it will take. So that was where my thinking came from, but I do see the benefit of further study, so that was my vote.

DR. LEBWOHL: Dr. Hunsberger?

DR. HUNSBERGER: I voted B for the reasons stated; that we just have to have the clinical outcome to understand the risks. Thank you.

DR. LEBWOHL: Dr. Chang?

DR. CHANG: I voted B, defer approval. I'm very open to having a risk mitigation strategy. I've used alosetron -- a different disease -- and other drugs, and it seems to proceed well with close guidance. But I think the issue that I had was that members of the committee raised the issue that they weren't sure the best way of monitoring the patients and that you would have to do it

frequently, and I thought that was going to be difficult to do in a large group of patients. So I felt that was a big challenge and that it was going to be more risks, so that's why I voted B.

DR. LEBWOHL: Dr. Heller?

DR. HELLER: I voted B for all the reasons stated, and I would eagerly anticipate the results of the study, and if the endpoints are met, it will be very exciting for this huge unmet need.

DR. LEBWOHL: Dr. Solga?

DR. SOLGA: Really nothing more to add. I'm really very interested to see if they're able to continue the study to see if the surrogate endpoint proves to show benefit in a couple of years. I think a lot of this discussion is about whether or not the guidance provided in the 2018 document is really useful, or the one-point fibrosis is just inadequate. I don't know.

DR. LEBWOHL: Dr. Wilson?

DR. WILSON: Peter Wilson. I also voted B, to defer, and I share Dr. Chang's concerns that we really need the clinical data. And this may come

down to some subgroups, and we need all those subgroups. We need the full outcomes. Thanks.

DR. LEBWOHL: Dr. Czaja?

DR. CZAJA: Mark Czaja. I also voted B for the reasons I stated under question 3, but I hope further studies might prove that this therapy is a valid one for a very important disease. Thank you.

DR. LEBWOHL: If I can summarize, I think many of the points raised sort of go back to the other voting question. But, really, I get the sense from this panel that there is an acknowledgement of a great unmet need and an acknowledgement that the surrogate outcome may indeed translate into patient important outcomes and their primary endpoint, ultimately. There was also great enthusiasm for seeing this full study in its entirety in terms of seeing that endpoint so that this drug can potentially be considered once that happens.

Before we adjourn, are there any last comments from the FDA?

DR. MEHTA: We would like to thank the

advisory committee meeting panel members and the members of the FDA, the applicant, and the members online who have joined us, for joining us today for the meeting. Thank you for a very fruitful discussion. We will take these points back and think how to proceed further. Thank you.

Adjournment

DR. LEBWOHL: And I would like to thank the FDA. I'd like to thank Intercept Pharmaceuticals, the public, the open public hearing presenters, and this panel. It really has been a privilege to serve as your chair. We will now adjourn the meeting. Thank you.

(Whereupon, at 4:45 p.m., the meeting was adjourned.)