FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE GASTROINTESTINAL DRUGS ADVISORY COMMITTEE (GIDAC)

Thursday, April 7, 2016

8:01 a.m. to 4:31 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

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P R O C E E D I N G S

(8:01 a.m.)

Call to Order

Introduction of Committee

DR. RAUFMAN: Good morning. I would like first to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Andrea Fischer. If you are present, please stand. Thank you.

My name is Jean-Pierre Raufman. I'm the chairperson of the Gastrointestinal Drugs Advisory Committee, and I will be chairing this meeting. I will now call the Gastrointestinal Drugs Advisory Committee meeting to order. We'll start by going around the table and introduce ourselves. We will start with the FDA to my left and go around the table, please.

DR. EGAN: Amy Egan, deputy director, Office of Drug Evaluation III.

DR. ROMAN: Dragos Roman, associate director, Division of Gastroenterology and Inborn Errors Products.

DR. DIMICK-SANTOS: Lara Dimick, medical team leader, Division of Gastroenterology.

DR. MEHTA: Ruby Mehta, clinical reviewer, Division of Gastroenterology.

DR. CHEN: Yeh-Fong Chen, statistical team leader.

DR. MARATHE: Dhananjay Marathe, pharmacometrics reviewer, OCP.

DR. ELLENBERG: Susan Ellenberg, University of Pennsylvania.

DR. DASARATHY: Dasarathy, Cleveland Clinic.

DR. ASSIS: David Assis, Yale University.

DR. VOS: Miriam Vos, Emory University.

MS. BELL-PERKINS: Elizabeth Bell-Perkins, consumer rep.

MR. KHURANA: Sandeep Khurana, Medical College of Georgia.

DR. HONG: Cindy Hong, DFO, Gastrointestinal Drugs Advisory Committee.

DR. CHANG: Lin Chang, UCLA.

DR. LIPMAN: Tim Lipman, Washington, D.C. VA Medical Center.

DR. FEAGINS: Linda Feagins, UT Southwestern.

DR. CONJEEVARAM: Hari Conjeevaram, University of Michigan.

DR. SILVEIRA: Marina Silveira, Case Western Reserve University.

DR. KUMAR: Atul Kumar, Stony Brook University, Department of Veterans Affairs, New York.

DR. PROSCHAN: Michael Proschan, statistician at NIAID.

DR. LEVINE: Doug Levine, medical affairs at Shire. I'm the industry representative.

DR. RAUFMAN: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's 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 topics during breaks or lunch. Thank you.

Now, I'll pass it to Lieutenant Cindy Hong, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

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

interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC 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 USC 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 his or her 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

interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC 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 new drug application 207999 obeticholic acid oral tablets, submitted by Intercept Pharmaceuticals, Inc., proposed for the treatment of primary biliary cirrhosis in combination with ursodeoxycholic acid in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. This is a particular matters meeting during which specific matters related to Intercept Pharmaceuticals obeticholic acid oral tablets will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. 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. Douglas Levine is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Levine's role at this meeting is to represent industry in general and not any particular company. Dr. Levine is employed by Shire.

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 has encouraged all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. RAUFMAN: Thank you.

We will now proceed with the FDA's

introductory remarks from Dr. Dragos Roman.

FDA Introductory Remarks – Dragos Roman

DR. ROMAN: Good morning, everybody, and on behalf of the FDA, welcome. We will be discussing today NDA 207999, obeticholic acid for the treatment of primary biliary cholangitis, previously called primary biliary cirrhosis.

You will hear in the course of the morning several presentations that will detail the efficacy and safety data from both Intercept and from the FDA reviewers. But in my brief introductions, I would just like to highlight a couple of issue that we think are of particular interest.

Obeticholic acid is an analog of the naturally occurring bile acid chenodeoxycholic acid. As chenodeoxycholic acid, it binds to the farnesoid X receptor and stimulates this receptor, which has a key role in bile acid metabolism and regulation.

Obeticholic acid has been formulated as a tablet for daily administration at a dose no greater than 10 milligrams daily, and the indication that is being sought is treatment of primary biliary cirrhosis

in combination with ursodeoxycholic acid in adults with inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA.

Primary biliary cholangitis is a rare disease. It has been estimated to have a prevalence between 2 and 40 patients per 100,000 individuals. Intercept followed a traditional approach to the development program for obeticholic acid. It contained two phase 2 clinical trials and a single phase 3 clinical trial. In the phase 2 trials, several doses were evaluated, and a single dose was selected for further evaluation in a 12-month, placebo controlled, randomized trial.

Of note, the primary efficacy endpoint in phase 2, as a measure of efficacy, was a biomarker, alkaline phosphatase. For the phase 3 clinical trial, the primary endpoint was a composite of alkaline phosphatase and total bilirubin.

Specifically, the primary efficacy endpoint measured at month 12 the following. It included alkaline phosphatase below 1.67 times upper limit of normal bilirubin and an alkaline phosphatase reduction of 15 percent relative to baseline.

This endpoint was leveraged from data from the PBC study group, an international registry. Data from this registry was shown in publications to indicate an elevated ALP and total bilirubin could be linked to the risk of death and liver transplantation.

It is important to note that this was very diverse in the PBC population. It included patients with early stage disease, moderately advanced disease, as well as advanced disease. In contrast, the patients that were evaluated in the phase 3 clinical trial represented the more narrow PBC population.

I would like to point your attention to the first bullet on the slide, which describes one of the key inclusion criteria for the pivotal trial. According to this criteria, a patient had to have at least one of the following qualifying biochemistry values: an alkaline phosphatase greater than 1.67 times upper limit of normal or a total bilirubin greater than upper limit of normal but less than 2 times upper limit of normal.

There was no specific criterion that requested that both the ALP and bilirubin should be abnormal in

the same individual. Consequently, because of this and/or inclusion criterion, the study enrolled primarily or mostly patients with early stage PBC. As an example, 99 percent of the patients enrolled in the phase 3 clinical trial had elevated alkaline phosphatase and 90 percent had a normal bilirubin, and about 99 percent had a normal albumin.

Because of this reliance on the alkaline phosphatase in both phase 2 and phase 3 clinical trials, the FDA reviewers went back to the PBC study group to conduct additional analysis. Just as a reminder, the PBC study group was a multinational, multicenter registry study and included approximately 5,000 adult PBC patients with longitudinal alkaline phosphatase information and clinical outcome data related to death or liver transplantation.

The FDA statisticians assessed the selected data and identified a subset of patients with characteristics that were similar to those in the phase 3 obeticholic acid trial. The FDA statisticians assessed the relationship between the changes in ALP values and the clinical outcomes of death and liver

transplantation and identified several ALP thresholds that may predict clinical response. Those analyses will be presented to you in the course of the morning.

I would like to make a couple of observations regarding alkaline phosphatase. First of all, alkaline phosphatase is not an assessment of a clinical outcome. It doesn't measure how a patient feels, functions, or survives. It is primarily a pharmacodynamic or response biomarker. It shows that a biological response has occurred as a consequence of an intervention, in this case, obeticholic acid.

Alkaline phosphatase is not a validated surrogate endpoint. In other words, it is not a substitute for a direct measure of how a patient feels, functions, or survives. And finally, alkaline phosphatase can be seen, at best, as a candidate surrogate endpoint that is an endpoint that is still under evaluation for its ability to predict clinical benefit.

At the end of this morning, following all the presentations from Intercept and from the FDA, you will be asked to discuss if, in your opinion, after

reviewing all this information, alkaline phosphatase can be seen as a surrogate endpoint reasonably likely to predict clinical benefit in the treatment of early stage primary biliary cholangitis. You will be asked if the data presented would support accelerated approval of obeticholic acid in the treatment of PBC, based on its effect on alkaline phosphatase.

In addition, you will be asked to comment on OCA dosing recommendations, on the use of OCA as monotherapy, on dosing in patients with hepatic impairment, and on efficacy across the entire spectrum of PBC. You are also asked to comment on the continued dosing in patients who do not meet some of the standard response criteria. And should you recommend approval under subpart H based on accelerated approval, you would be also asked to comment on the proposed phase 4 confirmatory study design. Thank you.

DR. RAUFMAN: Thank you.

Before we proceed, I'd like to ask Ms. Lupole and Ms. Cryer to introduce themselves.

MS. LUPOLE: Patricia Lupole, patient representative.

What else did you need, sir?

DR. RAUFMAN: That's fine. Thank you.

MS. CRYER: Donna Cryer, patient representatative, CEO, Global Liver Institute.

DR. RAUFMAN: Thank you very much.

Both the Food and Drug Administration, 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, the FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon 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 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's presentations.

Applicant Presentation – Kris Kowdley

DR. KOWDLEY: Good morning. My name is Kris Kowdley. I'm director of the Liver Care Network and Organ Care Research at Swedish Medical Center in Seattle, Washington. I'm also a clinical hepatologist with over 25 years of experience caring for patients with PBC and involved in clinical trials in this condition.

My comments here are as a consultant for Intercept Pharmaceuticals, and the slides I'm about to present have been prepared in consultation with the FDA. Intercept Pharmaceuticals is supporting my attendance at this meeting.

Here's an outline of my comments. I'd like to review the epidemiology of PBC. I'd like to say a few words about the diagnosis of PBC. I'd like to review the associated conditions that patients with PBC experience since management of these conditions

frequently is dependent upon the hepatologist or gastroenterologist caring for them. I'd like to say a few words about the natural history of PBC and the role and effect of ursodeoxycholic acid treatment for this conditions.

As you've already heard, PBC, or primary biliary cirrhosis, has been recently renamed primary biliary cholangitis, and this reflects the fact that now, the majority of our patients are diagnosed prior to the development of cirrhosis and are being diagnosed at earlier stages of the disease. This name change has been endorsed by several patient groups and learned societies such as the American Association for the Study of Liver Disease and the European Association for the Study of Liver.

Now, PBC is an autoimmune liver disease that is thought to be due to a combination of a genetically predisposed individual who then develops the liver disease due to a combination of environmental triggers. The central histologic feature in this disease is lymphocytic inflammation targeting the small bile ducts within the liver or the interlobular bile ducts.

The serologic hallmark of PBC is the anti-mitochondrial antibody, a highly disease-specific autoantibody found in 90 to 95 percent of patients and fewer than 1 percent of healthy blood donors. Serum liver biochemical tests typically show what we call a cholestatic pattern of abnormalities with an elevation in serum alkaline phosphatase, or ALP, which is disproportionately elevated when compared to the serum AST and ALT or aminotransferases. In late stages of the disease, serum bilirubin may gradually rise and may precipitously rise as end-stage disease approaches.

Features of PBC include that it is a chronic, cholestatic liver disease with a progressive course, which may extend over many decades. However, the individual patient's journey through this disease can be highly variable with an accelerated progression within a few years of diagnosis or a more gradual natural history.

So the rate of progression varies greatly between and among individuals. Characteristically, in early-stage PBC, patients are asymptomatic. However, over time, patients often develop fatigue and pruritis,

although some patients may develop this at the time of diagnosis.

Concomitant autoimmune diseases are very common, such as thyroid disease and some other conditions which I will mention briefly. PBC is a rare disease. It affects 1 in 1,000 women age over 40 years. However, it remains an important indication for liver transplantation in this population.

The prevalence of PBC appears to be rising. This is a study from The Netherlands that shows that between the periods of 2000 and 2008, there is about a twofold increase rate in the prevalence in women per 100,000 inhabitants, from 10 to over 20. Over that same period of time, the prevalence of the disease in men has remained relatively constant, maybe risen slightly.

This slide shows global trends in temporal PBC prevalence over time, starting with the early 1970s and extending up to the early 2000s. As you can see, in the '90s and early 2000s, there appears to be a significant increase in the prevalence of PBC, possibly heralded by the availability of ursodeoxycholic acid

and increased diagnosis and awareness and earlier diagnosis for patients.

The incidence of PBC has also been rising, once again in women more than men. And the incidence per 100,000 in the study from The Netherlands shows approximately a doubling, from about 1.5 to somewhere around 2.5 per 100,000 inhabitants. This systematic review and meta-analysis was presented in abstract form at the AASLD meeting in 2012 and remains one of the few comprehensive data sets on incidence and prevalence of PBC.

As you can see in the upper part of this slide, a collection of studies presented with patient recruitment prior to 1990 established the incidence of PBC at approximately 1.2, whereas in studies with predominant recruitment after 1990, the incidence of PBC is closer to 2.38 with an overall incidence of 1.68. Highlighted is the one study from the United States by Ray Kim, which showed an incidence of 2.7.

I provided a little more detail from this one U.S. study, and this study showed that the age-adjusted incidence, adjusted to 1990 U.S. whites in 1975 to

1995, was 4.5 per 100,000 per women and 0.7 per 100,000 for men. The age- and sex-adjusted prevalence as of 1995 was 40, 65 for women and 12.1 for men. Shown on the bar graph is the age at which the incidence is reported, and you can see that a smaller proportion of patients are diagnosed in their 40's and somewhat higher in somewhat older age.

PBC is a chronic, progressive autoimmune liver disease, and we believe there are a variety of factors that lead to the phenotype of this disease. Genetic factors are undoubtedly involved, and environmental factors contribute to an aberrant immune response that targets the interlobular bile ducts, leading to bile duct injury and progressive cholestasis and possibly cirrhosis. So PBC is characterized by the destruction of the interlobular and septal bile ducts that may lead to cirrhosis.

Concomitant autoimmune diseases are present relatively frequently in women with PBC; Sjogren's syndrome in up to one-third of patients; inflammatory bowel disease less often, joint symptoms and thyroid disease; and Raynaud's syndrome may be seen in up to

10 percent of patients. And overall, any autoimmune disease is reported in approximately half of patients with PBC.

Clinical features, however, vary greatly between patients, although some common symptoms that seem to be present in many patients include fatigue, pruritis, concomitant autoimmune diseases, and patients with PBC, especially postmenopausal women, are at increased risk for osteopenia and osteoporosis. Elevated cholesterol levels are frequently observed in PBC and often may be characterized by high levels of HDL.

Pruritis is a common and often vexing symptom in patients with PBC. The prevalence is reported as high as 69 percent. The etiology is not known, although a number of causes have been implicated such as bile salts, histamine, autotaxin/ lysophosphatidic acid as possible pruritogens. There is a diurnal variation to the itch, which is most intense in late evening. The localization is frequently in the limbs, such as the soles of the feet, palms of the hands, and the itching is frequently exacerbated in the setting of

pregnancy or in contact to wool or heat.

Fortunately, we have a variety of treatment options to help manage the pruritis that are quite effective. These range from general recommendations such as skin hygiene and relaxation techniques. First-line therapies include bile acid sequestrants such as cholestyramine. Second-line therapies such as rifampicin are frequently effective. And we have third- and fourth-line therapies such as opioid antagonists and selective serotonin reuptake inhibitors that may work for some patients.

Now, this is the classic histologic feature of PBC. As you can see, this is a portal area with an intense lymphyocytic infiltrate surrounding an edematous and senescent or dying bile duct, and the inflammation is an intense lymphocytic infiltrate. You can also see the non-caseating granuloma characterized by histiocytes in the upper part of the slide.

However, although liver biopsy can be helpful in patients who have a negative antimitochondrial antibody, it is no longer required to make the diagnosis of PBC. This study by Claudia Zein and Keith

Lindor, among others, suggested that if a patient has a positive antimitochondrial antibody, an alkaline phosphatase more than 1.5 times the upper limit of normal, and an AST less than 5 times the upper limit of normal, then the positive predictive value for PBC was greater than 98 percent with a sensitivity of 80 percent and a specificity of 92 percent.

Now, the progression of PBC is variable and may go through a long course, which may be characterized by clinical stages and preclinical stages. And I've taken the liberty of showing this cartoon to highlight how this progression may occur. In the preclinical phase of the disease, the only test that may be abnormal is the antimitochondrial antibody. At this point, bile ducts may be intact and cholestasis is not present.

Over time, as lymphocyte-mediated and inflammatory-mediated injury to the bile ducts occurs and there is evidence of cholestasis characterized by elevated ALP, patients may develop symptoms but frequently may not. Then there is a period where symptoms are manifest and the disease is progressive.

Patients have more evidence of cholestasis. And finally, the stage that we hope to avoid with therapies is the onset of decompensation and complications such as portal hypertension, ascites, and end-stage liver disease.

Without intervention, a substantial number of patients progress to liver failure, need liver transplantation, or experience a liver related death within 10 years. Complications of chronic cholestasis maybe not limited to the liver may include fat soluble vitamin deficiencies, bone disease that can be seen in a substantial minority of patients.

In addition, patients with PBC in the setting of cirrhosis are not immune from hepatocellular carcinoma, and the incidence of HCC in this population with cirrhosis is about 1 to 6 percent per year, comparable to other causes of cirrhosis. Furthermore, in addition to the development of varices, associated with portal hypertension, in PBC, approximately 6 percent of patients may develop varices and signs of portal hypertension even in the absence of cirrhosis.

This slide shows data from the Global PBC

study group showing that the cumulative HCC incidence 20 years after diagnosis or onset of ursodeoxycholic acid or UDCA therapy approaches 10 percent.

Now, there are recommendations for long-term management and monitoring of patients with PBC. In this case, I've taken these from the AASLD guidelines, and they recommend monitoring liver tests every 3 to 6 months, thyroid status annually, monitoring bone densitometry, fat soluble vitamins in patients with profound cholestasis, and routine surveillance with endoscopy and for hepatocellular carcinoma in patients with cirrhosis.

Now, ursodeoxycholic acid was first approved in 1997 for the treatment of PBC. It's an orally administered hydrophilic bile acid administered at a preferred dose of 13 to 15 milligrams per kilogram per day. It is the only currently FDA-approved therapy for PBC. And after treatment with ursodeoxycholic acid, or UDCA, improvement in liver biochemistry such as ALP can be seen within a few weeks. Ninety percent of the improvement usually occurs within the first nine months. However, up to 40 percent of PBC patients

treated with UDCA have a suboptimal response, and another subset may be able to poorly tolerate UDCA.

UDCA has been shown to improve survival free of transplantation, as shown in this study. The UDCA graph shows patients who were treated with UDCA for 48 weeks, and the placebo to UDCA graph shows patients who were initially treated with placebo and then offered the opportunity to take open-label UDCA. And even in that group that received two years of UDCA, there is a significant survival benefit in the group that received UDCA for the entire 48 weeks.

There are data showing that treatment with UDCA improved survival when compared to the predicted survival using the Mayo model, as shown on the graph on the left. And furthermore, in a 10-year follow-up study from France, a population of patients treated with UDCA had a long-term survival that approached the general age- and sex-matched population in France without any disease. The difference in survival here is 85 percent or so in the treated patients, 88 percent in the control population, showing an approximation of normal life expectancy with UDCA treatment.

Currently, recommendations for monitoring patients on treatment and treatment guidelines are quite variable. The AASLD guidelines were last written in 2009. There is no specific definition or guidance for how to monitor patients on treatment or how to measure or assess treatment response.

The statement of 20 percent of patients will have normalization of liver biochemistry and 15 to 35 percent of the total will have normalization by 5 years, and the effective treatment can be based on response to Mayo risk score or serum alkaline phosphatase, is the most specific statement that's in that guideline.

The European guidelines, published in the same year, makes more specific comments, such as a good biochemical response is currently defined by a bilirubin that is less than 1, a reduction of alkaline phosphatase to less than 3 times the upper limit of normal, or a decrease of 40 percent or more, or normalization of the alkaline phosphatase.

Given the somewhat vague and not totally consistent recommendations, there have been other

attempts to develop response criteria models, and I'd like to spend a few minutes just talking about those at this point.

These can be categorized into those models that include primarily alkaline phosphatase as a treatment indicator with or without bilirubin such as Barcelona, Paris I, Paris II, Toronto, or the early biochemical response which incorporates multiple criteria into a six-month time point. The Rotterdam criteria incorporates serum albumin and bilirubin.

More recent or current response models have been developed using biochemical response with APRI score, the UK-PBC score, or the GLOBE, or Global PBC score to try and develop a more precise estimation of response to treatment and prognostication, and Professor Jones will be discussing these in greater detail.

It seems likely that with the advent of ursodeoxycholic acid therapy, the need for liver transplantation in patients with PBC has been reduced. This graph on the left shows a number of liver transplants over time, and the graph on the right shows

liver transplants for PBC that do appear to show a somewhat downward curve between 1995 and 2006.

Similar data are available from the UK. Shown on the left are liver transplants for PBC performed per year, showing a similar downward trend. However, I call your attention to the graph on the right that shows the age at which patients are transplanted has remained relatively constant, suggesting that there may be a population of patients with PBC who do poorly and have aggressive disease for whom more urgent need for therapies remain.

So in summary, PBC is increasing in prevalence, may have a substantial impact on the quality of life both due to liver related and associated conditions, may progress to end-stage liver disease, and may be complicated by hepatocellular carcinoma. However, the rates of progression in individual patients can be quite variable. UDCA has been the cornerstone of therapy, but a substantial number of patients have a suboptimal response or intolerance to UDCA, pressing the need for other therapies to be available for our patients. Thank you.

Applicant Presentation - Linda Robertson

DR. ROBERTSON: Good morning. My name is Linda Robertson, and I'm the vice president of regulatory affairs and quality assurance from Intercept Pharmaceuticals. I wanted to thank the chairman, the committee, and the FDA today for the opportunity to present our program for obeticholic acid for the treatment of primary biliary cirrhosis or PBC.

Obeticholic acid, or OCA, is a modified bile acid specifically designed as an agonist of the nuclear receptor FXR. As you heard from Dr. Kowdley, PBC is a rare, chronic, life-threatening disease with limited treatment options.

Development of new therapies for PBC has several inherent challenges with regard to approvable clinical endpoints. There's a slow variable rate of disease progression. Symptoms do not correlate with clinical outcome. Therefore, it is difficult to measure clinical benefit in a timely fashion using conventional endpoints.

Given these challenges, we considered regulatory procedures that can facilitate development

such as accelerated approval as outlined in recent guidance entitled Expedited Programs for Serious Conditions, dated May 2014. The criteria for this procedure is that the drug is meant to treat a serious condition, provide a meaningful advantage over existing therapies, and is based on a surrogate endpoint that's reasonably likely to predict a clinical benefit.

As stated by FDA in the framing of today's meeting, the criteria for the surrogate endpoint should be based on an entirety of clinical evidence, including correlation with clinical outcomes and relationship to disease pathophysiology. Accelerated approval also requires that a confirmatory trial is underway at the time of filing to confirm clinical benefit.

The regulatory history for OCA has involved an extensive interface with regulatory authorities both in the U.S. and in the European Union. We submitted our IND in 2006 and were granted orphan designation April 2008. As defined by the expedited programs for serious diseases, we were granted fast-track designation May 2014. This allowed us to submit an NDA December 2014 under rolling procedure. We completed that procedure

in June 2015 and were also granted priority review in August 2015.

As described by FDA in their introductory statements, the basis for accelerated approval for this application is one pivotal phase 3 trial in combination with UDCA supported by two phase 2 studies, one in monotherapy, one in combination with UDCA.

The data we will show you demonstrate a statistically significant effect on the composite endpoint of ALP change and maintenance of normal bilirubin. These have been shown to be associated with clinical outcomes based on data from independent study groups, which were reviewed and verified by FDA. OCA is generally safe and well tolerated in over 1,500 subjects exposed to the drug, including over 400 patients with PBC, with durations in exposure of up to five years.

Importantly, following discussions with FDA, we initiated a confirmatory trial consistent with accelerated approval criteria. As you heard, this confirmatory trial design is an important topic of today's meeting. Furthermore, in preparation for this

meeting, there was consensus with FDA on a number of the descriptive elements of the program. These will be highlighted in subsequent presentations.

As you heard, the proposed indication is as follows: obeticholic acid is indicated for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA and as monotherapy in adults unable to tolerate UDCA. The recommended starting dose is 5 milligrams once daily. And based on assessment of efficacy and tolerability, after 3 months, the dose should be increased to 10 milligrams once daily to improve response.

In support of this indication, we're going to hear the following presentations. Professor David Jones, professor of liver immunology at University of Newcastle will begin our presentation with the discussion of the PBC therapeutic void following standard of care therapy, UDCA, and the data from independent study groups, UK-PBC and Global PBC, that support the predictive value of these biomarkers ALP and bilirubin.

Dr. David Shapiro, Intercept's chief medical

officer, will be providing an overview on obeticholic acid's mechanism of action as a bile acid specifically designed as an FXR agonist to compliment UDCA and bridge this therapeutic void.

Dr. Leigh MacConell, vice president of clinical development at Intercept, will discuss the details of the OCA phase 2 and phase 3 clinical trials and how the efficacy results demonstrate that OCA has the potential to respond to the medical need Dr. Jones has described.

Dr. Roya Hooshmand-Rad, executive director of medical safety and pharmacovigilance at Intercept, will be providing a summary of the safety and showing that the drug is well tolerated and safe with the primary adverse event being pruritis.

Finally, Dr. John Vierling, chief of hepatology at Baylor College of Medicine and a former president of AASLD, will present his interpretation of OCA's benefit-risk profile from his perspective as a transplant hepatologist in the context of PBC and the unmet medical need.

I'm now very pleased to introduce Professor

David Jones to provide an overview of the unmet medical need for PBC.

Applicant Presentation – David Jones

DR. JONES: Thank you and good morning. I'm being supported by Intercept Pharmaceuticals to attend this meeting, but I have no personal interest in the outcome of today's proceedings.

I, too, have worked in PBC for 25 years, and I run the clinical service in Newcastle, which is one of the largest PBC clinics in the world. And an area of real interest to me for a number of years has been the question of unmet need, the problems that remain even in an era with effective therapy in this condition.

Dr. Kowdley introduced very well the fact that we have effective therapy in PBC with UDCA and with transplantation. However, there are important limitations with both of these management approaches. Dr. Kowdley introduced the concept of response to UDCA, however, the implication of response is that there must also be non-response, and the critical figure is up to 40 percent of PBC patients are un- or under-responsive to UDCA. And an additional 5 percent of patients are

intolerant of the therapy with problems such as weight gain, GI disturbance, or hair loss. And this is a real area of unmet need. What do we manage patients, who are under-responsive to UDCA or intolerant of the drug, with?

Transplantation, of course, is fantastically effective. It is, however, a salvage procedure. It has a number of limitations. It is a high-cost procedure. It is associated with significant morbidity from the procedure and from expensive drugs. A real interest for us is the often poor functional status of people transplanted with end-stage liver disease. And, of course, there are the challenges of limited timely organ availability and differential access. So transplantation is a wonderful rescue treatment but, however, it has substantial limitations.

Progress in PBC is a real challenge in terms of clinical trials. It's a rare disease which requires large numbers of centers for study, and it's also a relatively slowly progressive disease, which means that it's very difficult to evaluate clinical outcomes as primary endpoints.

So what does UDCA non-response look like? This is the original French data from Corpechot, and I think this makes a really, really important point. The group of patients who respond well to UDCA in the top solid line show a survival which is identical to age- and sex-matched populations. These people really do very well, indeed, with PBC, and if asymptomatic, have a normal length and quality of life.

However, the group of patients who do not respond adequately to the drug have a substantially different outcome with quite a rapid deterioration in their survival. This group represents in this study just under 40 percent of patients. So the question is, what do we do to manage these patients with currently no licensed therapy that we can use in them?

Our understanding of risk in PBC has been transformed by the advent of very large global cohorts of patients, and you will hear referred to, throughout the course of today, two of these, the Global PBC study and UK-PBC. The data that has come from these groups that work closely together has been transformative for our understanding of the disease.

The Global PBC study group, formally known as the Super group, is a group across North America and Europe. It's a retrospective study with very large long-term cohorts from numerous centers with detailed clinical data on over 6,000 patients, with a significant number of endpoints because of it's retrospective nature.

The UK-PBC Consortium, which I have the pleasure to lead, is a different approach. This is prospective follow-up cohort. This is across the whole United Kingdom. All hospitals in the UK are involved in this study, and we've recruited over a third of all UK-PBC patients who are in detailed information capture and long-term follow-up; and we, too, have recruited over 6,000 patients with detailed outcome data. And working synergistically, we now have detailed information on over 10,000 PBC patients, which I think is an astonishing effort in a rare disease and has really transformed our understanding of what risk means in this disease.

This is a simple graphic from the Global PBC study group, which I think puts it into perspective,

and this is across the 6,000 patients from Global PBC. It looks at transplant-free survival in the UDCA era, the era when there is almost universal use of our one-license therapy. And in that era, by 15 years of follow-up, only 63 percent of patients are still alive free of transplant. So 37 percent of patients have died of the disease or have required transplantation. And again, this encapsulates unmet need; how do we change this graphic?

You've heard in the introductory comments about the outcome measures for the OCA phase 3 trial using the measures alkaline phosphatase and bilirubin, which are indeed biochemical measures. But they are also biochemical measures that are inextricably linked to the process of the disease in PBC.

PBC is a disease in which biliary epithelial cells lining the bile ducts are damaged. They're damaged initially immunologically but subsequently by cholestasis with the toxic effects of bile acids. And those bile acids cause further attention and a sequence of cyclical damage to the biliary epithelium.

Alkaline phosphatase is released by stressed

biliary epithelial cells, and is, therefore, a marker of that sequence of damage. And once bile duct cross-section area is lost, bilirubin is retained. So therefore, bilirubin build up is a marker of loss of biliary epithelium. So these chemical markers are very useful ones linked into the biology.

One thing that's very important to see if that for both of these measures, there is a linear association between the measure and worse outcomes across the range. Rising alkaline phosphatase in the Global PBC study group is sequentially associated with worse outcome, and the same is true for bilirubin. And one important point to notice about bilirubin is that the risk for mortality goes up even within the normal range.

So bilirubin is a marker of worse survival even in those patients who have a notionally normal level of this marker. And it's about an issue I'll come back to, which is the distinction between stage of the disease and future risk.

If you look at these individual markers dichotomized at the optimal point, which is alkaline

phosphatase of greater or less than 1.67 times the upper limit of normal, as mentioned, this is the criteria for one phase 3 trial for obeticholic acid. What you can see, again, for Global PBC data is that patients who have an alkaline phosphatase less than 1.67 times upper limit of normal have a dramatically better survival than patients whose alkaline phosphatase remains elevated, which would suggest the presence of ongoing active bile duct damage.

If you look at bilirubin, the same effect is there, with the presence of abnormal bilirubin, which is a marker that the disease has become more advanced, being associated with a really significant deterioration in survival.

Now clearly, these parameters are not independent, as patients with elevated bilirubin typically also have a marker of the elevated alkaline phosphatase. But even if you look at the group of patients with normal bilirubin, you see that alkaline phosphatase level is highly predictive of outcome. And this is the group of patients who in stage terms might be regarded as being early stage.

But stage indicates how much damage has already taken place. We are principally concerned with risk, which is the extent to which ongoing damage will cause a rapid deterioration of disease. So even in patients whose stage is relatively early, there is a group of patients in whom the risk is significantly increased. And what we aim to do to avoid transplantation in the future is to find patients at high risk ideally in early stage and give those patients better therapy. This is the important distinguishing factor.

If you look at patients whose bilirubin is abnormal, as you might expect, alkaline phosphatase has an additional distinguishing factor. But in all patients with abnormal bilirubin, survival is markedly worse than in patients with normal bilirubin even with therapy. So therefore, we always want to treat patients before bilirubin becomes abnormal; treat risk, not stage.

The beauty of the UK-PBC and the Global PBC approach is that they're entirely complimentary of their distinct data sets. And if you apply the same

approach to UK-PBC, you see exactly the same patterns, and the difference is an absolute value to do with the fact that UK-PBC looks at liver related outcomes and Global PBC looks at all-cause. But we have validated this approach in a second 4,000 patient-plus cohort.

One of the findings that came out from UK-PBC, which I think is really important, is that this factor of non-response to UDCA is not uniformly distributed across the population. It is, in fact, enriched significantly in younger presenting patients. In the UK, if you present below the age of 30 with PBC, you have a chance of over 70 percent of not responding to UDCA, whereas the older presenting patients in fact respond very well indeed.

This I think explains why we are still transplanting for patients with PBC at the same age. As Dr. Kowdley demonstrated, it is because the older group of patients respond very well to therapy and transplant is not an issue for them. However, in the younger group of patients, they are not responding to UDCA. We have no alternative second-line therapy. They are progressing, and they are moving forward to

transplantation. So if UDCA non-response is the place where unmet need lies in PBC, that is most likely to be found in younger patients who have most of their life in front of them.

So where are we in 2016 for the management of PBC and moving on from the 2009 guidelines? I think today, UDCA should universally be used to all PBC patients, that argument is now over. And I think the evidence is there, there should be routine assessment of response to therapy after one year. We should apply the tools we have to identify the minority of patients in whom death liver transplant risk resides and of course the low-risk patients in whom therapy could be stepped down, we could make the whole of PBC management more effective.

In the future, as we have therapies that we can apply to this group of non-responders, we should apply them. In the meantime, we should monitor them for the risk of progression of the disease. We should use our tools to target these emerging therapies in high-risk patients, being very mindful of the point that I've emphasized, that we are looking for early

stage but high risk to give the likely optimal response to therapy. And I would argue that we now have very robust trial measures to assess the response to therapy, which are applicable in practice.

So what is my personal vision for somebody who thinks carefully about unmet need? We need better treatments targeted in better ways for the group of patients who need those therapies. For me, there are three key attributes for the new therapies. They should be targeted for patients with unmet need through appropriate risk stratification. The era of stratified medicine in PBC is now, and we should be able to target these therapies.

We should have proof of benefits of therapies in appropriate patient cohorts so we can justify the value of these therapies to our patients. PBC patients do have symptoms, and therefore, there should be manageable and tolerable side effects. And if we can meet these criteria with a second-line therapy, that will go a very considerable way to addressing unmet need in PBC.

I would now like to move on and introduce

David Shapiro, who is the chief medical officer of Intercept Pharmaceuticals, to outline the program rationale.

Applicant Presentation - David Shapiro

DR. SHAPIRO: Thank you.

So given the high, ongoing, unmet medical need in PBC, we initiated a drug development program that would focus on the pathophysiology of the disease. The goal of the program was to address the key features of PBC and develop a therapeutic agent that could improve impaired bile flow, or cholestasis, and decrease hepatocyte bile acid concentrations and, hence, attenuate hepatobiliary damage and inflammation.

We determined that the farnesoid X receptor was an attractive therapeutic target. Since its discovery in 1999, FXR has been showed not only to be the nuclear receptor that acts as a primary regulator of bile acid homeostasis, but also to have pleotropic hepatic and metabolic properties.

FXR is a member of the super family of nuclear receptors whose primary function is to regulate gene transcription. Nuclear receptors all have two binding

domains, a ligand binding domain and a DNA binding domain. When a receptor is bound to the binding domain, this complex translocates to bind with chromosomal DNA, and then to activate or repress the appropriate target genes.

The structure of the FXR ligand lends itself to structural modification. This shows the structure of the endogenous FXR ligand, the primary human bile acid chenodeoxycholic acid, or CDCA. Its FXR EC50 is around 10 micromolar.

On the left, you see the structure of also ursodeoxycholic, or UDCA, the only currently approved therapy for PBC. It has a nearly identical structure to that of CDCA, except for the orientation of the hydroxyl group highlighted. This change in the hydroxyl orientation is associated with dramatically different physicochemical properties and is also accompanied by complete loss of FXR agonist properties.

On the right, you see the structure of obeticholic acid. Its structure differs from that of CDCA by the addition of a single ethyl group in the 6th position. This addition is associated with around a

100-fold increase FXR activity and an EC50 in the nanomolar range. The result is therefore a greatly enhanced FXR agonist with a bile acid structure.

As you might expect from this, the pharmacokinetic properties of obeticholic acid are very similar to that of endogenous CDCA. OCA does not bind to other nuclear receptors, thus minimizing its chance for off-target effects. It's rapidly absorbed from the gut, and like endogenous bile acids is extensively conjugated with the dietary amino acids glycine and taurine. And these conjugates become the main circulating forms of the drug and are equipotent FXR agonists to the parent drug.

Like endogenous bile acids, OCA undergoes extensive enterohepatic recirculation and, hence, has a lengthy, steady-state half-life of around 4 days. And like other bile acids, it's excreted principally into the feces.

OCA has now been shown in numerous preclinical and clinical studies to decrease endogenous bile acid synthesis through its effects on CYP7A1 and to improve bile flow. It consistently has been shown to decrease

hepatic inflammation and inflammatory markers, and it's notable also it's been shown to attenuate fibrosis, a notable feature for a non-viral, chronic liver disease.

This slide compares and contrasts the properties of UDCA to those of OCA. UDCA is typically dosed in fairly large doses between 900 and 1200 milligrams a day. It has no FXR properties, and therefore is thought to exert its effects purely through post-transcriptional mechanisms.

Administration of UDCA greatly expands the bile pool and increases the hydrophilicity of the bile acid pool, and UDCA then becomes the major circulating bile acid and constitutes around two-thirds to three-quarters of the circulating bile pool. It's also been shown to stimulate bicarbonate and fluid secretion in the biliary epithelium, and these likely also contribute to its mechanism of action.

In contrast, obeticholic acid is administered at doses of only 5 and 10 milligrams and acts by regulating gene transcription. It significantly inhibits endogenous bile acid synthesis, and yet comprises less than 2 percent of the circulating bile

acid pool in patients taking UDCA. Thus, OCA acts at low doses and by mechanisms that are distinct but complementary to those of UDCA.

In all, we have conducted over 20 studies over the past 10 years in this program, and these were obviously submitted to the FDA. These studies constitute a robust package in 1500 subjects in all, including about 430 patients with PBC and reflecting 675 patient-years of exposure.

Four studies evaluated bioavailability and bioequivalence across the different formulations we evaluated in the program; 12 studies evaluated its pharmacology and potential for drug-drug interactions. These studies show that OCA does not have any meaningful effects on the major drug metabolizing enzymes or their transporters.

A 150-subject cardiovascular safety study showed no cardiac repolarization effects. Several studies were conducted in other non-hepatic diseases other than PBC, and these will not be discussed further today. And lastly, we conducted three double-blind, placebo-controlled studies in PBC patients, which we're

now going to present in more detail to you.

Dr. Leigh MacConell, head of clinical development, is now going to present the efficacy data. Thank you.

Applicant Presentation – Leigh MacConell

DR. MacCONELL: Good morning. Thank you, Dr. Shapiro.

The efficacy of obeticholic acid has been evaluated in approximately 430 patients with PBC with exposures out to 5 years in a subset of those patients. This is a substantial database in the context of the rarity of PBC.

The database is comprised primarily of data from two phase 2 studies and a single phase 3 study. These were all very similar in design, randomized, double-blind, placebo-controlled. They predominantly assessed the effect of obeticholic acid in combination with standard of care or UDCA with a subset of patients treated with obeticholic acid as monotherapy. Alkaline phosphatase and bilirubin were the key efficacy biomarkers assessed across the three studies.

These studies all included long-term,

open-label, uncontrolled extension phases conducted to evaluate the durability of response and longer term safety. This is important given the chronic nature of PBC.

The framework for our clinical program includes the two large observational PBC databases as was described by Professor Jones. These databases provided justification for the alkaline phosphatase and bilirubin endpoints in our program, the data having supported that patients with elevations in alkaline phosphatase or bilirubin after one year of treatment with UDCA have an increased risk of liver transplant or death.

As part of accelerated approval as described by Dr. Robertson, we are conducting currently a phase 4 clinical outcomes study to ultimately confirm the clinical benefit of obeticholic acid in PBC. The study is evaluating the effect of obeticholic acid versus placebo on transplant-free survival in approximately 350 patients. The study is currently being conducted at over 150 clinical study sites across 28 countries.

The first of our two phase 2 studies evaluated

obeticholic acid as combination therapy in patients with an inadequate response to UDCA. The entry criteria are noted in the left panel. Patients were to have been diagnosed with PBC based on the subject presenting with at least two of the following: a history of elevated alkaline phosphatase levels for at least 6 months prior to enrollment; a positive AMA titer; and/or a liver biopsy consistent with PBC.

Screening alkaline phosphatase levels were between 1.5 and 10-fold the upper limit of normal with conjugated bilirubin no greater than 10-fold the upper limit of normal. These patients were not to have had a prior history or presence of hepatic decompensation.

Ultimately, approximately 165 patients were randomized to placebo, 10 milligrams of obeticholic acid, 25 milligrams, or 50 milligrams. These were all administered as once-daily oral doses for 3 months. The primary endpoint in this study was the percentage change in alkaline phosphatase from baseline after 3 months of treatment.

This phase 2 study met its primary endpoint. Obeticholic acid therapy resulted in significant

improvements in alkaline phosphatase in patients not able to achieve their treatment goals with UDCA. All 3 doses were associated with an approximately 25 percent improvement in alkaline phosphatase after 3 months.

The time course of effect is presented on the right. Consistent with these patients showing an inadequate response to UDCA, baseline alkaline phosphatase levels were highly elevated, approximately 2.5-fold the upper limit of normal. With the addition of obeticholic acid therapy, improvements in alkaline phosphatase were observed as early as 2 weeks. And after 3 months of treatment, levels were approaching 1.67-fold the upper limit of normal. There was no apparent dose response relationship with 10 milligrams being the maximally efficacious dose in this phase 2 study.

The second phase 2 study evaluated obeticholic acid as monotherapy. The key entry criteria were consistent with the prior study just prescribed, however, in this study, patients were not to have taken UDCA for at least 3 months prior to study entry. Sixty patients were randomized to one of three treatment

arms: placebo, or a 10-milligram dose of obeticholic acid, or the higher 50-milligram dose. The primary endpoint was consistent with the prior study and was the percentage change in alkaline phosphatase after 3 months of treatment.

Once again, the phase 2 study met its primary endpoint. Obeticholic acid as monotherapy delivered significant improvements in alkaline phosphatase, but with a 40 percent improvement after 3 months, again, no differentiation between the doses. At baseline, alkaline phosphatase levels were approaching 3.5 to 3.9-fold the upper limit of normal.

With placebo treatment, alkaline phosphatase levels remained stable and unchanged from baseline. In contrast, with obeticholic acid, we saw early marked improvements in alkaline phosphatase with monotherapy with levels approaching, again, 1.67-fold the upper limit of normal consistent with the prior phase 2 study.

In both trials, dose-related pruritis was observed with an increase in both the incidence, the severity, and discontinuation rates with doses beyond

10 milligrams. Taken together, the phase 2 data provided strong proof of concept for obeticholic acid in PBC and supported further development in a longer phase 3 study. The increased incidence of pruritis with the higher doses ultimately informed dosing undertaken in the phase 3 program.

Moving on to phase 3, this study evaluated patients earlier in disease but representative of a high unmet medical need. The majority of patients were on concomitant UDCA therapy with a small percentage of patients intolerant to UDCA.

For those patients on concomitant UDCA at entry, patients were required to have been taking it for at least 12 months and on a stable dose for at least 3. Patients unable to tolerate UDCA should have not been on UDCA for at least 3 months prior to study entry.

Alkaline phosphatase levels were a minimum of 1.67-fold the upper limit of normal with no upper limit in this study and/or total bilirubin levels between the upper limit of normal and twofold the upper limit of normal. In this study, patients with a presence of

hepatic decompensation were excluded. Patients were randomized to placebo or one of 2 doses of obeticholic acid. The 10-milligram dose was based on that shown to be maximally efficacious in the phase 2 program.

In the third arm, a titration regimen was explored based on those dose-related increases in pruritis observed in phase 2. Patients randomized to this arm initiated therapy at a lower 5-milligram dose. At 6 months, patients were to up-titrate to the higher 10-milligram dose if they had not yet achieved the primary endpoint and were tolerating therapy.

It's important to note the study compared obeticholic acid with standard of care. For the 93 percent of patients entering the study on UDCA, the UDCA dosing was to be continued at a stable dose over the course of the study.

The primary endpoint of this phase 3 study was a composite endpoint of bilirubin and alkaline phosphatase. Specifically, the proportion of patients achieving an alkaline phosphatase level below 1.67-fold the upper limit of normal, and an alkaline phosphatase decrease of at least 15 percent, and total bilirubin

either achieved or maintained within the normal limits.

This endpoint was based on several key clinical considerations. Alkaline phosphatase is a marker of cholestasis seen across the disease spectrum and used globally in clinical practice for the diagnosis and management of patients with PBC.

Bilirubin was also a very important component of this endpoint. As a marker of hepatic function, it's a well established predictor of risk across multiple chronic liver diseases. As an elevation of total bilirubin is a hallmark of advanced disease, stabilization within normal limits in earlier stage compensated patients was considered a key goal of therapy.

Lastly, and has been discussed by Professor Jones, the Global PBC study group analyses have demonstrated that both alkaline phosphatase and bilirubin are independent predictors of risk and together show additive prognostic utility.

Importantly, this endpoint was shown to be predictive of risk across multiple subpopulations. This is data based on the Global PBC database. The

forest plot provides the hazard ratios for the risk of liver transplantation or death associated with the phase 3 endpoint across subpopulations of interest using the Global PBC database.

Across all subgroups, including UDCA treated and non-treated, early and advanced disease stages, the primary endpoint used in our phase 3 study was associated with reduced risk of liver transplant or death. Looking at a patient population consistent with that studied in our phase 3 program, shown at the bottom of this forest plot, again, the endpoint predicted significantly decreased risk.

Secondary endpoints of the study were designed to assess the impact of obeticholic acid on markers of disease progression and the underlying pathophysiology of the disease, including endpoints related to cholestatic liver injury, loss of excretory function, hepatocellular injury, immunological abnormalities, and systemic inflammation.

It's important to note that these secondary endpoints were not adjusted for multiplicity, so the statistical analyses that will be presented in this

presentation are exploratory, and the p-value is considered nominal.

217 patients were randomized, and of these, 216 were dosed and made up the intent-to-treat population. The intent-to-treat and safety populations were one in the same. There was great retention in this study with 91 percent of patients completing the 12-month, double-blind study duration. There was a slightly greater retention in the placebo group, the primary reason for early discontinuation with obeticholic acid therapy being treatment related pruritis, which will be discussed in further detail in the safety presentation.

Overall, the patient demographics were well balanced across the three treatment arms and typical of a PBC population. Patients were predominantly Caucasian females of middle age, however, there was fair representation of more elderly patients with about 20 percent of the population being older than 65 years of age.

Baseline PBC characteristics were also balanced across the three treatment groups. The

majority were on a background of UDCA and on an adequate dose ranging from 15 to 17 milligrams per kilogram once daily with over 90 percent of the patients on a dose of at least 10 mgs pr kg.

Although earlier in the spectrum of disease, these patients reflected a population at high risk for disease progression, the majority of these patients were diagnosed at a young age with a mean age of 47 years at diagnosed. Sixty percent of patients were diagnosed before the age 50. The UK-PBC study group as described by Professor Jones has demonstrated that these young presenters have a far worse prognosis.

Alkaline phosphatase levels were significantly elevated approximating 2.4-fold the upper limit of normal, indicative of an inadequate response. Mean baseline total bilirubin values ranged from 10 to 12 micromole per liter across the treatment groups with 92 percent of subjects within the normal range. Mean conjugated bilirubin levels were above the upper limit of normal, between 1.5 to 2-fold the upper limit of normal, indicating evidence of some hepatic dysfunction in this study population.

A limited number of patients had more advanced disease as defined by several parameters, including the proportion of patients with abnormal bilirubin at baseline, those with cirrhosis based on the pre-study diagnostic biopsies, and those meeting the criteria for moderately advanced disease per the Rotterdam criteria, a classification of disease stage using the biochemical parameters of bilirubin and albumin.

The characteristics of the phase 3 study population were representative of a typical PBC population as demonstrated by this comparison of the patient demographics from the clinical phase 3 study and the Global PBC database. In both studies, patients were middle-aged females, and the majority were on the concomitant UDCA therapy.

Alkaline phosphatase levels were elevated approximately twofold the upper limit of normal at baseline in both populations. The majority of patients in both databases had normal bilirubin levels. Our phase 3 clinical study included 8 percent of patients with abnormal bilirubin at baseline compared with 20 percent in the Global PBC study database.

Importantly, the general distribution of disease stage was consistent between the two study populations with a majority of patients classified as early stage disease within the two studies. Based upon this comparison, then, the phase 3 clinical study reflected that expected for a PBC population, the data being generalizable to PBC patients typically seen in clinical practice.

In this population of patients of significant unmet medical need, the phase 3 study met its primary endpoint. At month 12, nearly 50 percent of patients treated with obeticholic acid at the 10-milligram dose level achieved the alkaline phosphatase bilirubin composite endpoint compared to only 10 percent of placebo patients.

The key secondary endpoint in this study was the pairwise comparison of the titration regimen and placebo. As with the 10-milligram dose, significantly more patients treated with titration achieved the primary endpoint compared with placebo. The overall responder rate of 50 percent was consistent with the 10-milligram dose suggesting this titration strategy

may be an optimal dosing regimen should it also improve tolerability concerns, to be expanded upon later by Dr. Roya Hooshmand-Rad.

Obeticholic acid at both doses resulted in a significantly greater proportion of patients achieving the primary endpoint not only at 12 months, but at all time points across the study. In this population of significant unmet medical need, treatment with obeticholic acid provided benefit in terms of biochemical improvement that was not achievable with standard of care alone.

Importantly, this result was consistent across a range of subpopulations. Subpopulations of interest in this forest plot are shown on the left along with their associated odds ratios and 95 percent confidence intervals. In this plot, odds ratios to the right favor obeticholic acid therapy. Across all subgroups for which odds ratios could be calculated, the odds favored obeticholic acid with approximate 10-fold greater probability of achieving the primary endpoint.

For four of these subgroups as noted by the asterisks, odds ratios could not be calculated as there

were no placebo responders in this subgroup. However, in these few subgroups, the difference between obeticholic acid and placebo for the change in alkaline phosphatase was statistically significant in favor of obeticholic acid, further demonstrating efficacy in these patient populations.

The efficacy of obeticholic acid as monotherapy was further evaluated based on a pooled analysis of data from the phase 2 and phase 3 studies. In this slide, month 3 data for the placebo and the 10-milligram dose are pooled. Based on the pooled data from the combined studies, mean baseline alkaline phosphatase for the obeticholic acid 10-milligram monotherapy group was 448 units per liter with 52 percent of these subjects exhibiting alkaline phosphatase levels over threefold the upper limit of normal.

As shown in the left panel, significantly more patients treated with obeticholic acid as monotherapy achieved the composite endpoint compared with placebo. Further, clinically meaningful improvements in alkaline phosphatase were observed with monotherapy. Treatment

from a baseline of 3.8-fold the upper limit of normal levels approached 200 units per liter with obeticholic acid therapy. Consistent with the overall population, total bilirubin levels remained stabilized below baseline levels with an approximate 4 micromole per liter reduction.

While UDCA at the recommended dosage is generally well tolerated, there is a subset of PBC patients who are unable to tolerate UDCA therapy, and as such are at an even greater risk of adverse outcome. Obeticholic acid is effective as monotherapy in this subset of patients unable to tolerate UDCA addresses a key underserved population in PBC.

Patients with more advanced disease were also responsive to obeticholic acid therapy. As noted earlier, the Rotterdam criterion is one of several methods of classification of disease stage and uses the biochemical parameters of albumin and bilirubin. Per the Rotterdam criteria, moderately advanced disease is defined by patients with either abnormal bilirubin or albumin levels, advanced disease being denoted by abnormal bilirubin and albumin.

Very few patients in the phase 3 study had advanced disease based on this categorization. However, 17 percent of patients were considered moderately advanced and are presented here. Shown in the left panel, obeticholic acid treatment resulted in more patients with moderately advanced disease achieving the primary endpoint compared with placebo.

Consistent with the overall population, clinically relevant improvements in both alkaline phosphatase and bilirubin levels were also demonstrated in this subgroup supporting the effectiveness of obeticholic acid in a more progressed patient population.

In addition to the categorical endpoint, we also looked at alkaline phosphatase and bilirubin as continuous variables. With the 10-milligram dose, significant improvements in alkaline phosphatase were apparent within the first 2 weeks of treatment initiation. The majority of response was attained within the first few months and significant reductions maintained through one year of therapy.

With titration, the pattern was generally

comparable with significant improvements at every visit through month 12. The magnitude of response was modestly lower with titration compared with 10 milligrams. In both obeticholic acid treatment groups, endpoint values approached 1.67-fold the upper limit of normal compared to placebo, where alkaline phosphatase levels remained highly elevated.

Taking a closer look at the titration arm, I will remind you that patients randomized to this regimen initiated on the lower 5-milligram dose for the first 6 months and were to up-titrate to 10 milligrams if they had not yet achieved the primary endpoint and were tolerating therapy. A total of 69 patients from the titration regimen completed the month 6 time point. Of these, 52 percent remained at the 5-milligram dose level and 48 percent up-titrated to 10 milligrams for the last 6 months.

In the subset of patients remaining on the 5-milligram dose level, shown here in a lighter orange, the change in alkaline phosphatase levels achieved by 6 months was generally maintained through 12 months of treatment. Alkaline phosphatase levels remained

somewhat lower than that achieved with the higher 10-milligram dose.

Within the subgroup of patients who up-titrated to 10 milligrams at month 6, now shown in a darker hashed orange, additional improvement in alkaline phosphatase was observed. With up-titration, changes in alkaline phosphatase at month 12 were now comparable to those achieved in the group originally randomized to that higher dose demonstrating incremental benefit of the higher 10-milligram dose in these patients compared to 5 milligrams.

On an individual patient basis, the majority of obeticholic acid treated patients showed some improvement in alkaline phosphatase levels. In these scatter plots, changes in alkaline phosphatase are on the Y-axis with baseline alkaline phosphatase levels presented on the X-axis.

This dashed line represents a 15-percent change from baseline. While 29 percent of placebo patients saw at least a 15-percent improvement in alkaline phosphatase, 77 percent of obeticholic acid treated patients saw such a magnitude of change. That

a 15 percent improvement was demonstrated in nearly 80 percent of obeticholic acid treated patients is highly relevant in that a reduction of this magnitude has been shown to predict a significantly reduced risk of liver transplant or death based on the Global PBC study group data.

In terms of disease progression, 36 percent of placebo patients experienced a worsening in their alkaline phosphatase compared to only 3 percent of obeticholic acid treated patients.

In conjunction with improvement in alkaline phosphatase, it was also important to ensure no deleterious effect on bilirubin. The majority of patients had normal bilirubin levels at baseline, as we've discussed. However, as elevations in bilirubin is a hallmark of advanced disease, it was important to show stabilization of bilirubin within the normal limits in these compensated patients.

In the placebo arm, shown here on the left panel in gray, bilirubin levels showed a gradual rise over time despite continued use of UDCA in the majority of these patients. This was in contrast to obeticholic

acid treated subjects whose bilirubin levels stabilized below baseline over 12 months of treatment with a significant difference compared with placebo at month 12. The effect of obeticholic acid on total bilirubin in later stage patients was also evaluated.

In the small group of patients with abnormal bilirubin at baseline, 63 percent of those obeticholic acid treated patients showed a normalization in their bilirubin after 12 months compared with only 14 percent of placebo patients. So in patients earlier in disease stage with normal baseline bilirubin levels, obeticholic acid was associated with the stabilization of bilirubin within the normal range.

In those few patients with abnormal bilirubin, active therapy was associated with a trend toward normalization. While it's true that bilirubin largely stayed within the normal limits in all treatment groups, the Global PBC database has shown that changes in bilirubin, even within the normal range, predicts outcomes.

Gamma-GT, a well established indicator of cholestatic injury, was significantly elevated across

all three treatment groups, approximately tenfold the upper limit of normal at baseline. Obeticholic acid treatment was associated with significant reduction in gamma-GT with improvements ranging from approximately 140 to 180 units per liter depending on the dose.

Transaminases, also elevated at baseline, showed a modest but statistically significant improvement with obeticholic acid. At baseline, ALT and AST values were approximately twofold the upper limit of normal. With the higher 10-milligram dose, ALT was reduced by 25 units per liter and AST by 15 units per liter.

This improvement in transaminases were consistent with the observed decreases in both alkaline phosphatase and gamma-GT. So although an exploratory assessment, these observations do suggest potential amelioration of hepatic cell injury secondary to the anti-cholestatic effects of obeticholic acid.

Primary biliary cirrhosis is an inflammatory liver disease characterized by elevations in the immunoglobulins across the three IG subclasses, but most distinctively by high IgM, the hallmark

immunoglobulin in PBC. As shown in the left panel, IgM was elevated at baseline in all groups as expected. While IgM remained stable with placebo treatment, there were significant improvements toward normality with obeticholic acid.

The most sensitive measure of systemic inflammation is CRP, which also showed a statistically significant fall with obeticholic acid therapy. The median decrease at month 12 was approximately 0.5 mgs per liter with the obeticholic acid treatment groups compared with a modest increase with placebo. Taken together, these data are consistent with the known mechanism of action of FXR and with the immunomodulatory and anti-inflammatory effects observed in our preclinical program.

The comparative incidence of clinical outcome events was also evaluated in the phase 3 program as a post hoc analysis. As most patients were earlier in disease stage, the incidence of outcome events in phase 3 was expected to be low especially in the context of the slow progression of disease and the relatively short duration of the study. In this

analysis, events used to define a clinical outcome in the phase 3 study were based on those being used in the ongoing phase 4 outcome study. These were not adjudicated and, again, this was a post hoc analysis.

In this table, each row represents events for an individual patient. A total of 3 placebo treated patients had 5 clinical outcomes, and 3 obeticholic acid treated patients had 4 clinical outcomes. These were all observed in the titration arm, so a comparative incidence of 2 percent with obeticholic acid versus 4 percent with placebo.

The ongoing longer-term clinical outcome study is enrolling more advanced patients to enrich for accrual of events and to allow for a more robust assessment of the effect of obeticholic acid on clinical outcomes, including adjudication of events.

At the end of the double-blind phase, patients could opt to continue into an extension phase of this study. Patients originally on placebo transitioned on to the 5-milligram dose of obeticholic acid. Those originally randomized to obeticholic acid were to down-titrate or remain on the 5-milligram dose to maintain

the study blind, and then after 3 months of treatment, the dose could be adjusted based on response.

Overall, greater than 98 percent of the patients who completed the 12-month double-blind phase opted to continue into the extension reflecting the general acceptance of obeticholic acid therapy by these patients. As of the 120-day safety update, data from the extension phase included up to 40 to 50 patients per treatment arm out to 2 and a half years.

Overall, obeticholic acid therapy demonstrated a durable response for up to 2 and a half years. In this subsequent slide, the 12-month, double-blind phase is presented on the left, and the subsequent 18 months of the extension phase is in the shaded portion on the right.

In patients originally randomized to obeticholic acid, improvements in alkaline phosphatase were maintained throughout 2 and a half years of treatment. For those originally randomized to placebo, shown in gray, a marked improvement in alkaline phosphatase was observed upon a transition to obeticholic acid with comparable levels of alkaline

phosphatase observed between all three groups at 2 and a half years.

Bilirubin levels showed a vary similar profile with longer term treatment. For patients who received obeticholic acid during the double-blind phase, bilirubin levels remained generally stabilized within the normal range with continued long-term treatment. Recall that with placebo, bilirubin levels showed a gradual deterioration over the initial 12 months. Following transition to obeticholic acid therapy in the extension phase, we saw a modest improvement in bilirubin, which was maintained out to 2 and a half years.

So taken together, obeticholic acid therapy demonstrated a significant increase in the proportion of patients achieving the primary endpoint, an endpoint predictive of reduced risk of adverse clinical outcomes. In addition, improvements in markers of cholestasis, hepatic function, hepatic damage, and markers of inflammation suggest an effect on the underlying pathophysiology of the disease.

Importantly, the effects of obeticholic acid

were consistent across many subpopulations, including patients at highest risk of disease progression, and the response was durable over the course of 2 and a half years of therapy. The efficacy profile of obeticholic acid supports a promising new therapy for the treatment of primary biliary cirrhosis addressing a tremendous unmet medical need.

Thank you. And with that, I'd like to introduce Dr. Hooshmand-Rad, who will present our safety data.

Application Presentation - Roya Hooshmand-Rad

DR. HOOSHMAND-RAD: Thank you, Dr. MacConell.

Good morning. I am Roya Hooshmand-Rad, executive director of medical safety and pharmacovigilance at Intercept Pharmaceuticals. In support of the company's filing, I will review the safety data from our PBC program with focus on the phase 3 study.

In this orphan disease, we have studied over 400 patients treated with obeticholic acid. The cumulative exposure of these patients adds up to 675 patient-years of exposure. The safety of OCA has been

further characterized in over 1200 patients in a number of other company sponsored and investigator initiated trials. We have not identified any new safety signals in these studies. The majority of our safety data in PBC is from patients with one year of exposure. 155 patients have been treated for at least 2 years, and 14 have been exposed for 5 or more years.

Patients' disposition in the phase 3 study is presented here. Overall, the vast majority of OCA treated patients completed the study with a 90 percent completion rate in the titration arm. Almost all patients who completed the double-blind phase chose to continue into the long-term safety extension.

The single most common adverse event leading to discontinuation in OCA treated patients was pruritis with no other trends observed. Overall, adverse events occurred at a similar rate in OCA and placebo treated patients. Between 90 to 95 percent of patients experienced an adverse event during the study. A greater number of patients in OCA treatment groups experienced serious adverse events, and I will go through these events in some more detail in the next

slide.

During the double-blind, phase 3 study, one 82-year-old male patient with extensive cardiovascular comorbidities died due to a worsening of his preexisting cardiac failure. In turning our attention to the SAEs, we noted that the higher rate of events in the OCA treatment arms was not accompanied by any obvious trend or clustering of the types of SAEs that occurred, nor were they dose dependent. It is also important to note that there was no pattern in the time to occurrence at these events. Furthermore, none of the SAEs were considered related to treatment by the investigator.

SAEs that occurred in at least two OCA treated patients were osteoarthritis, which were in essence reflective of hospitalizations for preexisting conditions and surgeries and stripping of varicose veins. In addition, approximately 80 percent of patients who had SAEs in the OCA treatment arms continued into the long-term safety extension.

Consistent with the overall symptomatology in patients with PBC, between approximately 40 to

70 percent of the phase 3 PBC study participants experienced pruritis during the study. Although the incidence of pruritis was higher in OCA treatment arms compared to placebo, the rate was relatively lower in the titration arm compared to the 10-milligram group. Therefore, as assessed by the incidence of pruritis, tolerability was improved in those that started the 5-milligram dose and were titrated up to 10 milligrams.

Other than pruritis, few events occurred in 10 percent or more of OCA treated patients. This slide presents adverse events that occurred more frequently in OCA treatment arms compared to placebo and is arranged by descending order of frequency in the titration arm since it represents the proposed clinical dosing regimen. Fatigue, abdominal pain, rash, and arthralgia were AEs that occurred in 10 percent or more in any OCA treatment arm. The incidence of AEs was otherwise no greater than may be expected in the patient population with relatively few patients experiencing any given category of event.

I will next provide some additional data regarding the most common adverse event, pruritis.

These pie charts compare pruritis in the three treatment arms. The proportion of patients who did not experience pruritis are presented in gray. Patients who experienced pruritis but didn't require any management are presented in cream. And patients who required management and were thus able to stay in this study are presented in blue. Lastly, patients who experienced pruritis and were discontinued because of it are presented in pink.

Comparing the cream colored sections of the 3 pie charts, between 21 to 26 of OCA treated patients who had pruritis did not require any management. Looking at the blue sections of the pie charts, the vast majority of those that were managed were able to tolerate the pruritis and remain in the study. In pink, we observed that pruritis rarely resulted in discontinuation with only one patient discontinuing due to pruritis in the titration arm. Separately, patient assessments of pruritis severity demonstrates improved tolerability over time.

This slide demonstrates the patient-reported Visual Analog Scale scores for pruritis in our phase 3

study. As referenced on the right axis, I have shown you the accepted classification of these VAS scores in practice, which divide the scores into mild, moderate, and severe.

As is evident for the 3 treatment groups, mean pruritis scores were overall mild. Nevertheless, one can see that treatment is associated with an early increase in VAS score for patients treated with obeticholic acid. However, by month 9, the average experience of pruritis was similar in all three treatment arms and the lines essentially merge from then on through to the end of the study. The severity of pruritis in the titration arm, as assessed by the patient themselves, was comparable to that of placebo throughout the end of the study.

Now, I'd like to switch over to adverse events that were hepatic in nature given the target organ for treatment with OCA is the liver. Clinical hepatic events were infrequent during the phase 3 study and event rates were similar across treatment groups. A summary of the individual clinical events that occurred in each arm during the double-blind phase are presented

here with no meaningful difference from placebo. We will continue to monitor long-term clinical outcomes in the phase 4 study.

Next, I'll turn my attention to laboratory assessments of interest from a safety perspective. In the double-blind, phase 3 study, we observed that patients more frequently experienced ALT and/or AST elevations if they were not treated with obeticholic acid. Critical elevations in transaminases to grade 3 or 4 were only observed in one patient in the titration arm and none in the 10-milligram arm.

The titration patient had interrupted OCA and UDCA treatment due to Helicobacter pylori infection, which occurred directly prior to the transaminase elevation. The patient did not experience a concurrent increase in total bilirubin, recovered upon resuming treatment, and continued into the long-term safety extension.

Other clinically relevant laboratory assessments included a review of lipid parameters. Consistent with the overall lipid profile of patients with PBC, mean HDL levels were well above the lower

limit of normal at baseline in all treatment groups and remained so for the duration of the study. The lower limit of normal for this study is marked by the dotted line.

The titration and placebo arms demonstrated similar HDL levels throughout the double-blind portion of the study. Patients who initiated treatment with 10 milligram demonstrated an early but relatively small decreased in HDL levels, which thereafter plateaued and remained stable for the duration of the study.

Other lipids of interest include LDL cholesterol, which was elevated in all three treatment arms as shown in the upper panel. There was a small transient increase early during OCA treatment but returned toward baseline by 6 months of treatment and was otherwise on average essentially overlapping with placebo.

Otherwise, the LDL and triglycerides, which are shown on the bottom, increased in patients treated with placebo while they remained stable with OCA. These lipid observations were not associated with a difference in serious adverse cardiovascular event

rates.

The long-term safety of OCA was consistent with that observed during the double-blind phase of the study with no meaningful change in the types of treatment emergent adverse events. Pruritis remained the most common adverse event and again was the single most common reason for discontinuation. Also, with long-term treatment, there was no pattern in the types of SAEs that occurred.

Events which were reported in two or more patients were osteoarthritis and variceal bleeding. A 69-year-old male patient with a prosthetic aortic valve placed 18 months prior to entering into the study experienced endocarditis and died due to ensuing complications, which included sepsis and renal failure. The event was not considered related to OCA by the investigator. Finally, lipid levels, including HDL and LDL cholesterol, remained stable.

Overall, our data collectively indicate that OCA was safe and well tolerated with the best tolerability observed in patients who initiated treatment at 5 milligrams. Pruritis, while a common

symptom of PBC, was also reported as an adverse event, but was manageable particularly in the titration arm, where only one patient discontinued. Clinical events were infrequent and occurred at a similar rate across all treatment arms.

There was an early and minor decrease in HDL, the magnitude of which was stable and on average remained well within normal limits, even with long-term use. LDL changes were small and transient with no notable difference between OCA and placebo treatment arms by the end of the study. The clinical significance of these changes in patients with PBC is unknown.

Lastly, no new safety signals were seen during longer term dosing. These data therefore support the safe use of OCA in the treatment of patients with PBC who have an inadequate response to UDCA or are intolerant of UDCA.

With that, I'll hand over to Professor John Vierling for a presentation of the risk-benefit of OCA.

Applicant Presentation - John Vierling

DR. VIERLING: Thank you and good morning.

I'm John Vierling. I'm being compensated for my participation here, but I have no personal financial interest in the outcomes of these deliberations.

I'm currently professor of medicine and surgery at the Baylor College of Medicine, where I also serve as chief of hepatology for our multi-hospital system and a transplant hepatologist in our busy liver center. I'm also director of advanced liver therapies, a clinical research unit dedicated to the studies of therapies and diagnostics in patients with acute and chronic liver diseases.

Now, from that perspective, I have been involved in the development that you've heard about, of the status quo of PBC treatment, since the introduction of ursodeoxycholic acid in 1997 through 2016. Indeed, I've had the privilege of caring for patients with PBC for nearly 40 years in practice, which preceded the UDC era when we suffered together trying to arrange life-saving transplants for these individuals.

After the introduction of urso, we were able to see a response. It was quite gratifying. And like all the clinicians here, we know that the unmet need

exists for those that do not respond. So where are we now that we have used urso successfully worldwide since 1997 in this country?

Well, we are diagnosing PBC patients with increasing frequency the appropriate application of our biochemical and serologic tests, and we're finding patients that are both symptomatic but also increasing numbers that are asymptomatic, and indeed patients that have earlier stages of disease.

Now, regardless of when we diagnose them, they have one approved therapy, weight based ursodeoxycholic acid. And it's obviously appropriate therapy for the majority. And you've heard that 60 to 65 percent of patients are responders based on their usual decreases in baseline alkaline phosphatase and bilirubin achieved after one year of therapy. And indeed, you have already seen data presented from the worldwide cohorts that such responders have reduced risks for liver related deaths and the need for life-saving liver transplantation.

Now, what about the 35 to 40 percent that are non-responders based on the same criteria? They are at

risk for progressive disease, including progression to and worsening of cirrhosis, complications of portal venous hypertension, and/or the development of hepatocellular carcinoma.

In this group, we still have patients undergoing premature hepatic related deaths, and only life-saving transplant is their alternative, where these individuals compete with another 15,000 Americans that are currently listed for orthotopic liver transplantation for approximately 6,000 available organs in any given year. And it's this that represents our unmet need and challenge therapeutically.

Now, Professor Jones shared his vision of the future of PBC management, and he identified three key attributes that new therapies should have. And I would like to review the evidence very succinctly that shows that OCA exhibits each of these three attributes, beginning with the first, is it targeted for patients with unmet need through appropriate risk stratification?

Now, you have seen data from the international

databases combined from the national health services databases of European countries and in Canada, and also the Global data shown here, that includes U.S. centers. And in this retrospective Global PBC study, you have also heard that alkaline phosphatase and bilirubin levels have additive predictive significance for outcome.

Here, transplant-free survival or all-cause mortality censored only for those that undergo transplant had shown that patients with normal bilirubin have the highest survival if on urso therapy they've achieved an alkaline phosphatase level of less than or equal to 1.67 the upper limits of normal. If they fail to do that, as you see in green, they have a slight decrement in survival probability.

Now, the worse survivals are those that have abnormal bilirubin and alkaline phosphatase is greater than 1.67, shown in red at the bottom. But even if you do achieve a reduction of alkaline phosphatase, it raises the probability of survival.

So in the study of OCA, I would submit that it has targeted the right population because the inclusion

criteria are specifically those that have been addressed in these analyses to find the high-risk patients for progression, those that have a value of alkaline phosphatase greater and equal to 1.67, the upper limit of normal, and/or bilirubin of greater than the upper limit of normal or less than 2 times the upper limit of normal in the pivotal phase 3 study.

What is the proof of benefit of this drug in studies of appropriate patient cohorts? Well, with the enrollment of that appropriate patient cohort at risk for progression, the efficacy was demonstrated by the statistically significant increase proportions of patients meeting the composite endpoint of alkaline phosphatase and bilirubin compared to placebo's in the 12-month, double-blind, placebo-controlled randomized phase.

In addition, the secondary endpoints were also met, specifically those for alkaline phosphatase and bilirubin, but also markers of hepatobiliary injury. And I'll call your attention to GGT, which corroborated the fact that the reduced alkaline phosphatase achieved in OCA treatment was a hepatobiliary isoform of

alkaline phosphatase, as well as the fact that the reductions of ALT and AST biomarkers of ongoing hepatobiliary inflammation.

Finally, it met the endpoints of immune and inflammatory markers. And I'm most struck clinically by the reduction in IgM, which is the immunoglobulin isotype, a signature elevation of which is seen in PBC, as well as a reduction in highly sensitive CRP, which is the most sensitive marker for systemic inflammation and also cardiovascular disease risk.

Now, the durability of response was maintained in the long-term safety extension study for over 2 and a half years of continued therapy. You see again the double-blind phase of the study without color, and to the right in the pink, the open-label phase. And you have heard that the patient acceptance of transitioning and enrolling in that study was extraordinarily high.

Well, what about the issue of whether OCA exhibited manageable and tolerable side effects? Let me first begin with pruritis. This is a common and very often distressing symptom for our patients. We know that this symptom unfortunately has not been

ameliorated by even the appropriate response to the therapy of UDCA. In other words, UDCA response does not prevent the existence of pruritis. However, pruritis can be managed in most of our patients, and Dr. Kowdley went through the standard of care regimens that we as clinicians use.

Now, pruritis was the dominant treatment emergent AE noted in the double-blind phase 3 study. However, it was generally well tolerated, as you just heard, with a proposed titration regimen, which appeared to give patients the ability to adapt to pruritis.

Now, the patient reported Visual Activity Scale score was comparable among the treatment groups after six months of therapy and was generally rated as mild. And among the population that experienced pruritis during the study, there was a substantial group not requiring any therapy for their pruritis whatsoever. In that titration group, with a proposed 5-milligram to 10-milligram titration being proposed here, only one patient discontinued due to that symptom.

Now, those that were treated were found to be responsive to a variety of endeavors, including interruption or cessation of therapy in some, alternate day dosing, and investigator initiated therapies most usually cholestyramine, a bile acid-binding resin. Now, from the patients' perspective, how did they see the tolerability of the pruritis being observed during the study. Well, you can see that they found it acceptable because of the high voluntary entry into the long-term safety extension.

Overall, I conclude that pruritis was well tolerated by patients and also note that when you have the history of the patients before you prior to their enrollment, up to 68 percent of the patients have had prior events of pruritis before they sought to volunteer for this study.

Regarding changes in lipids, you've heard that PBC is associated with hypercholesterolemia, which is usually driven by HDL elevations and is generally not associated with increased cardiovascular risks. OCA was associated, as you've seen, with reduction in HDL. And that was noted soon after initiating therapy, and

then it seemed to be maintained at mean levels within the normal range. And this was a true exception of only two patients. HDL showed only a transient elevation which returned to baseline within 3 to 6 months.

What about the hepatic safety profile of a drug used long term in a patient population by definition with preexisting and somewhat serious liver disease in up to 17 percent of those enrolled? Well, overall, the clinical hepatic AEs were infrequent in treatment and placebo arms.

At the proposed clinical doses of 5 milligrams titrating to 10 milligrams once daily, the treatment emergent changes in ALT and AST were observed, however, the elevations in the OCA treatment arms were actually less frequent than in the placebo arms, and the elevations were predominantly transient, and none were accompanied by total bilirubin abnormalities. Thus, there were no signals to suggest the risk of serious bili [indiscernible.]

Based on all of these findings, I have reached the personal conclusion that OCA offers a favorable

benefit-risk ratio. Its benefits address the unmet needs in patients who are non-responsive to or intolerant of UDCA. Its efficacy has been shown by the fact that it met both its primary and secondary endpoints. And durability has been seen in the long-term safety extension up to 2 and a half years of therapy.

Its risks, in contrast, have been identifiable and manageable. The adverse events have included pruritis, which we've discussed in detail; the mild HDL reductions, the mean of which stays within the normal range of these transient HDL increases; and there have been very infrequent liver related safety observations. Indeed, any of the on-treatment effects of OCA have been found to be reversible with discontinuation.

So what do I envision in 2016 and onward? Well, clearly we intend to diagnose as many patients as early in the course of their disease as possible to afford them the greatest potential benefit from medical therapy, which will rely on weight-based ursodeoxycholic acid and will be sufficient for approximately 60 to 65 percent of patients who will

respond to it. But for those non-responders, I submit that the addition of obeticholic acid holds promise to move them from a non-response population to a responder population and to decrease their risk of progression of disease to cirrhosis, portal hypertension, the risk of hepatocellular carcinoma, and premature death. Thank you very much.

DR. ROBERTSON: Thank you, Dr. Vierling.

In addition to Dr. Vierling, we have several other experts that are available to comment, Dr. Hansen and Dr. Hirschfeld, Dr. Jones, and Dr. Kowdley.

Clarifying Questions for the Presenters

DR. RAUFMAN: Thank you.

Are there any clarifying questions for Intercept? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Dr. Lipman?

DR. LIPMAN: Dr. Lipman. Unfortunately, I'm not going to be able to address to a specific presenter. But I am concerned the validation of the surrogate endpoint of alkaline phosphatase, and this seems to be, I think, the primary issue as why we're

all here. All of the data from the Global studies, the UK and the European, the international studies, are observational data, and observational data can only establish association, not causality.

So my, really, question for anybody who wants to respond is what is the clinical randomized controlled data which establishes alkaline phosphatase as a valid surrogate endpoint? Has reduction of alkaline phosphatase been actually clinically validated as a surrogate endpoint, not just a predictor, which is an association as manifested by observational data. Anybody?

DR. ROBERTSON: As FDA stated in their initial comments, the criteria for accelerated approval is not a validated surrogate endpoint, and alkaline phosphatase indeed has not been fully validated. However, the premise is that there are data to suggest that it is reasonably likely to predict. And I'd look to FDA perhaps to share what that criteria is in context of accelerated approval.

DR. DIMICK-SANTOS: We are going to present on that later, and I think that maybe the panel would want

to ask us questions after our presentation.

DR. RAUFMAN: That's fine.

Other additional questions? Ms. Cryer?

MS. CRYER: Donna Cryer, and perhaps Dr. Vierling can address this question. Do we have a sense, at this stage, of a way of predicting non-responders?

DR. ROBERTSON: Dr. Vierling, would you like to speak to that?

DR. VIERLING: I think that's a very important question, and it is one that's going to require additional analysis. I think that analysis should also include other relevant treatment databases. But most important to the question of OCA and its use, I think that key data will be developed for the purpose of multivariate analysis of predictors of response and non-response at baseline, which is the characteristic I believe you're asking about, as we acquire more data for the phase 4 confirmatory study, which is also enriched in people who are more likely to have events of progression over a relatively short period of time, meaning 5 to 8 years of time.

The purpose of this is going to be to expand our ability to predict within subgroups what the predictors are of response or non-response. We have not the data to show that yet.

MS. CRYER: Thank you.

DR. ROBERTSON: We could speak a little bit to some limited data, though, from the phase 3 study. Dr. MacConell?

DR. MacCONELL: I think it's important to note that in terms of alkaline phosphatase improvements, by far, the majority of patients treated with obeticholic acid saw at least a 15 percent improvement in alkaline phosphatase. In terms of the analysis that we conducted specifically to look at predictors of response, the significant covariates associated with a lowering of alkaline phosphatase were higher levels of alkaline phosphatase at baseline, higher levels of gamma-GT at baseline, and higher levels of IgM.

In terms of predictors of response for improvements in bilirubin, it was based on -- higher levels at baseline bilirubin -- bilirubin at baseline predicted a better response, and higher mL values also

predicted a greater response as well.

In terms of specifically looking at the demographics of the non-responders per the primary composite endpoint, predominantly, it was due to those patients having a higher baseline alkaline phosphatase. So in terms of achieving a categorical endpoint, the farther that patient was from the categorical endpoint cutoff of 1.67-fold the upper limit of normal, resulted in a non-response.

However -- slide 3 up, please -- if you look at those patients that technically were non-responders per the primary endpoint, you see a significant improvement in their alkaline phosphatase and bilirubin levels. So looking at the variables on a continuous level, you see significant improvements, even in the non-responders per the primary endpoint.

MS. CRYER: Thank you.

DR. RAUFMAN: Dr. Proschan, you had a question?

DR. PROSCHAN: Yes. I was just wondering in the observational studies that were used to support your case, how are people treated in those studies.

I'm assuming no one in those studies got OCA. Is that correct?

DR. ROBERTSON: Correct.

DR. PROSCHAN: Okay.

DR. RAUFMAN: Dr. Silveira?

DR. SILVEIRA: Yes. This is Marina Silveira. I had a couple of questions with regard to the composition of the population in some of these studies. One of the questions is the effect of OCA on moderately advanced disease and more advanced disease stage.

The packet that we have, Intercept provided that even though only 8 percent were moderately advanced or advanced biochemically, they do provide that about 72 patients, or 33 percent, met criteria for advanced stage disease by meeting a few things.

Some of those criterias were a mix of risk, so for example, alkaline phosphatase above 5 times rather than real advanced disease, and others were histologic cirrhosis. I was wondering what was the breakdown, high risk? How many were actual alk-phos criteria in that group and how many were other features such as previous decompensation and cirrhosis.

So histologic cirrhosis looks like 20 percent, 20 patients. How about the other 50 patients? How do they break down?

DR. ROBERTSON: Just to clarify, there are several different criterias that have been used, as you mentioned. There's the Rotterdam criteria that was used by FDA. There's the Rotterdam criteria that was prespecified that had slightly different cutoff for albumin. And then in addition, there's the criteria that you mentioned, which is a post doc criteria that we used, using clinical assessment and biochemical assessment.

Dr. MacConell, could you come to speak to that, please?

DR. MacCONELL: Slide 2 up, please. So based on that criterion of more advanced disease -- and again, that was a definition meant to describe not only patients with advanced disease but also at high risk for progression.

These percentages are based on the sample size that met the criteria overall. So approximately 25 percent of the patients met the -- and an individual

patient could have actually qualified based on multiple criteria. But the distribution is shown here, and I think to get to the crux of your question, the majority of the patients met that criterion based on having a baseline transient elastography greater than 10.7 kilopascals at baseline.

DR. SILVEIRA: Okay. So this slide does demonstrate that mostly more clinical acceptable evidence of advanced disease rather than high risk.

My other question that I have is the graph showed nicely that even patients after the long-term safety extension had lower levels of bilirubin compared to baseline. But I didn't see a number as to how many patients had normal bilirubin at entry and at the end of this extension study.

DR. MacCONELL: So over 98 percent of those patients that achieved that 12-month time point went on into the long-term safety extension. As far as the proportion of patients that had abnormal bilirubin, keep in mind that in the overall population, it was a very small percentage; 8 percent of patients had abnormal bilirubin. Of those 8 percent of patients,

63 percent of those treated with obeticholic acid saw a normalization of bilirubin as opposed to only 14 percent of patients with placebo. So the majority of those patients transitioned on into the LTSE.

DR. SILVEIRA: But do you have the numbers?

DR. MacCONELL: I do not have the specific numbers.

DR. RAUFMAN: Thank you. Dr. Conjeeveram?

DR. CONJEEVERAM: We know that pruritis is one of the symptoms in PBC, and it also happens to be one of the distressing symptoms on the drug as well. Was there any correlation between the presence of baseline pruritis and the fact that you see more pruritis on the drug, or would say no correlation?

DR. ROBERTSON: Dr. Hooshmand-Rad, could you come to speak to this?

DR. HOOSHMAND-RAD: We did observe that patients who already had baseline pruritis upon entry into the study appeared to more frequently experience pruritis and report pruritis during the study, and those who did not have baseline pruritis appeared to less frequently report pruritis during the study and

with obeticholic acid.

DR. RAUFMAN: Dr. Chang?

DR. CHANG: Lin Chang. I had two questions. The first one was to Professor Jones. Looking at all the database that you have and maybe existing literature, I want to know your opinion if you just took the patients from these databases that were very similar to the study population -- so relatively early disease, more normal total bilirubin, level of alkaline phosphatase, age, gender -- what do you think are the best predictors for meaningful outcomes?

If it is alkaline phosphatase, are there any other factors or variables that you think are important, whether it was collected or not, to predict long-term outcome?

DR. ROBERTSON: Professor Jones?

DR. JONES: I think moving forward -- this answers another question as well, which is can we predict in advance patients who are going to have a risk other than by failing therapy, which involves sequential periods of time using therapies, then doesn't work. So at the moment, using the easily

available markers, it's alkaline phosphatase.

Now, if we could have slide 2. This was alluded to, and I think it's a very useful thing, that we can move forward to have a more sensitive way of understanding risk. And these are the two integrated, continuous variable models that came from the UK-PBC and Globe, the Global PBC study group. And actually, they're very convergent and they cross-validate.

These for clinical use address the fact that these are continuous variables, so the dichotomization issue. And these are extremely useful tools for predicting baseline risk. And they are a combination of factors associated with activity of the disease, ALT, alkaline phosphatase, and bilirubin, and also those features that would quantify severity, say albumin and platelet count.

So those are baseline predictive scores. These have evolved after the phase 3 pivotal trial. And if you apply the data from these models, these are also very predictive of outcome in the trials but weren't part of the formal assessment. I think in 2017, if you like, these scores will come into routine

practice, and they are very usable clinical tools optimized for practice.

I think moving down the line into the science of it, I suspect there may well be molecular characterization approaches that will allow us at the very beginning of the disease to identify very high-risk patients, because I think we would all like to be able to treat high-risk patients, particularly younger patients, effectively from the very beginning. But that is not relevant to this discussion. That is the science for the future, but there's a lot of work going on around identifying risk earlier on so we can treat patients better.

DR. CHANG: But are you saying that you would use this score at the end of treatment, like say 12 months, to also determine if someone really had a beneficial effect from a treatment?

DR. JONES: Yes. So those scores are usable both at baseline and then at 12 months of therapy.

DR. CHANG: So couldn't this score, with those values that were collected, be applied to the data that was collected in the phase 3 trial?

DR. JONES: Yes. We have that data. Can I have slide 2?

So as I said, this science came along after, if you like, the trial was designed. This is the application of the UK-PBC risk score, which gives you a percentage likelihood of needing transplant or dying of liver disease.

As you can see, on the left-hand side, this is the projected risk for patients. The score gives you 5, 10, and 15-year projected percentage risks. And as you can see at baseline, the groups are actually very well matched, so that projected risk is the same. But following OCA for a year or placebo, what you can see, very effectively, is whereas, the placebo group, the risk is significantly higher than it is in the titrated group and then the 10-milligram group.

So there has been a significant decrease in the projected risk of death or transplantation. And this is in fact a more finely tuned way of looking at benefit. But as we said, this wasn't part of the evaluation of the drug, and it is a post hoc analysis. But these tools are optimized to be used in the clinic,

and the UK-PBC score is widely available as the Globe score isn't, and I think clinicians will increasingly use them. So that's the application of the data into those models.

DR. CHANG: Thanks. I wanted a second, hopefully quick question, and I think it's for Dr. MacConell. When I looked at the long-term data, it looked like the bilirubin -- in the placebo group, patients that actually got treatment afterwards in a long-term study, the bilirubin went down. But then near the end, it started looking like it was going up again.

So I guess I was just wondering how stable that was. But I guess my question is -- and I know there are limitations of doing this. But if you took the patients with an elevated bilirubin who were randomized initially and also the patients who had elevated bilirubin on the placebo that now were entering this long-term study, what percentage of those actually had normalization of their bilirubin?

DR. ROBERTSON: Dr. MacConell?

DR. MacCONELL: So in response to your

question around that time point for the end of the study, where it appears that bilirubin levels are actually rising, that seems to be attributed to a single patient who -- at the visit prior to that, that last visit -- actually started to experience kidney failure, some decompensation. And their bilirubin levels increased significantly, up to over 80 micromole per liter. And that patient actually went off therapy for some time, and then has since gone back on therapy and is continuing in the study. And their bilirubin levels are improving with time.

So that's what's driving that single kind of aberrant time point at the end.

In terms of bilirubin levels over time -- slide 2 up, please -- this shows the actual completer population. So these are patients that were on a weighted average daily dose of less than 10 milligrams -- at least 10 milligrams once daily of obeticholic acid. And you see that, again, on average, those bilirubin levels show a modest decrease and then stabilize over time.

In terms of the actual percentage of patients,

I think that was asked previously as well, the percentage of patients that normalized when they had abnormal bilirubin, I only have that data for the double-blind phase, which I could present in, not at this time, for the LTSE phase.

DR. RAUFMAN: Thank you. Dr. Lipman?

DR. LIPMAN: Dr. Lipman. I had one last question on pruritis risk. Was there any correlation with response to treatment with decrease in alkaline phosphatase with the development of pruritis in these patients?

DR. ROBERTSON: No, there was no correlation with the pruritis adverse event and response to treatment.

DR. LIPMAN: Thank you.

DR. RAUFMAN: Dr. Vos?

DR. VOS: Thank you. I think this will also be for Dr. MacConell. I just wanted to clarify on the titration arm. It looks like a little bit more than 50 percent of the patients at 6 months had remained at 5 milligrams. But then when that group changed, or the ones that changed to 10 milligrams, we have the mean

change. But I wondered what percent of patients who changed dose had a further improvement in their alk-phos or responded.

DR. ROBERTSON: Dr. MacConell?

DR. MacCONELL: Slide 2 up, please. So overall, we did see a significant incremental benefit gained by up-titrating from the 5-milligram dose to the 10-milligram dose in that titration arm. Of the non-responders who up-titrated -- so this is shown in the far-left panel -- an additional 39 percent of that subgroup of patients met the primary endpoint at month 12. This incremental response was driven, in part, due to an additional 30 percent improvement in alkaline phosphatase levels. And that does underscore our recommendation that patients do try and achieve the 10-mg dose if possible due to tolerability.

DR. RAUFMAN: Dr. Ellenberg?

DR. ELLENBERG: How long did it take to accrue the patients in the phase 3 trial, and where were these patients? Is this a worldwide study?

DR. ROBERTSON: Dr. Shapiro, would you like to speak to that?

DR. SHAPIRO: I can't exactly recall the number of months we took to recruit, but I think we can hopefully find that fairly quickly at the break. However, in order to recruit into this study, in a rare disease in the second line, we recruited -- some 59 centers actually enrolled patients into the study to 8 countries. So it was a pretty global and intensive effort to recruit the patients.

DR. ELLENBERG: And what proportion were North American?

DR. SHAPIRO: Again, we'll come back to that. A minority were North American; more came from Europe. But we'll come back with a specific percentage.

DR. RAUFMAN: Dr. Assis?

DR. ASSIS: David Assis. A question perhaps for Professor Jones. I think, as been discussed and will be further discussed the Global PBC group's data was used in part to formulate the questions, which were used for the phase 3 drug development, in your presentation, you had pointed to -- in one of your slides, I think slide 18 -- that the UK-PBC cohort, those with a normal bilirubin but yet with a decreased

alkaline phosphatase had a curve that was not normal.

It appears, based on comparison, that the transplant-free survival was still higher in the UK-PBC group compared to the Global PC group. And I'm wondering if you think that is directly comparable, if there was a change in terms of the time period in which these patients were analyzed, and whether that could be a factor in the modeling for the phase 3 study.

DR. ROBERTSON: Professor Jones, could you speak to the differences in the methodology.

DR. JONES: Yes. Global PBC and UK-PBC are complementary but different. The Global PBC study group is retrospective and includes data from patients going back a number of years. And that offers real advantages in terms of the length of follow-up and the number of events, whereas UK-PBC is a prospective recruitment and is for recruitment into trials and to look at delivery. So the follow-up has been shorter, so therefore the number of events have been lower.

The difference is, I think, that you alluded to, have to do with the issue of the UK-PBC looking at liver rated deaths or transplantation and the Global

PBC looking at all-cause mortality. So they are slightly different, and I think underpins some of the differences.

The other thing I would say is that UK-PBC is more current. In fact, the distribution of patients across UK-PBC is absolutely identical to that seen in the phase 3 trials. So UK-PBC is a current data set, but it has fewer endpoints, so therefore is less valuable for the type of work that is being done.

What I think I would say is that they are international, global, and they cover different jurisdictions, different time periods. But it is striking, the extent to which the findings are the same across the two cohorts, suggesting that there is real complementarity, and I think we're sort of getting towards the truth with them. But I think it's to do mainly with era and to do with a different endpoint that we're looking at.

DR. ASSIS: Thank you.

DR. RAUFMAN: Dr. Dasarathy?

DR. DASARATHY: This question is for Dr. Hooshmand-Rad. You had said that there were 675

patient-year follow-up for safety. I'm just a little concerned about this reduction in HDL and this transient increase in LDL. Now, the duration of follow-up for this was only two years, and it is possible that the lack of increase in cardiovascular mortality in PBC is to some extent due to the protective effect of the increased HDL.

If this drug lowers the HDL and it constantly shall increase, then a decrease, I don't know whether there's going to be a cyclical effect or it's going to be persistence of this LDL not going up. What do you think would be the consequences on long-term cardiovascular mortality of these patients?

DR. ROBERTSON: I'm going to take that in two stages. First, I'm going to have Dr. Hooshmand-Rad speak to evaluations we've done estimating risk based what we have, using Framingham's score, et cetera, and then I'd like to have Dr. Hirschfeld come up to speak to his interpretation from a clinical perspective.

It is important to note that we have not had extensive long-term follow-up of patients, and we are committed within the confirmatory trial to continue to

follow up patients.

Dr. Hooshmand-Rad?

DR. HOOSHMAND-RAD: In our phase 2 study, there was a long-term safety extension that followed the double-blind phase. And indeed, we have patients in that study that are continuing and have been exposed for now approximately 4 years or more. We do have some information regarding the adverse events that had occurred in that patient population who has been exposed the most extensively.

There were 2 patients over the course of this period of time who experienced cardiovascular events. However, as my colleague mentioned, Dr. Robertson, we have simulated the Framingham score. We didn't collect all the necessary information at baseline in our phase 3 study. For example, we didn't collect smoking history or smoking habits. However, we took the worst-case scenario and assumed that all patients were smokers and assessed their Framingham score, tenure, CD risk at baseline and subsequently after one year of treatment.

Slide 3 up, please. In this assessment, you

see the colors that designate the different treatment arms. The left-hand panel assesses the Framingham score, the assumed Framingham score at baseline and then subsequently after 12 months of treatment. The majority of patients remained within the less than 10 percent risk, even after 12 months of treatment.

DR. RAUFMAN: Thank you. Dr. Silveira, did you have a question?

DR. SJOGREN: Yes. I have a question for the presenters. And that is, right now, we treat with ursodeoxycholic acid for life of the patients. What did they envision? Did they envision that we would be using OCA also for a long, long time, or would it be more like in autoimmune hepatitis, in which we stop drugs in some patients and then observe, do a prolonged follow-up.

Knowing what they know, what is their assumption? Is this also for life, or would it be a possibility of stopping the drug? What would happen to those patients?

DR. ROBERTSON: Well, from a company perspective, our intent was a chronic treatment and to

continue treatment with OCA. It is not akin to what you see in HCV, where there is a cure. This is a chronic treatment.

However, I would like to have Dr. Gideon Hirschfeld speak to this from a clinical perspective because I think that might be informative.

DR. HIRSCHFELD: Good morning. My name is Dr. Gideon Hirschfeld. I'm a transplant hepatologist from the United Kingdom. I've been reimbursed for my time, but I have no personal interest with the licensing of this drug.

I think your question is a very important question. PBC is a chronic disease, and it's very different to autoimmune hepatitis. So my expectation, just as with my patients who are given lifelong treatment with UDCA, that in those patients who achieve a clinically meaningful response to obeticholic acid, which I think will be a large proportion of the patients who use it, that they will continue to use this drug if they tolerate it.

What we know about the nature of PBC is it's very different to autoimmune hepatitis. In autoimmune

hepatitis, it is quite possible to move patients into drug-induced remission, and it's possible to maintain that remission using drugs like azathioprine.

When you look after a patient with PBC, what you see is if they interrupt their treatment with UDCA, that the alkaline phosphatase goes back up. So these are important modifying agents, but we presently do not know the cause of the disease. And therefore, the therapies for the future and as present will be chronic and lifelong.

DR. RAUFMAN: Thank you. We have time for only two more questions, Dr. Silveira and then Dr. Khurana.

DR. SILVEIRA: Yes. My question is for Dr. MacConell with regard to the patients with moderately advanced disease. It's interesting. Even though it was a very small sample, it did show that patients on titration had a better response for the alkaline phosphatase compared to 10 milligrams, 22 to 47 percent. Do we have an explanation for that? Was that due to dropout, due to poor tolerance to 10 milligrams?

DR. ROBERTSON: Could you repeat the question, please?

DR. SILVEIRA: My question is, do we know why the patients with moderately advanced disease achieved better reduction in alk-phos with titration whether than 10 milligrams? The graph that was shown showed 42 percent responders in the titration group versus 27 in the 10-milligram group. And my question is, is that difference from dropout to poor tolerance to 10 milligrams, or is it just due to the small sample size differences?

DR. ROBERTSON: Dr. MacConell?

DR. MacCONELL: Slide 2 up, please. This is a slide from the core presentation that you're referring to. The underlying reason for the number of patients not achieving the difference, differential between the titration and the 10-milligram dose is interesting. It's not actually related to those patients with the 10-milligram arm having a higher baseline. Alkaline phosphatase actually had a lower alkaline phosphatase, and bilirubin actually consistently improved between those two subgroups.

But if you think about the very small percentage of patients overall, that differential could reflect the difference of one or two patients. I think it's important to focus as well on the magnitude of reduction in alkaline phosphatase and bilirubin itself as opposed to the percentage attaining that primary endpoint.

DR. KHURANA: Sandeep Khurana. For the sake of general audience, I would like you to comment on what is the life expectancy of patients with primary biliary cirrhosis and how does it match with the general population.

DR. ROBERTSON: Dr. Kowdley, could you come to speak to that?

DR. KOWDLEY: Since we don't have data that have longitudinal evaluation of patients in the absence of ursodeoxycholic acid, it's clear that the life expectancy of patients, if you look at time to transplantation or need for transplantation has reduced, suggesting the life expectancy has increased significantly.

Certainly, in my clinical practice, I would

say the majority of my patients live well into their 60's, but there is a very dichotomous relationship in those patients who present in their 30's, or even 20's or 40's, who have a much more accelerated course. And in that population that is at high risk, a substantial percentage would need liver transplantation or have liver related death within 10 years.

But since this is a moving target and ursodeoxycholic acid has been available since 1999, the data with regard to life expectancy I think is best imputed from the data with regard to transplantation prevalence.

DR. RAUFMAN: Thank you. We're running almost 20 minutes behind schedule. Nonetheless, we'll take a 10-minute break right now, and we'll resume 10 minutes from now at 10:57. Panel members, please remember that there should be no discussion of the meeting topic during the break, amongst yourselves, or with any members of the audience. Again, we'll resume at 10:57. Thank you.

(Whereupon, at 10:47, a recess was taken.)

DR. RAUFMAN: We'll reconvene now. Intercept

wanted to address one question. They have a couple of minutes to do that.

DR. ROBERTSON: Dr. Chang, we have the response to your question. Apologies. We didn't have it before.

So the U.S. was 25 percent of patients for the phase 3 study, and North America, 29 percent. As Dr. Shapiro said, the majority was indeed in Europe. And then, with regard to the recruitment, it was 10 months.

DR. RAUFMAN: Thank you. We will now proceed with the FDA presentations.

FDA Presentation – Min Min

MS. MIN: Good morning. My name is Min Min. I'm an FDA statistical reviewer. In this presentation, I will discuss our Global PBC study group, the study group data analysis for the clinical trial population.

The applicant submitted three efficacy trials to support the accelerated approval of OCA in treating adult patients with PBC. Following FDA's advice, the applicant collaborated with the Global PBC study group to investigate whether alkaline phos, ALP, and the

total bilirubin could be used as biomarkers reasonably, likely, to predict clinical outcome, liver transplant, or death.

The applicant leveraged the findings from Global PBC project to support the use of ALP and the TB as biomarkers reasonably likely to predict clinical outcome that is liver transplant or death, in the phase 3 pivotal trial, Trial *747-301.

Next, I will discuss the rationale for the FDA re-analysis of Global PBC data. We have noted that one inclusion criterion of phase 3 trial 747-301 required patients to have baseline ALP at least 1.67 times upper limit of normal and/or total bilirubin above upper limit of normal. As a result, 90 percent of patients in Trial 747-301 were at early disease stage of PBC, while in the Global PBC, only 42 percent of the patients were at early disease stage.

Here, the determination of early disease stage is based on Rotterdam criteria. As you can see from this table, a much broader disease spectrum of subjects was included in the Global PBC data than was studied in Trial 747-301. The population studied in Trial 747-301

is not directly comparable to the Global PBC data. Therefore, it was unclear whether a patient's ALP at 12 months alone may reasonably likely predict a clinical outcome that is liver transplant or death in the patient population studied in Trial 747-301. In addition, even if this data could be used for this purpose, would the cutoff stay the same or a different cutoff may be considered?

In my next set of slides, I will provide you with the details of FDA's statistical analysis plan for re-analysis of Global PBC data. Here is the flowchart for the statistical analysis plan. The Global PBC data contains about 4800 patients. After applying three criteria used in Trial 747-301, our subset had 909 patients. Note that the first criterion is early disease stage based on Rotterdam criteria. The second criterion is patients with UDCA use. The third criterion is baseline ALP at least 1.67 times upper limit of normal.

To assess if ALP at 12 months as biomarker may reasonably and likely predict clinical outcome. And to explore the cutoff for ALP at 12 months, we randomly

divided 909 patients into two groups. The first group, 25 percent of 909 patients were used for model selection. Seventy-five percent of 909 patients were used for exploration of potential cutoff. Also, among the 909 patients, there are 14 percent of patients who had a clinical outcome, either liver transplant or death, compared to the event rate of 23 percent in the Global PBC data.

Regarding the statistical analysis for the cutoffs, we conducted 10 random splits and 5-fold cross validation. For simplicity, we call them 10 splits and 5-fold, respectively, in the rest of this presentation. To further assess the consistency and the robustness, subgroup analyses were conducted based on a total of 909 patients. In the next two slides, I will discuss the details of model selection.

As noted earlier, our first step was to evaluate the impact of ALP at 12 months on the prediction of the clinical outcome. We also needed to identify other important covariates that would potentially contribute to the prediction model. After discussion with the FDA clinical team and understanding

the Global PBC data provided, we focused our model selection on five covariates. They were age, age at diagnosis, year of diagnosis, region, and the duration of PBC.

In terms of ALP, both absolute and the percent change are important, so they were included in our candidate models. Please note that we denote percentage change from baseline for ALP at 12 months as PGALP12.

We used the Akaike information criteria AIC for the model selection. The model we used was a Cox regression model. Here, AIC measures goodness of fit as assessed by the likelihood function. Given a set of candidate models for the data, the preferred model is the one with the minimum AIC value.

This table shows the range of AIC values across all the models; in particular, models with and without PGALP12 and the baseline ALP raw values. As you can see from this table, the models that included PGALP12 and the baseline ALP raw values were about 10 percent smaller than the AIC values for the model without them. Age was identified as the most important

covariate. The smallest AIC value is displayed in blue for the chosen model. The model with factors of age, baseline ALP raw lab values, and the PGALP12 was chosen to predict death or liver transplant.

Before I discuss the cutoff exploration results, I will briefly introduce C-statistic that we used to determine the cutoff. The C-statistic is commonly used to demonstrate the predictability of a biomarker. I have prepared a demonstration example to show you how C-statistic is calculated here.

Assuming that we have 5 total possible pairs for the positive and negative prior outcomes, we have a probability of positive outcome calculated from a model. Now, among these 5 pairs, we find the proportion of having disconcordance or tie. When there is a concordance, we count it as 1. When there is a tie, we count it as 0.5. When there is a discordance, we count it as zero. The summation of all the proportions is called the C-statistic.

In this example, as you can see, the C-statistic is equal to 0.7. Here is a graph. The X-axis is for the false positive rate, and the Y-axis

is for the true positive rate. The 45-degree line shows C-statistic as 0.5, where the chance of observing a concordance is just like tossing a coin. When the values of C-statistic are above 45-degree line, the true positive rate exceeds false positive rate. The larger the C-statistic is, the better it predicts the positive outcomes. Some literature suggests that acceptable is when C-statistic is at least 0.7 and excellent when it exceeds 0.8.

Now, I will share with you our cutoff exploration results. Recall that the primary endpoint for Trial 747-301 is a patient ALP at 12 months, less than 1.67 times the upper limit of normal and at least a 15 percent decrease from baseline. Also, the total bilirubin is less than equal to upper limit of normal.

Here is the applicant's cutoff. Besides the applicant's cutoff, we looked at other combined cutoffs using 2 times the upper limit of normal as the absolute cutoff with either 15 percent or a 40 percent decrease from baseline for ALP at 12 months. Note that 2 times the upper limit of normal, or 40 percent decrease, is based on Lammers papers, recommendations.

This table shows you our results for the combination of 2 times the upper limit of normal and either 15 percent or 40 percent reduction cutoff. As you can see, they appear to perform numerically better than the applicant's cutoff, and also, 1.67 times upper limit of normal and the 40 percent reduction based on the mean of all the C-statistics for both 10-splits and the 5-fold method.

If we are going to use 2 times the upper limit of normal and the 15 percent or 40 percent decrease as cutoff, remember that the phase 3 Trial 747-301 has one inclusion criterion as baseline ALP, at least 1.67 times upper limit of normal. However, we have concerns associated with using this proposed cutoff. We were concerned that we have a patient population with baseline ALP at least 1.67 times upper limit of normal. Patients whose baseline ALP or between 1.67 times upper limit of normal and the 2 times upper limit of normal can only be responders based on the percent reduction criterion if we consider 2 times upper limit of normal as cutoff.

Now, for the responders definition. To

capture improvement in those subjects with baseline ALP between 1.67 times upper limit of normal and the 2 times upper limit of normal, as well as those with at least 2 times upper limit of normal, the FDA proposed stratified cutoff appears more reasonable.

The following flowchart indicates the details. If patients whose baseline ALP are at least 2 times upper limit of normal, then the cutoff for ALP at month 12 was less than 2 times upper limit of normal and at least 40 percent decrease from baseline. If patients whose baseline ALP are between 1.67 times upper limit of normal and 2 times upper limit of normal, then the cutoff for ALP at month 12 was less than 1.67 times upper limit of normal and at least 15 percent decrease from baseline.

The next slide will show the 17 potential cutoffs we considered. We have considered 17 cutoffs. The first line shown in this table are the single absolute or percent change cutoff. Let's pay special attention to the 4 stratified cutoffs in the red box. Here, based on the baseline ALP values, we have 2 strata. For each stratum, we have the corresponding

cutoff.

Here is the FDA proposed stratified cutoff. This table only shows the results for 2 cutoffs based on the 10-splits method. The applicant's cutoff is displayed in black. The FDA proposed stratified cutoff is displayed in red. From this table, we found that the FDA proposed stratified cutoff resulted in larger point estimates for C-statistics and hazard ratios than the applicant's cutoff as shown in the red circles.

Again, here this table only shows the results for the two different cutoffs based on the 5-fold method. Based on this table and the table in the previous slide, we demonstrated that the FDA proposed stratified cutoff as 1.67 times upper limit of normal and a 15 percent decrease or 2 times upper limit of normal, and a 40 percent decrease appears to predict a patient's clinical outcome slightly better based on C-statistics and numerically better based on hazard ratios as shown in the red circles.

In my next two slides, I will discuss the details of subgroup analyses results. The 5 subgroups we considered were age, age at diagnosis, ALP baseline

raw values, region, and the year of diagnosis to assess the consistency and the robustness of subgroup analysis. For 3 cutoffs, the applicant's cutoff, the FDA proposed stratified cutoff, and a more stringent stratified cutoff using at least a 40 percent decrease for both strata, were conducted and displayed in the next slide.

This forest plot shows subgroup analyses results for the 3 cutoffs in addition to the applicant's cutoff for the left graph, and the FDA proposed stratified cutoff is the middle graph. The third one is a more stringent stratified cutoff for the right graph, as the more stringent cutoff as 1.67 times upper limit of normal and 40 percent decrease or 2 times upper limit of normal and 40 percent decrease.

As shown in the red box on the right corner, it's interesting to note that when we consider this cutoff for both age groups, the 95 percent confidence intervals for hazard ratios rule out 1. This confirms the utility of the stratified cutoff. However, for patients in the second stratum whose baseline ALP was between 1.67 times upper limit of normal and 2 times

upper limit of normal, this criterion as a 40 percent decrease appears too stringent.

In addition, for the diagnosis year less than 1990, please note that for the applicant's cutoff, 95 percent confidence interval for hazard ratio covered 1 as shown in the red box on the left corner, but both of the stratified cutoffs rule out 1.

In this display, the left graph represents Kaplan-Meier curves using the applicant's cutoff, while the right graph displays the results using the FDA proposed stratified cutoff. Axis is the years; Y-axis is survival probability. In comparing those Kaplan-Meier graphs, it appears that the responder results based on the FDA proposed stratified cutoff yields a somewhat larger separation after 10 years.

I will talk about some limitations of Global PBC data first, then summarize all of our findings in the last two slides.

In this slide, we bring up the limitations of Global PBC data. Only years of all the important variables were provided such as date of diagnosis of PBC, UDCA date of start therapy, and others. Region

information was only categorized as USA, Canada, and Europe, not as countries or centers.

The Global PBC database was composed of observational and the retrospective registry data. There is a large amount of missing information/data. In addition, lab data were collected locally without centralization. Among 909 patients, we have about 8 percent missing ALP values at month 12.

The model with factors of age, baseline ALP raw value, and the PGALP12 was chosen for the model to predict death or liver transplant in the study population. The FDA proposed stratified cutoff results in similar point estimates of C-statistics compared to the other combined or stratified cutoffs. The FDA proposed stratified cutoff as less than 2 times the upper limit of normal and the 40 percent decrease of less than 1.67 times upper limit of normal and at least 15 percent decrease has demonstrated numerically better performance than the applicant's cutoff.

Subgroup analyses results demonstrate that the estimated hazard ratios of association between the cutoffs and the clinical outcome appear to be

consistent, although their 95 percent confidence intervals are narrower or wider. Thank you. That's the end of my presentation.

Next, Dr. Ruby Mehta will talk about safety and efficacy assessment.

FDA Presentation -- Ruby Mehta

DR. MEHTA: I have nothing to disclose.

In my presentation, I will be talking about obeticholic acid, which I will refer from now on as OCA, general aspects, efficacy of phase 2 and phase 3 trial, and safety, particularly related to hepatic adverse events and HDL reduction.

About 40 percent of PBC patients achieve partial biochemical response as assessed by the responder criteria with UDCA, which is the only FDA-approved treatment. Of note, UDCA was approved in 1997. Over the years, many responder criteria to assess the clinical benefit of UDCA have been proposed. A few of them are shown in this table.

The applicant chose alk-phos less than or equal to 1.67 times upper limit of normal and total bili less than or equal to upper limit of normal as a

threshold for treatment success, which was consistent with Toronto 2010 and Mayo 2011 criteria. A 15 percent or greater reduction from baseline was included as a part of the composite endpoint to ensure that only subjects with a minimal clinical effect were judged to have a successful response.

The proposed indication of OCA is for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults who are unable to tolerate UDCA. The proposed dosing starts at 5 milligrams for 3 months, and based on tolerability and biochemical response, up-titrated to 10 milligrams. OCA is not marketed in the U.S. or any other country.

Moving on to clinical development program, the applicant conducted two phase 2 trials of which Trial 201 is the OCA monotherapy and 202 is OCA plus UDCA combination therapy trial. Both phase 2 trials were 3 months in duration. The pivotal trial was 12 months in duration and 93 percent of the patients were on concomitant UDCA. Fifty-nine patients were enrolled to Trial 201 treated with 3 doses OCA 10

milligram, 50 milligram, and placebo. In Trial 202, a total of 138 patients were enrolled in 4 treatment arms, placebo, OCA 10 milligram, 25 milligram, and 50 milligram.

The patient inclusion criteria for both the phase 2 trials were alk-phos between 1 and a half times and 10 times upper limit of normal. The primary endpoint was percent change in alk-phos from baseline to month 3. For Trial 201, the applicant intended to enroll 120 patients, however, they were only able to enroll 59 patients. The enrollment was stopped prematurely because it was difficult finding patients who were not on UDCA treatment.

Trial 301, 216 patients were enrolled to 3 treatment arms, placebo, OCA 5 milligram -- and patients were up-titrated at 6 months based on biochemical response, and tolerability. The patient inclusion criteria for alk-phos greater than or equal to 1.67 times upper limit of normal and/or total bili greater than upper limit of normal but less than 2 times upper limit of normal.

I will refer to this criteria as inclusion

threshold. The primary endpoint was alk-phos less than 1.67 times upper limit of normal and greater or equal to 15 percent reduction in alk-phos, and total bili less than or equal to upper limit of normal at month 12.

I will be referring to the following stages of disease throughout the presentation. Each category is defined by Rotterdam classification criteria where early stage denotes elevated alk-phos, normal total bilirubin, normal albumin. Moderately advanced is either low albumin or high total bili. Advanced is both low albumin and high total bilirubin.

Across the trials, a majority of the patients had early stage disease. In the pivotal trial, 90 percent of the patients were in early stage disease and 10 percent of patients had moderately advanced stage disease. Of the 21 patients, 18 patients had high total bili and 3 patients had low albumin. As expected, the overwhelming majority of patients enrolled in the trial were female, 90 percent; white, 95 percent; and a mean age of 55 years of age.

Moving on to OCA as monotherapy, Trial 201

enrolled 59 patients. There were 16 patients enrolled to OCA 50-milligram arm, and 9 of these patients completed the trial for treatment duration. The remaining 7 patients dropped out within one month of initiating OCA treatment. And as noted, a majority of the patients were in early stage disease. Change from baseline to end of treatment and mean alk-phos over time was seen as early as 2 weeks and was sustained for the duration of the trial.

Patients in Trial 201 had alk-phos 3 and a half times to 4 times upper limit of normal in each arm. A graphical representation and a table for primary efficacy endpoint is presented in this slide. Relative to placebo, similar reductions in percent change in alk-phos were seen with both OCA doses. The observed reductions were statistically significant for both OCA doses relative to placebo.

Moving on to Trial 202, 165 patients were enrolled in Trial 202. A majority of the patients were in early stage disease. Again, the mean alk-phos reduction was observed as early as 2 weeks with a sustained reduction throughout the trial. This trend

of alk-phos reduction over time was similar to as seen in Trial 201.

The mean percent change was between 21 and 24 percent for the three OCA treated arms compared to 2.5 percent in the placebo treated group. The applicant chose 10-milligram dose for the pivotal trial, and the FDA recommended that a lower dose should be investigated as well. As a result, the applicant included 5-milligram dose in the phase 3 trial.

Moving on to the pivotal trial, the primary efficacy endpoint was achieving serum alk-phos less than 1.67 times upper limit of normal and a decrease in alk-phos of greater than or equal to 50 percent and total bilirubin less than or equal to upper limit of normal.

Please note, serum alk-phos and total bilirubin together were proposed as a composite endpoint. The three treatment arms include placebo arm; OCA titration arm, in which patients were titrated to 10 milligrams at 6 months based on tolerability and by a chemical response of achieving the threshold; and OCA 10-milligram arm for the duration of 12 months.

A total of 216 patients were enrolled in the pivotal trial of which 73, 70, 73 were in 10-milligram OCA titration and placebo arm, respectively. And as seen, a majority of the patients were in early stage disease as per the Rotterdam classification criteria.

A total of 96, 90, and 88 percent of patients completed the trial in the placebo, OCA titration, and OCA 10-milligram arm. There was one death, which was considered not related to OCA use. At screening, patients with severe pruritis were excluded. However, severe pruritis that occurred during the trial led to discontinuation of 7 patients in the OCA 10-milligram arm and one patient in the OCA titration arm.

Approximately 46 percent of patients in the OCA 10-milligram and OCA titration arm achieved reduction in alk-phos compared to 10 percent in the placebo arm. Mean alk-phos over time, as seen for the duration of the trial, the initial decline was seen at 2 weeks and alk-phos was maintained for the duration of the trial. Please note that the alk-phos reduction was at the mark of 200.

This graph depicts alk-phos reduction in three

treatment arms as observed during the double-blind phase up to 12 months after which the placebo patients were crossed over to OCA treatment. During the long-term safety extension phase, placebo patients were started on OCA 5 milligrams and titrated to 10 milligrams. After the crossover of the placebo arm, the alkaline phosphatase reduction was seen in the placebo treated patients. The data is shown up to the point of last data cut as submitted by the applicant.

Now, I will discuss individual components of the primary composite endpoint. Please note, these components were not adjusted for multiplicity. As shown, 55 percent in OCA 10-milligram arm, 47 percent in OCA titration arm, and 16 percent patients in the placebo arm achieved alk-phos less than 1.67 times upper limit of normal at month 12; 78 percent in OCA 10 milligram, 77 percent in OCA titration arm, and 29 percent in the placebo arm achieved alk-phos reduction of greater than 15 percent at month 12; 82 percent of patients in OCA 10-milligram arm, 89 percent in OCA titration arm, and 78 percent of patients in the placebo arm achieved a total bilirubin less than upper

limit of normal at month 12.

The baseline total bilirubin concentration in the pivotal trial were in the normal reference range for 90, 94, and 90 percent patients in the OCA 10-milligram titration and placebo arm, respectively. Seven patients in the OCA 10-milligram arm, 4 patients in OCA titration arm, and 6 patients in the placebo arm had total bili greater than upper limit of normal but less than 2 times upper limit of normal.

The patient in the placebo arm had total bili greater than 2 times upper limit of normal. The mean baseline total bilirubin concentration in upper limits of normal was as follows: 0.55 in OCA 10-milligram arm, 0.51 in OCA titration arm, and 0.598, which is rounded up to 0.6 in the placebo arm.

This slide depicts subset of patients with elevated total bilirubin at baseline and the month 12 result. Five patients out of 7 enrolled to OCA 10-milligram arm; 2 patients out of 4 in the titration arm and one patient out of the placebo arm -- 7 patients of placebo arm achieved total bili less than upper limit of normal at month 12. However, the

prespecified primary composite endpoint was achieved by 2 patients in the OCA 10-milligram arm, one patient in the OCA titration arm, and zero in the placebo arm.

Trial 301 was not designed to show efficacy with respect to reduction of total bilirubin within normal reference range. Total bilirubin remained within normal reference range in majority of patients for the duration of the trial across all treatment arms. That includes placebo arm, not just OCA treated arm.

The significance of small decremental marginal changes in total bili that remained within normal reference range over a 12-month duration is unknown. The extent of variability in total bilirubin over time in PBC is unknown. Changes in total bilirubin during treatment trials must be considered in the context of background changes in the total bilirubin.

As exemplified in Trial 301, 22 patients had high total bilirubin at screening; 15 patients had high total bilirubin on a repeat measure that was done within 8 weeks, i.e., at day zero. The average of the two values, screening and day zero, led to a total of

18 patients with high total bilirubin.

As seen here, total bilirubin fluctuates over time, and it can be appreciated more so for the placebo arm in this graph and the patients who were crossed over at 12-month mark. Additionally, these changes are marginal with overlapping confidence intervals.

As presented by Dr. Min earlier in the presentation, the re-analysis of Global PBC data were performed utilizing the following cutoff points for the patients enrolled in the pivotal trial. If the baseline alk-phos was greater than or equal to 2 times upper limit of normal, then a patient was designated as a responder if both the following criteria were met: alk-phos less than 2 times upper limit of normal at month 12 and greater than or equal to 40 percent reduction at month 12.

If the baseline alkaline phosphatase was between 1.67 times upper limit of normal but less than 2 times upper limit of normal, the patient was designated as a responder if both the following criteria were met: alk-phos less than 1.67 times upper limit of normal and greater than or equal to 15 percent

reduction at month 12.

In order to match the 909 patients that were in the FDA statistical review of Dr. Min's analyses, we isolated the same analogous patients from the trial data. In that, the baseline alk-phos was greater than or equal to 1.67 times upper limit of normal, the UDCA concomitant usage, and early stage disease as per Rotterdam criteria. This resulted in 181 patients total. And as you can see, there were 60 patients in each OCA arm and 61 patients in placebo arm.

According to the applicant's threshold, as shown, 58 percent, 47 percent, and 11.5 percent patients in 10-milligram OCA titration and placebo arm, respectively, achieved alk-phos reduction. Using the FDA's threshold, 43 percent, 38 percent, and 5 percent patients in OCA 10-milligram, OCA titration, and placebo arm achieved alk-phos reduction. In conclusion, relative to placebo, a statistical significant proportion of patients in the OCA 10-milligram and titration arm achieved alk-phos reductions.

I'll now move on to the monotherapy. Pooled

data from phase 2 and phase 3 trials were analyzed at month 3 as the phase 2 trials were 3 months in duration. Twenty-six patients received OCA monotherapy for 3 months and 10 patients -- that is 38 percent -- achieved reduction of alkaline phosphatase below the threshold as specified by the applicant, which is noted above.

Compared with the patients who received OCA 10 milligram and UDCA combination therapy, 41 percent of patients had reduction in alk-phos according to applicant's specified threshold. The baseline alk-phos was higher in those patients who were enrolled to OCA monotherapy arm in Trial 201 compared to those who received OCA in combination with UDCA.

At 3 months, patients treated with OCA monotherapy therefore achieved reduction in alk-phos levels that were similar to those on combination therapy, although the absolute reductions in patients treated with OCA monotherapy were greater. Again, this slide shows the same conclusion, the absolute alk-phos reduction in monotherapy arm was greater than OCA plus UDCA combination therapy and statistically significant

than placebo.

In conclusion, the proportion of patients who achieved a biochemical response in the OCA monotherapy treatment arm was numerically greater than in the placebo arm. In this small subset of patients, response rates in the OCA monotherapy treatment arm appeared similar to OCA plus UDCA treatment arm. Safety and efficacy data are limited to support the long-term use of OCA as monotherapy.

Moving on, I will now discuss the safety with respect to hepatic adverse events and HDL cholesterol reduction. As presented earlier by the applicant -- this is the same table for summary of adverse events -- pruritis and fatigue were the two most common treatment emergent adverse events; that is new adverse events noted when the patient was started on OCA therapy. The patients with baseline severe pruritis were excluded from the trial. The incidence of new onset fatigue was higher in both OCA treated patients -- I'm sorry, in both OCA-arm treated patients.

Moving on to the hepatic adverse events, the

hepatic adverse events that occurred during the trial were treatment-emergent adverse events. No patient in the placebo group experienced hepatic adverse events in the Trial 202 compared to 9 patients on OCA 50-milligram dose who experienced hepatic treatment-emergent adverse events, which included both biochemical changes or hepatic decompensation events. Three of these 9 patients had decompensation events which were new onset jaundice, PBC flare, ascites, and gastro-esophageal bleeding.

Since the phase 2 and phase 3 trials were of different duration, the exposure adjusted incidence was utilized for assessing hepatic adverse events. One patient exposure PEY is equivalent to one subject exposed to the investigational product for one year. Similarly, two patients who are exposed to investigational product for half a year together would contribute one patient-exposure year.

As you can see, the incidence of hepatic adverse events in the placebo arm was 2.4. Within increasing OCA dose, the incidence continues to increase with maximum adverse events seen in the OCA

50-milligram dose. These adverse events were, in the placebo arm, non-serious liver biochemical test of abnormalities and one serious adverse event in a patient with 3 episodes of esophageal variceal bleeding.

In the OCA 10-milligram and titration arm -- I have to apologize, ascites requiring parencentesis is for the next group. It was only ascites and esophageal variceal bleeding, jaundice, hepatic encephalopathy, and liver biochemistry changes. In the OCA 25 milligram and 50 milligram, the serious adverse events included new onset ascites and ascites requiring parencentesis, PBC flare, jaundice, and portal hypertension. And the non-serious adverse events were changes in biochemistries.

Moving on to the HDL reductions, this is Trial 201. These are the mean HDL reductions shown in this slide from baseline to month 3. A 14-point and 16-point reduction in the mean HDL was noted in the OCA 10 milligram and 50 milligram, respectively, compared with very minimal change in the placebo treated arm from baseline to month 3. A 10-point and a 17-point

reduction in the mean HDLc was noted in OCA 10-milligram, 25-milligram, and 50-milligram arm compared to a positive change in HDL in the placebo arm from baseline to month 3.

Changes in the mean HDL at baseline to month 12, as noted in this table, a 20-point mean HDLc reduction was noted in OCA 10-milligram arm, a 12-point reduction in the OCA titration arm, and no change in the mean HDL cholesterol was noted in the placebo arm. The HDL reductions were seen in the 3-month trial as well as the 12-month trial. The duration of exposure did not diminish the HDL reduction in PBC patients.

Four patients in the OCA titration arm, 5 patients in the OCA 10-milligram arm had HDL reduction greater than or equal to 2 standard deviation, which was about 44 milligram per deciliter change. One patient in the placebo arm, 14 patients in the OCA titration arm, and 16 patients in OCA 10-milligram arm had HDL reduction greater than 1 standard deviation but less than 2 standard deviation.

Each row is a unique patient designated as outlier. As highlighted in the red box in the middle

column, there were patients whose HDLs reduced to 8 and 7 milligram per deciliter with OCA treatment for 12 months duration. Similarly, in the third column, reductions as big as 85.5 and 78 and 59 milligram per deciliter were noted in 12-month duration treatment for OCA.

This slide is OCA titration arm, and similarly, there were outliers in this group also. Each row is a unique patient designated as a outlier. Again, HDL as low as 22 milligram per deciliter were noted with exposures to OCA 5 milligram.

Again, each row is a unique patient designated as an outlier. In the placebo arm, very few patients had changes in HDL as seen in the pivotal trial, however, few patients did have changes as much as 40 to 18 milligram per deciliter over a 12-month duration. The two patients that are in red boxes inadvertently received OCA, and these changes can be attributed to OCA exposure.

A dedicated lipid assessment open-label trial utilizing OCA 10-milligram dose was conducted. Lipid modifying agents were prohibited. Treatment duration

was 8 weeks with a follow up at week 12; that is 4 weeks after OCA discontinuation. And as you can note, the baseline HDL concentration was 75 milligram per deciliter, and at week 8, the mean HDL concentration was 58 milligrams per deciliter. Each row is unique patient and 2 patients in this particular trial had reductions greater than 2 standard deviation, and one patient had reduction of HDL to 16-milligram per deciliter as highlighted in the red box.

This graph depicts HDL reductions that are seen as early as week 4. The HDL reduction is sustained with the OCA treatment when the trial was discontinued at week 8. Then upon a follow-up at week 12, 4 weeks after discontinuation, the HDL returned back to the baseline, i.e., showing the reversibility of the HDL concentration, at least in an 8-week duration trial.

Conclusions. HDL reductions were noted across all PBC trials. Majority of patients experienced some degree of HDL reductions. Some patients experienced reductions in HDL level greater than or equal to 2 standard deviation. HDL in some patients decline from

within normal limit to lower limits of normal, and these reductions were quite significant.

Even though there were few patients on concomitant medication that might have altered the lipid profile, the lipid changes were consistent across all four trials in the PBC patients. There was a dose-dependent trend in HDL reduction.

In conclusion, OCA doses higher than 10 milligram may lead to higher rates of hepatic adverse events. Our overall efficacy and safety conclusions are statistically significant reductions in alk-phos were observed across all tries in OCA treated patients. OCA doses higher than 10 milligram may not provide further benefit in terms of alk-phos reduction.

There were no major safety concerns observed in the clinical development program with OCA at 10 milligram in PBC patients who have inadequate response to UDCA.

Additional long-term safety data are needed in patients with moderately advanced and advanced stage disease for use as monotherapy in patients who are intolerant to UDCA and in patients who develop HDL

reductions.

FDA Presentation – Dhananjay Marathe

DR. MARATHE: Good morning, everybody. I'm Dhananjay Marathe, and I'm a senior reviewer in the Division of Pharmacometrics within the Office of Clinical Pharmacology at CDER FDA. Today, I'll be presenting dosing concentrations for obeticholic acid or OCA for primary biliary cirrhosis.

I will be covering three topics in my presentation; first, appropriateness of the applicant's proposed dosing for overall patient population; then secondly, dose adjustment for patients with moderate or severe hepatic impairment; and third, discontinuation of OCA for lack of biochemical response.

Now, for the first topic, I'm going to discuss the three specific aspects of proposed dosing for overall population; that is appropriateness of the starting dose of 5 milligram once daily, that is QD; titration after 3 months; and titration to 10 milligram once daily.

Regarding the starting dose, the applicant studied two different starting doses, 5 mgs QD and 10

mgs QD in the phase 3 trial. And this placebo-controlled trial, there was a dose-dependent increase in incidences of pruritis related discontinuations with zero percent in placebo, 1 percent on OCA 5 mgs, and 10 percent on OCA 10 mgs. Overall, there was a better tolerability profile with time with a lower starting dose, with less discontinuations as shown above, less days of severe pruritis, that is 9.1 days per subject year at 5 mg dose, and 31.4 days for subject-year with 10-mg starting dose.

There was also delayed time to first onset of pruritis with a low starting dose. Efficacy-wise, as previously elaborated by our colleagues and also by the applicant, the titration arm with 5-mg starting dose had similar efficacy as the 10-mg arm at one year with 46 percent and 47 percent responders, respectively. Thus, from efficacy and safety perspective, we think a starting dose of 5-mg QD is appropriate.

Regarding appropriateness of titration at 3 months, the phase 3 trial involved up-titrations from 5 mgs to 10 mgs at 6 months, while the proposal is to

initiate the up-titration at an earlier time, that is 3 months; the rationale being, then, the reduction in ALP plateaus at 3 months with 5 mg QD OCA treatment.

The graph here shows the change in ALP with time for subjects who remain on OCA 5 mgs and who up-titrate to 10 mgs at 6 months. Now, both these subgroups show plateauing of ALP reduction at 3 months, which justifies the titration at or after 3 months.

Now, there's a possibility -- prior to month 3, data was collected only at week 2, so there's a possibility that the plateauing of response could be earlier, somewhere between week 2 and month 3. So this begs the question that why not have up-titration earlier than 3 months? To address this, we utilized evidence from safety data.

Across OCA treatment arms, almost all -- that is 7 out of 8 -- subjects had discontinuations due to pruritis occurring over the first 3-month period in phase 3, and there were rarely any discontinuations due to pruritis after 3 months. So a minimum duration of 3 months will give a fair idea of tolerability of starting dose and identification of subjects with

tolerability for further up-titration. Thus, efficacy and safety justifies titration at or after 3 months.

The third aspect is titration to 10 milligram, and it is an important component to towards efficacy. As shown in the graph here, for subjects who remain on OCA 5 milligram for the duration of 12 months, you can see that on a mean level, more time on 5 mg QD did not achieve a better ALP response. On the other hand, for subjects who got up-titrated, the titration to 10 mg QD certainly achieved a better response of further reduction in ALP.

To further buttress this point, here I have tabulated the subjects in titration arm of phase 3 as per the responder status at month 6 and month 12. The titration arm is further split to show subjects staying on 5 mg and subjects up-titrating from 5 mg to 10 milligram.

The plus/plus sign here denotes that the subjects achieved primary endpoint criteria, responders at month 6 as well as at month 12. Similarly, the plus/minus sign denotes responders at month 6 who became non-responders at month 12 maybe as a result of

disease progression. The minus/plus sign denotes non-responders at month 6 who became responders at month 12, and the minus/minus sign denotes subjects who were non-responders at month 6 as well as at month 12.

Now, the table here shows that due to up-titration from 5 milligram to 10 milligram, there were 13 additional responders that got added from month 6 to month 12 in the titration arm. Further, there were around 19 percent of the responders at month 6 who became non-responders by month 12. So we believe that some of the subjects could have also benefited from further up-titration to 10 milligram. Thus, overall, titration to 10 milligram is justified.

Just summarizing this topic, firstly, we believe the proposed starting dose of 5-milligram QD with titration to 10-milligram QD at or after 3 months is appropriate for overall population. Secondly, earlier as I showed you, there were some responders who became non-responders with time with continued 5-milligram dosing despite earlier response. So we recommend that the physician should continue to evaluate biochemical response of reduction in ALP

longitudinally and utilize the up-titration rule any time after 3 months from treatment initiation.

Let's move on to the second topic, dose adjustment for patients with moderate or serious hepatic impairment. To start off, I would like to just lay out the basics of how the labeling of dosing for a population with hepatic impairment is done. Usually, a small single-dose trial is conducted in healthy subjects with normal hepatic function, and age, weight, et cetera, match subjects with hepatic impairment, and these include cohorts with Child-Pugh A, B, and C classification.

The changes in concentrations and clearance for these subjects with hepatic impairment with the same dose is quantified, then using pharmacokinetic principles, usually the dose or dosing regimen is derived that can achieve matching exposures to general patient population with normal hepatic function.

Typically, plasma exposures are used for such matching purposes. PBC is a special case in that the site of efficacy and probable safety is the same as the site of drug biotransformation, which impacts its

clearance. Thus here, the quantification of anticipated changes in liver exposures could have value in addition to plasma exposures.

Towards this end, the applicant developed a physiology based PK model to characterize the plasma exposures and to predict liver exposures. Such models are useful to predict exposures with different doses or different dosing regimens that have not been explicitly evaluated in the trials.

Here's a result from applicant's dedicated hepatic impairment trial with a single 10-milligram dose and 8 subjects in each cohort. Here, I would like to mention that OCA gets biotransformed to active conjugates like glyco- and tauro-OCA inside the liver, and these conjugates have similar potency as OCA, as has been mentioned previously. Thus, the relevant concentration metric would be a total OCA, which is a summation of plasma concentration of OCA and OCA equivalents of conjugates.

The plot here shows temporal profile for total OCA plasma concentration for normal subjects and subjects with mild, moderate, and serious, that is

Child-Pugh A, B, and C hepatic impairment cohorts.

In the table, we have quantification of exposure metric of area under the concentration time curve. It is represented as fold changes with respect to normal. You can see that compared to the normal subjects, the subjects with mild hepatic impairment have similar exposures while the moderates have 4-fold, and serious hepatic impairment have 17-fold exposures with the same single dose of 10 mgs.

As stated earlier, in order to quantify the changes in plasma and liver exposures of OCA and its conjugates with hepatic impairment, the applicant developed a physiology-based PK model. The model incorporates various features, including oral input of OCA into gut, systemic, and hepatobiliary fluxes, flux to gall bladder and gut, biotransformation of OCA to glyco- and tauro-OCA in liver, and back transformation to OCA in gut.

The model also incorporates meal induced gall bladder emptying of drug and conjugates to gut and clearance of OCA through gut. The hepatic impairment is accounted for by changes in the biotransformation

rate and intra-hepatic shunting of flow. Finally, the OCA specific biotransformation and transport rates were fitted using data of plasma PK of OCA, glyco- and tauro-OCA from the dedicated hepatic impairment trial that I showed just earlier.

Since hepatic impairment in a patient will encompass interplay between several physiological mechanisms, this physiological PK model provided an integrated mathematical framework that could be utilized to project both plasma and liver exposure simultaneously with various dosing regimens.

The table here shows the comparison of fold changes in the observed plasma exposure with model predicted plasma exposure for the single dose hepatic impairment trial that I mentioned earlier. The model reasonably describes exposure in different HI groups, specifically normal, mild, and serious HI. Although, I would like to mention that there is some over-prediction for moderate HI group.

Subsequently, the applicant's liver exposure prediction showed around two-fold total OCA liver exposures in subjects with severe HI compared to normal

subjects. Based on this, at the time of NDA submission, the applicant proposed no dose adjustment for any hepatic impairment category, the rational being that these are modest changes in liver exposure, and any dose adjustment might lead to lower liver exposures, which could be suboptimal for efficacy.

Now, FDA's position in this regard is that the dose adjustment is desirable, and that is for the following reasons.

Firstly, given that there was 17-fold high exposures for the same dose with linear PK, a starting dose of 5 mg QD in severe hepatic impairment would exhibit plasma exposures equivalent to around 85 milligram QD dose in normal subjects.

As mentioned previously by our clinical colleague, there was no further increase in ALP response seen beyond 10-milligram dose in the PBC patients. So there's no clear benefit of such high exposures since the reduction in ALP plateaus at plasma exposures are equivalent to 10-milligram QD dose.

Further, from safety perspective, there was a dose response relationship for pruritis with higher

discontinuations at higher exposures in PBC. As in the table with the explored doses in the phase 2 and phase 3 trial, the incidence of discontinuations due to pruritis could be as high as 24 to 38 percent at the 50-milligram QD dose itself. Also, our clinical colleague elaborated earlier that there were hepatic adverse events that were observed with exposures corresponding to high doses.

So with the given information, here's our thought. It is unknown whether pruritis is driven by plasma exposures or liver exposures. Even if the pruritis were to be driven by liver exposures, it is unknown as to what would be the impact of certain x-fold changes in the liver exposures on pruritis. With the same dose of 5 mgs QD, there's a potential for high plasma and liver exposures, which will lead to problems of discontinuation and hepatic adverse events for patients with moderate and severe hepatic impairment.

Thus, we propose that the starting dosing regimen in moderate and serious hepatic impairment should have similar plasma exposures to normal PBC

subjects, which would likely avoid potential safety and discontinuation issues and which will allow identification of subjects for up-titration after 3 months; then further up-titration with dose or dosing regimen could be carried out to meet individual efficacy goals.

With help from the applicant, we explored several dosing scenarios in order to match the plasma exposure for the starting dose. Since 5 milligram the lowest strength formulation available, we did not explore the starting dose lower than 5 mgs. However, the frequency of dosing administration is one variable that we could explore for this purpose.

Here, I have depicted the temporal profiles of total OCA plasma concentration on the left and the total OCA liver concentration on the right. The blue and red lines show total OCA concentration in normal subjects and mild hepatic impairment subjects with the starting dose of 5 mg QD.

Here, you can see that if the same starting dose of 5 mg QD were to be given to the subjects with moderate or serious hepatic impairment subjects, the

resulting plasma and liver concentrations are very high compared to normal subjects. Now, I would like to remind the audience that the plasma concentrations here are drawn on a log scale to cover the large magnitude of exposure changes.

After exploration of various alternative dosing regimens, a starting dose of 5 mg once weekly in moderate and serious HI seemed to achieve similar total OCA plasma exposures to 5 mg QD dosing in normal or mild HI subjects as shown by the green and the purple lines on this plot. Although, ensuing predicted liver exposures may be on the lower side with the 5 mg once weekly dosing, as mentioned earlier, we can always utilize up-titration with a combination of dose and dosing regimen to meet individual efficacy goals.

Here is FDA's recommendation for moderate and severe hepatic impairment patients. Start at 5 milligram once weekly, and after 3 months, based on response and tolerability, titrate to 5 mgs twice weekly and then subsequently to 10 mgs twice weekly.

For the sake of ease, I have shown these dose titrations in blue over here. During the recent round

of labeling negotiations, the applicant made a new proposal which mirrors the first two steps of FDA's recommendation, the only difference being that they want to have the third step to be 5 mg every other day rather than 10 mg twice weekly. Also, they have added a highest possible titration dose of 5 mg QD for this population.

Now, we believe that the 5 mg twice weekly to 10 mg twice weekly transition would be easier from patients' perspective compared to transitioning to every other day regimen. Also, compliance-wise, it will be easier to remember 2 fixed days separated by 3 to 4 days apart, say Monday and Thursday, every week rather than cycling through different days week after week in every other day dosing regimen.

Regarding the 5-milligram QD as the highest possible titrated dose, I would like to remind you that it will achieve 8-fold plasma exposures compared to the highest titration dose of 10-milligram QD in normal population. Since the safety consequences of such high exposures are unknown at this time, 5 mg QD is not recommended for this subpopulation of moderate and

severe hepatic impairment.

The third topic deals with the question of discontinuation of OCA for lack of biochemical response. There are two specific aspects to this topic. First, consideration for discontinuations based on no or marginal ALP response; and second, the recommendation of time frame for such discontinuations.

Here, I would like to mention that there are no clear instructions in the proposed label for continuation or discontinuation of OCA for patients who have no or marginal reduction in ALP. Also currently, there is insufficient evidence of mechanism for anticipating long-term efficacy of OCA in subjects who have such no or marginal reduction in ALP. Thus, the continuation of therapy should be weighed against the possible unfavorable lipid profile that is decrease in HDL that has been elaborated by our clinical colleague and its relation to possible cardiovascular risk.

Now, to understand this issue in detail, let's compare and contrast population level and individual level ALP responses in OCA treatment vis-à-vis placebo. Here, I have plotted percentage change in ALP at 6

months on X-axis against the percentage change in ALP at 12 months from baseline on Y-axis. I have also drawn a diagonal line of identity.

Any data point on this line left of the zero on the X-axis means that there is a reduction in ALP at 6 months from baseline, but the same reduction persisted at 12 months; that is there is no further reduction in ALP or shall we say no further improvement in ALP response with continued treatment from month 6 to month 12.

A data point above this line of identity would mean that ALP response is reduced from month 6 to month 12, while a data point below this line of identity would mean that the ALP response improved from month 6 to month 12.

Now, let's overlay the plot with actual data from placebo arm shown in the blue circles and data from 5 to 10 mgs up-titrated subjects in OCA treatment arm shown in red diamonds. You can see that some of the placebo patients had ALP response at 6 months maybe as a result of carry over effect of background UDCA treatment, but this response does not sustain after

12 months. This results in lower ALP response at 12 months than at 6 months, as you can see the data clustered above the line of identity for placebo patients.

In contrast, the data for subjects up-titrated to 10-milligram OCA treatment clustered below this line of identity showing that, overall, there is further improvement in ALP response at the population level going from month 6 to month 12. Nonetheless, at an individual level, there are some patients, about 15 percent of them, who have no or marginal ALP response as shown by these red diamonds.

These subjects resemble -- you can see more like a placebo response rather than the OCA treatment. And the value of continuing to dose these patients with OCA for long term is questionable as laid out in the earlier slides. Consideration should be given for discontinuation of OCA in these patients.

To recommend appropriate time of discontinuation, we need to understand the temporal evolution of ALP response in individuals. Here are the temporal profiles of ALP for some representative

individual subjects in phase 3. All subjects had up-titration from 5 milligram to 10 milligram at 6 months as depicted by the vertical dotted line in each of these plots.

The first two plots show subjects who had no or marginal ALP response on 5 mgs OCA for the first 6 month, and they continue to show no ALP response in spite of titration to 10 milligram in the next 6 months.

The third plot shows a subject who responds to up-titration to 10 milligram and shows improvement of ALP response within the first 3 months of up-titration. Then there are subject shown in 4th and 5th plot who respond to up-titration to 10 milligram, though in a delayed manner. The improvement of ALP response in them is not evident at 3 months but evident at 6 months from up-titration.

Thus, we think that it would be premature to evaluate and conclude lack of response at a time earlier than 6 months, so we recommend that the physicians could potentially consider discontinuation for lack of meaningful reduction in ALP after the

patient is on a stable dose of OCA for at least 6 months.

Regarding this issue, I would like to also mention that there is an ongoing phase 4 confirmatory trial with continued dosing of OCA for subjects with PBC. This trial is aimed at measuring clinical endpoints and not just endpoints based on biochemical response. This trial allows continued OCA dosing irrespective of biochemical response. So the evidence of efficacy from this confirmatory trial could be analyzed later on to reconsider continuation of therapy for patients who have no or marginal ALP responses.

Finally, just to conclude my presentation, here's the overall summary. For dosing in the overall population, the proposed starting dose of 5 mgs once daily with titration to 10 mgs once daily after 3 months is appropriate. Physicians should continue to evaluate biochemical response of reduction in ALP longitudinally and utilize the up-titration rule any time after 3 months from treatment initiation.

For dosing in moderate and severe hepatic impairment population, FDA's recommendation is to start

at 5 mgs once weekly, and after 3 months, based on response and tolerability, titrate to 5 mgs twice weekly, and then subsequently to 10 mgs twice weekly.

Regarding the discontinuation issue, consideration should be given for discontinuation of OCA for patients who show no or marginal reduction in ALP from baseline, and physicians could potentially evaluate and consider discontinuation after the patients are on a stable dose of OCA for at least 6 months.

Thank you. And with that, I would like to hand it over to Dr. Lara Dimick for her presentation on the safety perspective. Thank you.

FDA Presentation - Lara Dimick-Santos

DR. DIMICK-SANTOS: Hello. I'm Lara Dimick-Santos, the clinical team leader for the application. I have nothing to disclose. I'm actually not talking about safety. I'm talking about the FDA's accelerated approval pathway and the design of the sponsor's phase 4 confirmatory trial.

Because the sponsor is seeking approval under that accelerated approval pathway, the FDA, according

to the Food and Drug Administration Safety and Innovation Act, the FDA may grant accelerated approval to a product for a serious or life-threatening disease or condition upon determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of availability of alternative treatments.

Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. For effectiveness, the standard is substantial evidence based on adequate and well controlled studies. For safety, the standard is having sufficient information to determine whether the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.

For purposes of accelerated approval, a surrogate endpoint is a marker such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical

benefit but in itself is not a measure of clinical benefit.

There are three categories of surrogates, a candidate surrogate, reasonably likely to predict, and validated surrogates. A candidate surrogate is an endpoint still under evaluation for its ability to predict clinical benefit. An endpoint that is reasonably likely to predict is an endpoint supported by a clear mechanistic or epidemiologic rationale but insufficient clinical data to show that it is a validated surrogate endpoint. Such endpoints can be used for accelerated approval for drugs.

A validated surrogate endpoint is an endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that the effect on the surrogate endpoint does predict the clinical benefit, and it can be used for regular or traditional approval.

Determining whether an endpoint is reasonably likely to predict benefit is a matter of judgment that will depend on the biologic plausibility of the relationship between the disease and the endpoint and the desired effect and the empirical evidence to

support that relationship. The empirical evidence may include epidemiologic, pathophysiologic, therapeutic, pharmacologic, or other evidence developed using biomarkers or other scientific methods or tools. However, evidence of pharmacologic activity alone is not sufficient.

Accelerated approval generally requires that a phase 4 trial be underway at the time of the marketing approval to verify and describe the clinical benefit, and this slide shows a schematic of how accelerated approval generally works.

Now, I'm going to review the applicant's design of the phase 4 confirmatory clinical benefit trial. It is a double-blind, randomized placebo controlled, multicenter trial evaluating the effect of OCA on clinical outcomes in approximately 350 subjects with PBC.

The trial is event driven with a total duration determined by the time required to accrue approximately 121 primary endpoint events. It is expected that it will take approximately 8 years for the trial to conclude, and subjects are expected to

have a minimum time of approximately 6 years in the trial.

The key inclusion criteria are a diagnosis of PBC, and this is the same criteria as was used in the phase 3 trial, but the bilirubin and alk-phos are different. This one is a mean total bilirubin greater than upper limits of normal and less than or equal to 3 times upper limits of normal, and/or a mean ALP greater than 5 times upper limit of normal.

Patients also need to be on a stable dose of UDCA or intolerant of UDCA and excludes other liver diseases and excludes cirrhosis, and the model for end-stage liver disease score must be less than or equal to 12.

The clinical benefit composite endpoint is the time to first occurrence of any of the following adjudicated events: all-cause mortality; liver transplant; MELD score of greater than or equal to 15; hospitalization for new onset or recurrence of variceal bleed; encephalopathy as defined by a West Haven score of greater than or equal to 2; spontaneous bacterial peritonitis confirmed by diagnostic parencentesis; and

uncontrolled ascites that is diuretic resistant ascites requiring therapeutic parencentesis at a frequency of at least twice a month.

Concluding, the FDA has several remaining issues that we would like to discuss. We would like to see that the clinical benefit for OCA is confirmed across the entire spectrum of PBC disease: early stage patients, moderately advanced stage patients, and advanced disease stage. And the FDA would like to see additional data on the use of OCA as monotherapy and additional safety data collected in patients with moderately advanced and advanced disease as Dr. Mehta pointed out. Thank you.

Clarifying Questions to the Presenters

DR. RAUFMAN: Thank you.

Are there any clarifying questions for the FDA? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter.

Dr. Silveira?

DR. SILVEIRA: This is Marina Silveira. Regarding the remaining issues that the FDA wants to

clarify about treatment for moderately advanced stage disease and advanced stage disease, I wanted a clarification. The information presented both by the FDA and the applicant showed a discrepancy between the number of patients with moderate and advanced disease. FDA presented that it was 10 percent of the patients enrolled in the phase 3 study, and the applicant presented 17 percent of the patients presented.

DR. DIMICK-SANTOS: So we used the Rotterdam criteria, and we used an albumin of less than 3.5 milligrams per deciliter as the cutoff for having a low albumin. The applicant at times used the Rotterdam criteria, but used an albumin cutoff of I believe around 4. And then, they also used the modified criteria that had Fibroscan, a history of cirrhosis, and other criteria in it. So that's where the discrepancy is.

DR. SILVEIRA: Thank you.

DR. RAUFMAN: Dr. Kumar?

DR. KUMAR: Atul Kumar. A question about the half-life of OCA and also what is the half-life in individuals with hepatic dysfunction.

DR. MARATHE: OCA's half-life -- typically, actually, the conjugate half-life is much higher than the OCA itself because only the OCA gets clear by -- the conjugates have to get transformed back to OCA for its clearance. So the half-life for hepatic impairment gets increased by many fold as compared to just in normal hepatic impairment. As you can see, there is the one thing for exposure increases.

DR. KUMAR: I have another question related to the analysis of the database, the large database. Essentially, responders are defined as those with an alkaline phosphatase of less than 1.67 or 1 and a half in the first phase 1 study.

So if you look at the large database, the UK or the Global database, can you stratify outcomes based on what are subnormal, that is normal alkaline phosphatase and below versus those higher? Even within those that are responders, there are patients, those who have higher than normal alkaline phosphatase.

Do these two groups have, over an extended period of time, different outcomes? I think the basis is, is lower better? That's the question.

DR. DIMICK-SANTOS: We didn't analyze the data for the outcome from a normal alkaline phosphatase. Maybe Dr. Hansen --

DR. MEHTA: Or even for alkaline phosphatase greater than --

DR. KUMAR: Than normal, right.

DR. ROBERTSON: Dr. Hansen, can you come to address this question?

DR. HANSEN: Hello. Bettina Hansen, biostatistician at Erasmus University in Rotterdam, The Netherlands, and also principal investigator of the Global PBC study group. I do not have any financial interest of the outcome of today's meeting.

What I can show you is -- can I have slide 2 up, please? What I did here was to look -- this is the bilirubin. Sorry. Could we have the ALP up, please? That's what your question was. Yes, slide 2, please.

What you see here is the alkaline phosphatase on the X-axis here as well as the baseline values, one-year follow-up and also the 5-year follow-up, and to see what is the relationship with liver transplantation-free survival. It's given here at a

hazard ratio on the Y-axis. You see there is a log linear relationship, which is found here. When using a spline, the spline gives us a free dimension in how the relation is between alkaline phosphatase and the hazard ratio of liver transplantation-free survival.

As analyzed, as well on baseline one-year follow-up, at 5-year follow-up, there is a clear linear or log linear relationship between these. And there's not really any clear cut-point. So indeed, searching for this kind of magic cut-point is a difficult thing.

What I could conclude from this analysis, whereas that lower ALP, all the way, is better. And that, we confirmed as well with slide 3, looking at the C-statistics, again, for different thresholds of ALP, taking all, a grid of thresholds across the ALP at one-year follow-up, from 1 to 3, and then calculating for each of these thresholds the C-statistics.

There, we found in our database an optimal cut-point, you could call it, around 2. But at the same time, you see that if you chose one of 1.67, it's not significantly different from 2, again, supporting that an ALP lower is better.

DR. CHEN: I want to add something on your slides earlier. I think that is for the entire PBC data set, right? Not for just the events of the patients.

DR. HANSEN: Yes, that's true. That is for the total Global PBC study group, and this represents 80 percent with mild disease symptoms and 20 percent with either moderate or advanced disease.

DR. RAUFMAN: Dr. Ellenberg?

DR. ELLENBERG: I have a question about the endpoint and a question about the confirmatory study. I wasn't sure whether the FDA -- with regard to what kind of endpoint was used in this study, are you considering this a candidate surrogate or one that's reasonably likely to predict? And if it's the former, what do you think is missing from what's reasonably likely to predict?

The second question, with regard to the confirmatory study, I'd like to know what hazard ratio is detectable with the study that is being planned. And also, I was a little surprised to see that the sample size was only 350. It looked like the sponsor

was able to enter 216 patients in the phase 3 trial in only 10 months. And it seemed like if they extended accrual for at least an additional year, the overall time of their study would probably be reduced. So I'm interested in those as well.

DR. CHEN: First of all, the sponsor's primary endpoint is actually on Dr. Min's slides earlier, is the applicant's cutoff. We didn't consider total bilirubin, and that's because the majority of patients within the total bilirubin range. So actually, we listed applicant's cutoff as indeed the primary endpoint.

DR. ELLENBERG: I want to know whether you're considering the endpoint that was used in the phase 3 study as a candidate surrogate --

DR. CHEN: Yes, that's --

DR. ELLENBERG: -- and not one that's reasonably likely to predict.

DR. DIMICK-SANTOS: Okay. So that's our question for you. That's our question for you today, is do you think that the endpoint is reasonably likely to predict.

DR. ELLENBERG: All right. Then what about the confirmatory study?

DR. WANG: This is Sue-Jane Wang from Office of Biostatistics. As you can see, the confirmatory study in this submission is only one, study 301. And the study doesn't have any clinical outcome data, only the ALP at one-year data. So what's lacking or missing here is the clear bridge of a, quote/unquote, "possible candidate," but we want to hear your opinion as to whether it is or it is not even a candidate.

So no randomized controlled trial really can support, at this point, whether it is or it is not.

DR. DIMICK-SANTOS: Did this answer your question?

DR. ELLENBERG: Yes, but now I'd like to have the question about the confirmatory.

DR. DIMICK-SANTOS: So the confirmatory trial is what will be necessary for us to give full approval. If you agree, and the FDA's final decision is that this drug can get marketing approval, that will mean we say, yes, this is not just a candidate endpoint; this is a surrogate.

So it will get the accelerate approval, which is granted on the basis that that confirmatory trial be completed and does show that the drug affects clinical benefit.

DR. ELLENBERG: What's the hazard rate that is expected to be detectable with the proposed sample size and the follow-up?

DR. EGAN: Amy Egan, deputy director, ODE III. We are still working out the details of what the total sample size should be, as well as what the total number of events should be. So that has not been agreed upon yet.

DR. ROMAN: If I may say something. With a mean surrogate, you mean like actually a surrogate endpoint that is reasonably likely to predict. I'm just adding to Dr. Dimick's comment.

DR. RAUFMAN: Dr. Dasarathy?

DR. DASARATHY: This is a question for Dhananjay. You said that you should discontinue the treatment if there is marginal response to ALP. How do you define marginal response, 10 percent, 20 percent, 50 percent?

DR. MARATHE: I was not thinking only 15 percent, but I think our clinical colleagues are of the opinion that we should not bind the clinicians with a certain threshold. It's up to the individual clinician to decide. I would say 15 percent is reasonable.

DR. MEHTA: As I had shown in the data, about 30 percent of the placebo patients achieved 15 percent alk-phos reduction spontaneously within a 12-month duration. So that has to be taken into consideration.

DR. DIMICK-SANTOS: And I think that in the confirmatory trial -- I don't think, I know. In the confirmatory trial, the sponsor is going to continue all patients on OCA, so whether they achieve any kind of response or not. So at the end of that trial, we'll have better data to help make this decision. In the interim, I think that we won't be able to give good firm recommendations.

DR. RAUFMAN: Dr. Chang?

DR. CHANG: Hi. Lin Chang. I had a comment and a question, but my comment was just regarding those comments about discontinuing at 6 months because

there's the whole question of whether you can use alkaline phosphatase alone as a good measure, and then to use it and say let's stop the drug when you don't even know if the patient will have some benefit later on. I think that's kind of preliminary, and you may be keeping patients from having a benefit from the medication.

But my question was about looking at the levels in these moderate or severe patients. From looking at the preparatory materials, it looks like there was recruitment of 8 per group by this liver disease, Child-Pugh status. But it didn't even say if they were PBC patients, so I don't know if these levels would be the same in a PBC patient.

But it looked like there was also an ongoing phase 3B study where they were recruiting more moderately severe patients. And I was just wondering if there are blood values taken of those patients so you get a better idea of what the blood levels were in the more moderately severe patients with PBC.

DR. DIMICK-SANTOS: Okay. So there was a little bit of difference in terminology. The sponsor

called their confirmatory trial 3B. We used the term 4. So when they wrote their background package, they called it a 3B, and we decided in conversation later that we would all just call it a phase 4 trial. But that 3B trial is the phase 4 confirmatory trial.

DR. CHANG: Oh. So it wasn't ongoing, because it sounds like --

DR. DIMICK-SANTOS: It is ongoing.

DR. CHANG: Oh. In 2014, it started, right?

DR. DIMICK-SANTOS: Yes, and they're still recruiting.

DR. CHANG: But don't they have blood levels, then, in patients that have more severe liver disease to see how the 5 milligrams or 10 milligrams a day would do in those patients?

DR. DIMICK-SANTOS: Yes. That is one of the discussion points and questions we have for you today. We have ongoing discussion about the fact that it is FDA's opinion that we need to modify the design of that trial to get better data.

DR. CHANG: I think the recommendations of this 5 milligrams twice a week -- and it's basing it on

these other patients, which I don't even know what their liver disease is due to with 8 per group. So I just feel like if you have data you can get from your PBC population, you should try to get that.

DR. DIMICK-SANTOS: Well, we don't have any data from the confirmatory trial yet. And you are correct. Those patients with cirrhosis were not PBC patients.

DR. RAUFMAN: Dr. Silveira?

DR. SILVEIRA: Yes. This is Marina Silveira. I have a comment and a question about the FDA's analysis of the endpoint. And I think that's pertinent with regard to whether to discontinue or not.

So all of the data has suggested that the lower the alkaline phosphatase, the better. But the data has also -- not only the PBC study group but all of the published data so far in terms of response to urso has included that bilirubin has a significant prognostic predictive ability. The PBC study group data, they do publish in the Lammers paper that bilirubin at 1 year does add to the alkaline phosphatase ability to predict.

In this phase 3 study, obviously, only 8 percent started off with abnormal bilirubin. But it does seem like a significant proportion of almost 10 percent of patients on placebo developed abnormal bilirubin during that phase 3 trial, at least on the data that was provided to us.

On the same time, on both arms that received obeticholic acid, they did have a reduction of those who did start off with an abnormal bilirubin, and they developed less. There was only one patient in the 10-milligram group that developed a newly abnormal bilirubin and none in the titration group.

So I was just wondering why was bilirubin completely abandoned when these analyses were redone?

DR. MEHTA: We're not abandoning those analyses. Where you get a placebo 10 percent drop is because the patients who drop out are treated as non-responders. So that's why their percentage sort of changes.

DR. SILVEIRA: Actually, in the table, it says "of the completers" --

DR. MEHTA: That's the next table.

DR. SILVEIRA: -- there were 13 patients that -- in the population that completed, still 13 patients had abnormal bilirubin at the end. So that must be misinterpreted.

DR. MEHTA: No, that's correct, 13 patients.

DR. SILVEIRA: Yes. Seven started off abnormal; only 1 normalized. So that would be 6 to begin with.

DR. MEHTA: Right.

DR. SILVEIRA: So that's 7 more new patients who developed abnormal bilirubin throughout the year. Am I understanding the 13 --

DR. MEHTA: No. No. So 7 patients in the placebo arm had abnormal bilirubin to begin with, and one patient normalized the bilirubin.

DR. SILVEIRA: But at the end of a year, 13 had abnormal bilirubin, so that means 7 new patients developed abnormal bilirubin.

DR. MEHTA: No. Seven patients started with abnormal bilirubin --

DR. SILVEIRA: Okay.

DR. MEHTA: -- one patient normalized. So 6

patients remained who had abnormal bilirubin, remained abnormal.

DR. SILVEIRA: Okay. I'll show you the table afterwards, then, because there's a discrepancy.

DR. RAUFMAN: All right. I know there are additional questions, but we're going to have to break for lunch, and we'll get to those questions later.

We'll now break for lunch. We will reconvene again in this room 45 minutes from now at 1:30 p.m. Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:47 p.m., a lunch recess was taken.)

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

(1:30 p.m.)

Open Public Hearing

DR. RAUFMAN: Good afternoon. We'll reconvene with the open public hearing session.

Both the Food and Drug Administration, 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, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, or if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at 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 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.

I believe we have three speakers. Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. SOBLE: Good afternoon. My name is Deborah Sobel, and I am a primary biliary cirrhosis

patient. I live in the Chicago-land area, and I have received no financial -- or I have no financial interest in the outcome of this meeting. I'm grateful to be here, and I thank you for the opportunity. They say that my sister and I sound alike. Our voices are similar, so I want you to listen very carefully, though, for her unique voice. She would have loved to have been here.

Sarah was the mother of two girls. She was a successful real estate broker, and she was an effervescent, charismatic, and intelligent woman. She was diagnosed with PBC prior to myself. I can tell you that we were two sisters growing up in the same town, but sadly we went down two very different paths with this illness.

Sarah launched herself immediately into patient advocacy work. She worked tirelessly and relentlessly for the benefit of newly diagnosed patients, giving them support and help. I'm a very private person. This is not my nature to be here today. And I can tell you that, for me, I did not want to be associated with t he C word, cirrhosis. The

stigma was just too powerful for me.

In spite of taking every viable treatment available to her, Sarah unfortunately did not respond well to urso. I don't respond well to it either. In fact, Sarah is really emblematic, as am I, of the patients that were spoken about early; young diagnosis. She was diagnosed at 38; I was diagnosed at 41. She would want you to know that she was the younger sister in all of this. We both struggled with urso. I actually have had my own issues with it, and Sarah had much far worse, and of course, this led her to the path of transplant.

For me and for Sarah, transplant is a very risky process, and I do understand that when nothing else is available, this is what is available. And if it's going to save your life, then so be it. But of course, there's the risk you won't get a liver. We heard testimony about that early. That's significant.

There is the risk of a very lengthy and challenging surgery. There is the risk of potential rejection. And of course, there is the long-term risk of being on immunosuppressants likely for the rest of

your life, and that leaves you vulnerable in many situations. That said, we moved forward with Sarah with the transplant process because the only alternative was death.

In March 2006, Sarah received her first liver at the Cleveland Clinic. She never left the hospital again. She was in an intensive care unit for the rest of her life. That liver failed. She received another unprecedented -- you'll not hear this too often -- liver transplant in May 2006. So what we're talking about is two liver transplants within 60 days. Unprecedented. You just won't hear this.

The last time I saw her in a way that I could communicate with her was June 25, 2006. She was still sitting up, a little bit stable, and able to speak to you. We had our rabbi up that day. On June 28th, I had headed back to Chicago to take a bit of a break and received that call that we all dread. Sarah had taken a turn for the worse; get back to Cleveland. So I did.

When I had gotten to her room, I found her swollen beyond recognition. I found her comatose. And I found that we couldn't even look in her eyes because

there was this green film over her eyes. I'm sure the doctors know exactly what I'm talking about. We put some Bruce Springsteen on for her, which she would insist on, and she left us that night.

Now, I praise the heroic efforts of her doctors. They fought for her. Everybody knows they fought for her. Sarah ran out of options, and she ran out of time. Living with PBC is very difficult. I have itching. I have fatigue. I work hard all day, and somehow you just power through. But what I want you to understand is that I have learned to live with those things. I can adapt to those things. Those two things are not going to end my life. They're annoying, frustrating, but they're not going to kill me.

Fatigue did not kill Sarah. Pruritis did not kill Sarah. Liver damage killed Sarah. And that's the very important difference here that I want you to understand. We need to control the liver damage. And right now, we just don't have those options available immediately in the marketplace.

I believe OCA represents an opportunity for us, a viable option for us, to begin to address the

issue of liver damage and to roll that damage back to extend the life of the organ that nature gave us, which is really the best way to live. I would life the rest of my life with pruritis and with fatigue if I knew that I would extend the life of my liver. I can tell you that right now.

My heart breaks over the loss of my sister. Nothing can ever compensate me or make me feel better about that. Every day, there is a moment where I think about that loss. But I can tell you something about the human heart. It grows stronger every time it breaks. We become stronger every time it breaks.

As a PBC patient looking down the road toward a transplant myself, someday may be what it all comes to. I also struggle with urso. I can tell you that I would much rather do more for the existing liver I have. So please hear me when I say to you, we need this option. We really need this option.

Now, I want to conclude by saying to you that in Judaism, the greatest gift you can give another person is one for which they can never thank you. Sarah will never be able to be here today to thank you

for the opportunity to present her story and her point of view, so I leave you with that.

DR. RAUFMAN: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MS. ROBERTS: My name is Carol Roberts, and I live in Rochester, New York. I am a stage 4 primary biliary cholangitis patient, and I'm here today representing the -- as a member of the executive committee of the PBCers organization, a national 501(c)(3) nonprofit.

The PBCers organization has received educational and programming grants from Intercept Pharmaceuticals. I personally have received compensation from Intercept for participating in a video last fall so that their employees would be allowed to get to know a PBC patient on a more personal level. And I also participated in a panel discussion at a 2014 PBC conference.

The PBCers organization is the largest U.S. based patient organization dedicated to people living

with PBC. Our community of over 3400 members is truly phenomenal in their support and sheer number, especially considering this is a rare disease, and it's run entirely by volunteers. There are no paid employees.

It exists today because three women from different parts of the world, who needed support in dealing with their own PBC, met online and formed the organization in March of 1996. Every day, we work to ensure that everyone who is diagnosed with PBC has access to support and education services that they need to better cope with their disease. One of our goals is that no one diagnosed with PBC ever feels alone.

As many of you know, PBC usually advances very slowly, and there is no cure. Most people lead normal lives for years without symptoms depending on how early their diagnosis is made. But for those that have symptoms, they can vary greatly, making it difficult for doctors to actually diagnose PBC.

Typical symptoms include fatigue, itching, skin problems, aches, and joint pain. Over the years, as PBC progresses, other symptoms can occur. Those

with PBC usually look healthy and many are 10 to 30 pounds overweight. Their slight bronze pigmentation of the skin is often present in the advanced stage of the disease making the individuals look tanned. The outward appearance does not tell the story of what is going on inside their bodies: inflammation, progressive scarring, and bile duct damage.

The course of PBC varies greatly. It does not always diminish the quality or the duration of life. Of patients who present without symptoms, 50 percent showed evidence of liver disease over the next ensuing 15 years. Our goal is to slow the progression in hopes of keeping our livers longer. Sadly, too many of us face liver transplantation with PBC, and that's the leading cause of liver transplants in women.

I first learned about the PBCers in 1999 shortly after I was diagnosed with the disease. Looking back to the first patient meetings that I attended, I remember sitting in the back of the room completely unsure of what to expect. What I experienced changed my life, both personally and in an educational way. The content was compelling, relevant,

and current. But the special part was the way the organization and its members connect you with others.

In my work with the organization, I've been blessed to connect with so many -- I'm having trouble here because Sarah was one of my best friends. Face-to-face encounter with another person with PBC was a woman named Nancy. She had had a transplant, and I met her. And I thought, if she can do this, so can I.

The feeling you have when you meet the first person face to face with PBC is phenomenal, but it pales in comparison to being that first person for someone else. I have met many people newly diagnosed and struggling to deal with their disease, and I have held the hands of people facing the end of their lives. Many have become very close friends, and it's difficult to lose them.

I have celebrated the gifts of life received by many and commiserated with those suffering from the various symptoms of the disease. I decided to do whatever I could to help raise awareness of PBC and to raise money for research. My fundraising has taken many forms over the years, from crabs [indiscernible]

fair profits, to attending raffle dinners, and organizing walks, and continues until this day. Coincidentally, funds raised at a walk in Cleveland were donated to a doctor there for her clinical trial for INT 747, which is the beginning of this process that leads us here today.

Today, you've heard about the devastating effects PBC can have on patients like me and their families. Simply put, PBC patients need another treatment option. Over the past 30 years, PBC patients have only had one treatment available to help us keep our precious liver longer. While we are grateful for Ursodiol, some people do not respond, become resistant, or cannot tolerate it.

It's our time for new drugs to come to market helping more PBC patients live longer with the liver they were born with. We found hope in the advancement of viable options that can allow us to keep our livers longer, specifically promising clinical trials resulting from obeticholic acid tablets. If approved, we believe this treatment will provide a desperately needed option to PBC patients. We need this approved,

and we need it now.

I stand here for all PBC patients today, and I bring with me a letter signed by more than 1500 PBC patients and their families urging the FDA to accelerate access to new treatment options for this disease. We need more options to help us keep our livers longer. On behalf of the PBCers organization, PBC patients and their families, thank you for hearing our plea.

DR. RAUFMAN: Thank you. Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MR. MARTIN: Thank you. My name is Jonathan Martin, and I'm with the American Liver Foundation. The following statement that I'm here to read today was prepared by Thomas F. Nealon, III, our board chair and chief executive officer. The American Liver Foundation is a 501(c)(3), and the organization does receive contributions from a number of pharmaceutical companies, including Intercept. We have received no compensation for our attendance here today, and this in

no way impacts our comments that we've prepared for you.

"As many of you know, the American Liver Foundation is the trusted voice and resource for patients with liver disease. Our mission is to facilitate, advocate, and promote education, support, and research for the prevention, treatment, and cure of liver disease. We have 16 divisions across the country to provide boots-on-the-ground support to liver patients and their families, as well as to the general public. There are more than 100 different liver diseases, which affect more than 30 million Americans.

"I come before you today to offer our insights about primary biliary cholangitis, or PBC, and the brave patients who live each day with this disease. Until very recently known as primary biliary cirrhosis, PBC is a chronic, long-term disease of the liver that slowly destroys the medium-sized bile ducts within the liver.

"Bile is a digestive liquid that is made from the liver and travels through the bile ducts to the small intestine, where it helps digest fats and fatty

vitamins. In patients with PBC, the bile ducts are destroyed by inflammation, and this causes the bile to remain in the liver where gradual injury damages liver cells and causes cirrhosis or scarring of the liver.

"In support of the American Liver Foundation's effort to assist patients with PBC, we recently welcomed four new members of the American Liver Foundation's National Patient Advisory Committee who have joined us as patient advocates representing this rare and complicated disease. The National Patient Advisory Committee is an important initiative aimed at ensuring that the patient's voice is heard and amplified through ALF's education, support, and advocacy programs, as well as to the public through traditional and social media.

"PBC is devastating in so many ways. The symptoms are serious, and the outlook for many patients is incredibly scary. You've just heard today from two patients about their journeys and struggles being a PBC patient. I would like to use my time today to focus on the outcome many PBC patients face, a liver transplant.

"Unfortunately, many patients with PBC can

expect a liver transplant, but we all know the waiting list for livers are long, and the process can be frustrating at best and tragic at worst. Currently, there are about 17,000 patients waiting for a liver suitable for transplant, however, there are only enough donated livers to perform about 5,000 transplants each year. As a result, more than 1700 patients die each year while on liver waiting lists.

"It is disappointing to say that PBC patients account for a disproportionate number of transplants. While PBC only affects 1 in 1,000 women over the age of 40, since 1988, PBC has been the second leading cause of liver transplants among women in the United States. So it is imperative that we slow the progression of PBC and avoid needing a transplant for as long as possible. We simply want to preserve a person's natural liver. This should be the primary goal of helping people living with PBC because the alternative is simply not acceptable.

"The current standard of care is not sufficient for all patients and does not effectively slow the disease. A new treatment is desperately

needed so we can delay liver transplantation as long as possible.

"At the American Liver Foundation, we believe that all patients who have liver disease deserve options. This ensures the best outcomes for all patients and should be our commitment to all who have liver disease. We believe science has the unique ability to improve quality of life, reduce a disease's impact, and to offer comfort and hope to those who are suffering with their families. And we believe that all efforts should be made to delay transplantation.

"We are in a crisis situation and need ways of lessening the demand for livers. As I have explained, PBC patients represent a large number of transplants, and with those come suffering, uncertainty, expense, and long recoveries; or much, much worse if the suitable liver cannot be found.

"As I said, ALF advocates on behalf of all liver diseases. It is important to note that if PBC patients can delay or avoid liver transplantation through new treatment options, it helps the thousands of other patients with other liver disease who have no

option but transplantation. This is one of the primary goals of our organization.

"One of the greatest challenges we face is that so few people understand liver disease and there are so few new treatments on the horizon. To my knowledge, patients living with PBC have not had a new treatment advance in over 20 years. We strongly support efforts by Intercept and other companies who are developing potential treatments for neglected liver diseases.

"We respectfully ask the committee to recognize the urgent need within the PBC community and to help bring new treatment options to the patients who need them. It is the belief of the American Liver Foundation that new medications can offer patients treatment options, relief, and most importantly delay liver transplantation. We thank you for the opportunity to speak with you today."

DR. RAUFMAN: Thank you. The open public hearing portion of this meeting is now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the

task at hand, the carefully consideration of the data before the committee as well as the public comments.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

DR. DIMICK-SANTOS: Dr. Raufman, this is Lara Dimick. I'm sorry. We were unable to answer the question from Dr. Silveira. Would you mind if we answer that now?

DR. RAUFMAN: Go ahead.

DR. MEHTA: Cindy, you have the email from Dr. Ben Vali. If you could please pull that up, there's a slide that he has sent.

DR. VALI: Dr. Ben Vali. Just to eliminate any ambiguity here, the top two lines are numbers you probably are already more than intimately familiar with by now. We are basically looking at shift tables. We're isolating patients that have baseline total bilirubin less than or equal to 1 times ULN and seeing

what happened at month 12 by treatment group.

Specifically, we're talking about placebo, so we see that 7 patients that had normal bilirubin at baseline actually had elevated bilirubin at month 12. And then, with the baseline total bilirubin being elevated, those patients, 6 of them, remained elevated, and hence, 13 total. So hopefully that will reconcile that for you.

Questions to the Committee and Discussion

DR. RAUFMAN: Thank you.

While we're getting ready, there are seven discussion points and one voting question. The first discussion -- and I'll read these as we go along.

Discuss whether the evidence from the Global PBC study group data presented today on the reduction in alkaline phosphatase supports the use of alkaline phosphatase as a surrogate endpoint reasonably likely to predict clinical benefit in the treatment of early stage PBC. Comment on the strength of evidence that supports the stratified responder criteria that were developed by the FDA statistical team's review of the Global PBC study group data.

So I'll open this to discussion.

DR. PROSCHAN: I'm Michael Proschan. One thing I'm concerned about that didn't get brought up earlier was suppose I come up with a drug that just interferes with the ability to detect high levels of ALT [sic]? So I'm going to get low levels of ALT in the drug group. I'm going to say, oh, look, it really helped. And then I'm going to use this external observational data to say, oh, yes, lowering ALT allows you to live longer, but in fact it may depend on how you lower it.

If you lower it artificially, the way I just did with my drug that doesn't really do anything other than make it harder to detect it, then clearly that's not going to have the same benefit. So I think that's a real concern to me. It would be different if you had data -- you had this observational database that told you how much you could expect survival benefit from various decreases and you also had observational data on people who are on the drug and off the drug. So you could see whether the change in their ALT did predict their change in survival. That would be a lot stronger

evidence for me.

We don't have that because the observational data, no one was on OCA. So it's hard for me to be conclusive about the fact that it does predict clinical benefit. I think for me, though, the fact that it had benefits not just on ALP -- sorry; I said ALT; I meant ALP -- had benefits not just on ALP but on other markers, so that sort of makes me feel a little bit better, but I do have that concern.

DR. RAUFMAN: Dr. Lipman?

DR. LIPMAN: Dr. Lipman. I think this goes to the point, to the question that I raised earlier this morning. I think the Global PBC group has a very nice observational database that suggests associations but doesn't prove causality. So I would think that this fits very nice with the FDA candidate surrogate marker, which is under evaluation for ability to predict clinical benefit.

Nobody gave me an answer that there was any harder data in terms of outcome data, so I don't think it's been validated as a surrogate endpoint, and I think because of the strong association and not

causality, I'm hard put to say it's reasonably likely to predict. So I think it's a candidate surrogate endpoint.

DR. RAUFMAN: Dr. Levine, I think your hand was up.

DR. LEVINE: Thank you. I was just going to ask a question, whether recognizing OCA is different than UDCA. Does UDCA serve as a reasonable analog to understand part of the question regarding the relationship between ALP decrements and harder endpoints? Simply because we've had a lot of experience with UDCA.

DR. RAUFMAN: The drugs do work differently. Dr. Sjogren?

DR. SJOGREN: Looking at the data, the Global PBC and the experience in clinic with liver patients with PBC, I think that alkaline phosphatase and bilirubin are the lab values that we look at to see if the patient is doing better or is getting worse. Certainly, there are other lab values, prothrombin time, albumin, what not. But these two I think have stood the test of time in the many, many trials that

are in the literature. So I would favor the use of the alkaline phosphatase as expressed by the FDA earlier in the morning.

DR. RAUFMAN: Ms. Cryer?

MS. CRYER: I just wanted to make sure and clarify the scope of the information that we're supposed to use to answer this question. So you want us only to consider the Global PBC study group data, not other data or trial data presented over the course of this meeting, and only the FDA statistical team's review of information and not other information.

Then thirdly -- forgive me, I'm a lawyer. I'm just trying to make sure I'm answering the question that you want answered. So we're only to ask if simply -- and this may be a follow-up to the previous question -- if just ALP alone, or as has been discussed during the course of this meeting, ALP plus other markers might be appropriate combinations or algorithmic endpoints.

So I just want to make sure that we're strictly -- we're literally answering this question with the limitations on all of the scopes or if we can

answer from a larger base of the information that's been presented today.

DR. DIMICK-SANTOS: I think we're asking you two questions today. The first sentence actually asks you on the strength of the totality of the data, so you can consider any data either presented or not. Then the second part of the question asks you more specifically about the stratified responder criteria based on the PBC study group.

DR. CHEN: I would like to add we have two independent statisticians. One analyzed the Global PBC data, and then the other analyzed the trial data. For Dr. Min, she never touched the clinical trial data, so she doesn't know what the result will look like. After we had our session, Dr. Ben Vali analyzed the trial data using our proposed cutoff.

DR. RAUFMAN: Dr. Ellenberg?

DR. ELLENBERG: I also was troubled by saying is ALP a surrogate endpoint because it was clear from the data that we saw that total bilirubin is a much stronger predictor of outcome than ALP. And while the data that was shown certainly suggested that ALP added

something, that total bilirubin really had a much stronger prognostic.

Looking at the data that I saw, if I hadn't seen any effect on total bilirubin, I would be more skeptical. Yes, the total bilirubin was mostly normal, but you did see movement in the bilirubin in different directions in the placebo and the treatment, and that was somewhat reassuring. So I wouldn't want to go with ALP by itself as a surrogate endpoint. I would hope that, somehow, a total bilirubin would be incorporated.

DR. RAUFMAN: Dr. Silveira?

DR. SILVEIRA: To answer the question, my opinion is that alkaline phosphatase is reasonably likely to predict. It does fulfill being supported by mechanistic and epidemiologic rationale. For patients off treatment, the data has also been able to show that it reasonably predicts clinical outcome.

Both the PBC Globe study group and UK-PBC study group, as well as other older smaller studies have all been able to show that patients treated with UDCA, that the response to alkaline phosphatase does predict clinical outcomes with a caveat that bilirubin

does add to that prognostic information. But based on the natural history of disease of PBC, that we cannot rely on that because that happens much later in the natural course of the disease.

Being devil's advocate, I agree that you can never know that same change in alkaline phosphatase could by a different mechanism by obeticholic acid and could end up not meaning the same thing in the end. Obviously, that's why confirmatory studies are important. But if that were to be confirmed, that would be two different drugs that would allow for it to be considered a validated surrogate.

The issue with PBC is currently there's only one treatment available. For example, hepatitis C, multiple drugs will lead to undetectable viral loads, and that's an acceptable surrogate marker. But for PBC, right now it's impossible to establish that because there is only one available treatment at the moment, so we just cannot know that reduction of alkaline phosphatase by drug is generalizable for other drugs. But the data presented so far does, I think, support it being reasonably likely to predict clinical

outcomes.

DR. RAUFMAN: Dr. Conjeevaram?

DR. CONJEEVERAM: I think it's important for all of us to recognize that this disease is defined and dictated by alkaline phosphatase and not bilirubin. Bilirubin's utilities is more later in the disease. So I think I'd be very cautious in making decisions on mild fluctuations of bilirubin in trials like this when you're really dealing with mild disease. I don't think it's going to be useful clinically.

So we really need to get back to alkaline phosphatase. And based on that, I think this data does support it. One thing we do know is that people who have response by alkaline phosphatase, based on what's been presented, does change the natural history of the disease. So you're kind of taking those patients now refractory and is more likely to have a bad outcome. And then you're introducing another drug, which is not 100 percent effective, but definitely effective; it's bringing it down further.

I do recall the comments that, yes, on one side, we don't know what the next 5 of 10 years will

bring in those patients, but using that as the best surrogate for the time being, given all the information that we have, is probably the best option.

DR. RAUFMAN: Dr. Assis?

DR. ASSIS: Yes. I just wanted to concur with some of the recent opinions that alkaline phosphatase, in my clinical experience and also research experience, is a reasonable potential surrogate endpoint for this disease and PBC specifically. I would say that I would hate to leave bilirubin behind completely, though, because I think both by Global PBC group data and UK-PBC group data, the biggest drop off in survival is once the bilirubin is elevated. And clearly, that does denote, to some degree, more advance stage.

But the biggest impact for a drug approval of this stage, in my personal view, would be to really prevent and potentially even rescue those who have more advanced disease. That would seem to be the likely impact that would be most beneficial for those current and in the future. Therefore, I would encourage continuing discussion about bilirubin as well, maybe not as the only marker because, clearly, it's a later

stage.

But I do bring that up also because of some concerns I had based on earlier morning discussions on what we really don't know about hepatic impairment. And I do think that that needs to be further studied robustly in a confirmatory trial, so that we can give a potential new drug to patients who have the biggest likelihood of avoiding transplantation.

DR. RAUFMAN: Dr. Dasarathy?

DR. DASARATHY: I concur with Hari that I'm a little nervous about this bilirubin change if the upper limit of normal is, let's say, 1.2 for us. So 1.3 to 1.1, it's almost a 20 percent drop. So would that be considered to be a major change? This is a joke. I mean, it's based on colorimetrics, and most of us who work in labs know that clinical labs are not obsessed with the levels of precision. Even when we do precise things, 10 percent is pipetting error.

I mean, I'm not sure whether we should be using something which has such a low sensitivity, and the maximum that we're asking for is 2 times upper limit of normal. I'm not confident adding that as

really a very useful way to improve the reliability of surrogates. I think alk-phos is a pretty reliable measure. We've all been using it for ages, and now we have objective data.

So I'm not confident putting bilirubin is really a good idea. I think alk-phos, for now at least, it's a stand-alone surrogate.

DR. RAUFMAN: Dr. Khurana?

DR. KHURANA: I somewhat do agree with concerns Susan has raised, although I agree that alk-phos is right now all we have. But I think we should not forget the fact that there's a discordant between where the drug is acting and what actually are we measuring. We are assuming rightfully that this is affecting on FXR and the hepatocytes, so a good measure would be bilirubin. But alkaline phosphatase comes mostly from cholangiocytes, so that discordance clearly raises the issue, which I agree what Susan has said. So that does bring to the fact that alkaline phosphatase is all we have, but clearly it's not the best that's available.

DR. RAUFMAN: Dr. Chang?

DR. CHANG: I just want to further comments that Hari made. I think that we have to think about PBC as a spectrum. If you have early disease or late disease, you can't apply the same thresholds, or cutoffs, or outcome measures in a disease that changes.

So whatever your patient population is, if you have a normal bili, of course you wouldn't use bili as an outcome measure because it doesn't make any sense to really do that, especially it's early disease. But if you're going to start recruiting patients with more moderate or severe disease where the bilirubin goes up, then it makes sense.

So this proposed stratified responder criteria, one thing you might consider is that in the patients with an elevated bilirubin in addition to this reduction in alkaline phosphatase, you might want to do the same thing with bilirubin. That would make sense to me. But I think we have to think about what patient population we're talking about because the data presented today is mainly on early disease.

So if that's what you're asking about, then alkaline phosphatase to me seems very reasonable to

use. But if you're going to talk about a more severe population, you may want to change your outcome measure. I mean, to me, that just makes sense.

But I do think that the mechanism of this drug -- I mean, it has a very plausible mechanism by it being an FXR agonist. So I could see why it would definitely lower alkaline phosphatase. I'm not really worried that it's falsely lowering it and has nothing to do with the biologic mechanism of the disease.

DR. CONJEEVERAM: I think that based on the question, I think it's important -- exactly what Dr. Chang was saying -- is that we do need to know where we are starting with the patient. I don't think any of us will ignore bilirubin, but we do think about it or really kind of focus much more on it based on the disease severity.

So you're collecting the data, but what we're really talking about here is given the patient population that is being studied, your best marker is still alkaline phosphatase. I think making huge decisions based on just bilirubin may not be very useful. But as the disease is more severe, especially

moderate-severe, I think bilirubin will definitely have a role as well.

DR. KUMAR: So I also favor alkaline phosphatase. Of course, in someone who's got advanced disease, we will not be ignoring bilirubin. But I think while we also wait, maybe non-invasive testing, which isn't perfect.

I mean, those might be helpful, but I think what we have today by way of alkaline phosphatase, which is also validated by the data, we heard lower is better, which really brings me to the issue of criteria that the FDA is proposing, that less than 2 times or 40 percent, which is less stringent than the 1.67 in the other, except in patients who have -- let me think about it mathematically.

So maybe there is a cluster of patients in this modeling that was done around 200 to 300 alkaline phosphatase range, because if you think about it, if the alkaline phosphatase is more than 300, getting to a 40 percent reduction is easier than getting to a 1.67, the upper limit of normal of alkaline phosphatase.

Just as an example, if the alkaline

phosphatase to start off is 400, you have to only get to, what is it, 60 percent of that, 240, to qualify as a responder --

DR. PROSCHAN: No, it's "and."

DR. KUMAR: I'm sorry. Yes, "and." So you only have to get to under 200 as a responder, assuming that 100 is normal and 200 is twofold. Under the older criteria, under the 1.67 criteria, you'd have to get to 1.67, 167.

So in reality, I think we need to think through this that only up to 325 or so is the -- only up to about 3.25-fold elevation of upper limit of normal, the criteria that you're proposing, the FDA is proposing, is it more stringent? So I think we need to think through whether we should leave it at -- leave a responder definition as being twofold or not, or we should keep it at 1.67. And possibly to keep it at 1.67 upper limit of normal would be a better outcome.

DR. RAUFMAN: If I could keep us focused on the question because I don't want to get lost in math.

DR. KUMAR: I'm sorry about that, the use of calculation.

DR. RAUFMAN: The question we're being asked is about the use of alkaline phosphatase and not the specific criteria.

DR. PROSCHAN: Actually, the second part of the question does ask about that. It does ask about the specific criteria.

DR. RAUFMAN: Well -- Dr. Ellenberg, can you take us out of this?

(Laughter.)

DR. ELLENBERG: Yes. I was certainly not suggesting that total bilirubin be used as the only marker. I suspect that if the data we had seen showed the kind of ALP changes that we saw, but the bilirubin results were different -- that is, you saw nothing happening in the placebo but you saw some increases in bilirubin and the people taking the drug -- people might be a little more anxious.

So when we talk about what should be a surrogate, I think, to me, you have to look at the bilirubin, too, because you want to make sure while you're looking at the ALP and be enthusiastic about what the drug is doing to ALP, you want to also know

that it's not doing something in the opposite direction. And that was what I was trying to get across looking at the data. I don't think you can just say we're only looking at ALP and we're not going to look at anything else. And if the ALP looks good no matter what else is happening, we're happy.

DR. RAUFMAN: Dr. Assis?

DR. ASSIS: I think just to reiterate a few points from my perspective, at least I guess the question is strictly define, address as early stage PBC. And to the degree that the new drug application is for early stage PBC, I do think that alkaline phosphatase is very reasonable in that setting.

I think the data that's presented, also included especially from the databases and the core studies, is more advanced disease, and perhaps mixing the two is leading to some of the confusion. I think alkaline phosphatase in early stages, again my personal opinion, is an absolutely reasonable way to go.

Perhaps, the follow-up question to that would be might there need to be different surrogates for advanced stage disease, because I think that's the real

conundrum here. How would you deal with somebody who already has advanced stage, then what would you use, and would the drug be appropriate? Is that what was studied? I don't think there were enough patients to have any comment on that.

DR. RAUFMAN: Is FDA satisfied that we've addressed this discussion? Because I can summarize.

Please, if anybody disagrees with what I'm saying, please speak up. But I'm hearing a consensus -- and again, primarily amongst the clinicians on the panel -- that supports the use of alkaline phosphatase as a surrogate endpoint, with some reservations, but a general consensus.

A few people opined that changes in bilirubin would be helpful, but the problem is that in early stage disease, as we've seen the data, it's generally normal. I think there are some reasonable questions about whether small changes in a normal value have any meaning. I know that some people on the sponsor side suggests that there is predictive value to changes within the normal range, but I think there is some degree of skepticism about that.

Regarding the latter part of the question and the strength of the evidence regarding the stratified responder criteria, there were some questions raised about what the cut-points should be, and I'm not sure that those have been resolved.

Any other comments?

DR. SJOGREN: In terms of the cutoff, I think simpler is better. Once it's on the package insert to clinicians, if you put 2, if you put 1.67, it's a bit confusing unless you know the subject real well, and you're going to spend time. But in a busy clinic, I think the statisticians need to help us with deciding what is the cutoff and let it be, so it's written very simply and very effectively for the clinic.

DR. PROSCHAN: I think from a purely statistical standpoint, I found the evidence persuasive for using the stratified responder analysis, but I don't think it's a purely statistical question. I think it's both a statistical and medical question. Just like the point I brought up earlier about it's theoretically possible to have a drug that artificially makes it look like you have lower ALP.

That's a theoretical concern, but obviously you have to take into consideration the opinions of the experts on how reasonable that would be, that a drug could have an effect like that on ALP, and it could be just completely artificial.

DR. RAUFMAN: Let's move on to the next discussion point. Discuss the appropriateness of the applicant's proposed dosage schema, i.e., a starting dose of 5 milligram of OCE with up-titration to 10 milligrams after 3 months. Include in your discussion and dosing recommendation the safety and tolerability of OCA in addition to the biochemical response, alkaline phosphatase, reduction.

Does somebody want to comment on that? This one looks a little bit more straightforward.

(No response.)

DR. RAUFMAN: Well, does anybody disagree? I think the data supporting a starting dose of 5 milligrams seem convincing to me with the titration after 3 months. We're not asked here when to stop if we don't get a response. That might be something to discuss, and I don't remember if one of the next

questions has that. Safety and tolerability at those doses also seem reasonable.

Dr. Assis?

DR. ASSIS: Just a very brief question. I don't know where is a good place to raise this, but I was very interested to see that in some of the patients who took even the lower doses, they had an unusual or more prominent decrease in HDL. And perhaps during any confirmatory study, it might be possible to tease out if at some point, at 3 months, it might be beneficial to take more significant change to cholesterol panel and to consideration in terms of safety. But clearly, there's no data on that. It's just something that potentially could be evaluated over time.

DR. RAUFMAN: Dr. Vos?

DR. VOS: I found the evidence reasonable and would support the 5-milligram starting dose. With the titration at 3 months, it seemed like a very reasonable approach given the data with the 6-month titration, both the rapid response in ALP seen at 1 and 2 months.

My one kind of concern or question would be the safety with regard to hepatic events. And we

really haven't talked about that too much, but it was a compelling chart presented by the FDA on page 22. And the adjusted incidence of hepatic events is quite high in the 10-milligram dose compared to placebo, and I wondered what some of the other panel members thought of those data.

DR. RAUFMAN: Go ahead.

DR. CONJEEVERAM: If you look at the data you're talking about, the high incidence really starts with the 25 milligrams. There doesn't seem to be much difference between the titration dose and the people who are starting with chance or 4 and a half to 5 percent, definitely with more than placebo.

DR. VOS: It's the 2 to 5.

DR. CONJEEVERAM: Two and a half to 5, yes. Keep in mind, 50 percent of the titration are already at 10 milligrams by 3 to 6 months, so it's a mixture.

DR. SJOGREN: From what I heard this morning, the side effect with 10 milligram was not comparable to the 25 or the 50 at all; thank, God. So it is quite -- in my view, in the clinical point of view -- acceptable, provided that it's going to give

the benefit to the patient, is going to prolong life or maybe life without transplantation.

So it all has to be taken, the pros with the cons. But overall, I thought that 10 milligrams for the patients that need it should be okay.

DR. PROSCHAN: But as I recall, there were more people who could not tolerate and had to drop out -- I think it was 10 percent -- in the 10 milligram dose, and far fewer when you start with 5.

DR. ASSIS: I could be mistaken, but looking at page 22, as was brought up, it seems as though the majority of the hepatic events seem to be complications of advanced liver disease such as ascites, variceal bleeding. So I don't know how this fits into the discussion, but it would almost seem as though, then, these patients were not early stage when they retreated.

So therefore, perhaps better clinical characterization and practice might be relevant, especially if this is a drug intended or studied mainly in early stage disease. I don't believe many patients with minimum fibrosis would be requiring parancentesis

or have variceal bleeding.

DR. CHANG: I definitely think for early stage -- I mean, I don't know if 3 months is that huge of a deal to do the lower dose and high dose. If you actually propose that -- and then in the clinic, they'll probably give it to patients that are a little bit more severe. Since the blood levels may be higher, then it probably is safer to do the titration and then go up to 10 milligrams. This is a certain patient population for this study. In the clinic, you're going to see patients with more severe disease, so it might be safer to do it that route.

DR. RAUFMAN: Other comments?

DR. KHURANA: Just one comment regarding that, because PBC is one disease where you can have portal hypertension despite having an advanced disease, as a pre-hepatic portal hypertension. So it's something that has to be kept in mind. It's not just trivial that all of them are going to be -- they all are advanced disease.

DR. CONJEEVERAM: Just sort of a comment. If you look at one of the earlier slides, it showed the

fact of placebo versus the titration dose, versus 10 milligrams, it looks like the titration dose kind of falls somewhere in between even the model that was shown. That's on one side the efficacy, and we know that about 50/50 -- some half of them are continued on the 5 milligrams and half of them are up to 10 milligrams.

It would be nice, especially in the confirmation study, if we can actually look at another outcome. The question is, if you have a response and if you're continuing on the 5 milligrams, is the overall efficacy in the long run, or the progression of disease, or decrease in complications, is it going to be much less compared to if you're actually up to 10 milligrams unable to maintain that 10 milligrams? Ultimately, is 5 milligrams the optimal dose? We don't know that.

I think it's very appropriate to start with 5 and then 10. But in the confirmation study, if we can look at other markers of disease progression, on people who just maintain, based on the biochemical response on 5, but assuming that might translate to decreased

progression or better outcomes. But we don't know that.

DR. RAUFMAN: Dr. Kumar?

DR. KUMAR: It seems like the patients respond within weeks, 4 weeks or 6 weeks if I recall the data. But I guess what's the urgency? I mean, this is a long-term outcome that we are looking at. We're looking at outcome in decades, years, so it may be a decade or so. I mean, 3 months seems very reasonable I think, especially given the fact that there is fewer dropouts.

DR. RAUFMAN: Dr. Vos?

DR. VOS: I'd just like to make one more comment about the safety. I think that it is always difficult in liver diseases because there are patients who are end stage in the trials or may have had advanced disease without having the high bilirubin, so they would have some events.

My opinion is that I think that there is enough demonstration of safety with the 10-milligram and the 5-milligram doses, but I think it will be really important that the phase 4 trial look at hepatic

events very closely and carefully, which I think it will. And then it will be helpful to prove that further safety.

DR. RAUFMAN: Maybe this discussion has matured, and I can summarize. And again, if I do so incorrectly, somebody please speak up. But there seems to be a general consensus that the proposed dosage scheme of 5 milligrams titrated up to 10 milligrams after 3 months is reasonable based on the data that we've seen this morning.

There was some question regarding the hepatic safety of he drug, and there does seem to be a dose related increase in hepatic events. But at the 5- and 10-milligram range, as I think one of the panelists said, that that seemed to be an acceptable risk based on the likelihood of benefit.

Discussion point 3, discuss the adequacy of the data to support the use of OCA as monotherapy for patients intolerant to UDCA. Include in your discussion whether the applicant should be required to study the use of OCA further as monotherapy.

DR. DASARATHY: A clarification. When you say

further study, does it mean before it is approved or it is felt that the data is insufficient, therefore, a decision cannot be met? Is this what it means, or does it mean further studies are required as post-approval marketing follow-up? I'm not clear what the question means.

DR. RAUFMAN: I believe it's the latter. It's post-approval. But if I could have clarification from FDA.

DR. ROMAN: I think we would like to have the question answered in a broad sense before and after approval -- yes, before and after approval. In other words, would it be satisfied with the amount of information that we have received and viewed at this time, based on the presentations, to be comfortable, that lays a demonstration of monotherapy, and what you would like to see if not.

DR. RAUFMAN: I think we saw data showing benefit as monotherapy in patients who couldn't take UDCA, although I think there was some discussion regarding more benefit in those who were on both drugs.

Dr. Silveira?

DR. SILVEIRA: I think the answer to this question is that the data presented was sufficient taking into account the amount of patients in clinical practice that are unable to tolerate UDCA. Even though we did hear in the open phase of at least 2 patients who don't tolerate the drug, it's typically 5 percent or less of the total population of patients with PBC. And actually, I'm pretty surprised at the amount of patients they were able to recruit for the monotherapy phase 2 study.

So my answer would be I think there's sufficient data to conclude that it can be used for monotherapy. I obviously would add that caveat that I do think these patients should still be included in the confirmatory study, as they predict, about 5 percent to be enrolled.

DR. RAUFMAN: Dr. Lipman?

DR. LIPMAN: I've got a question that I think probably fits well in here because I didn't get a chance to ask this morning. It seems to me there's a population of patients that we're not addressing, which are those who are tolerant to UDCA, but do not respond.

And I don't know how big that population is, but assuming that there are 50 percent, plus or minus 10 percent, who don't respond to UDCA, and I assume many of them are tolerant, I don't hear that that patient group is being addressed.

So I certainly think, unless my numbers are incorrect, that that patient group needs to be studied. And I would ask either the FDA or the applicant to comment on this patient population group that is not responsive but not intolerant to UDCA. Based on available data here, I think that as the question is asked, there is reasonable information that the patients who are intolerant to UDCA can get monotherapy, but they should be studied in the postmarketing phase 4 trial.

DR. DIMICK-SANTOS: So the enrollment criteria for the clinical trial were patients who -- I mean, the majority of patients in the trial, 93 percent, were non-responders or inadequate response to UDCA but tolerated it. So they were on UDCA during the trial.

DR. LIPMAN: Why continue a drug that's not working? I don't understand.

DR. DIMICK-SANTOS: That was a question that we discussed prior to the design of this clinical trial with the sponsor, and the experts -- there were several experts that were involved in that discussion. And they felt that even though patients might have an inadequate response to UDCA, almost all patients had some response to UDCA. And they felt that if they tolerated it and they had some response, it would be unethical to withdraw them from UDCA.

But that is something that we think probably will need to be explored in the future for patients who have a minimal response to UDCA, should they be withdrawn and get OCA as monotherapy. And I think that's a good question.

DR. RAUFMAN: Ms. Cryer?

MS. CRYER: Yes. I want to underscore Dr. Lipman's comments and put them into the context of shared decision-making and patient choice. We certainly heard from the public comments, from patients who were non- or under-responders to this -- I'm putting my personal patient hat on, I would have been in that category, and I think it is subject to a

conversation and to consent into an arm for patients who might choose to stop taking a drug of minimal benefit.

I think that given the demonstrated efficacy of OCA as monotherapy and the significant number of patients either intolerant or non-responding to the drug, I think the data that was presented should be used to move forward, and an additional study would be very welcomed I think by a significant portion of the patient population affected.

DR. CHANG: Can I make a comment on that? I'm just curious on this 747201, that's the monotherapy study, where the patients couldn't be on UDCA for at least 3 months. But were most of those patients on it at some point found to not respond, and that's why they weren't on it anymore. So maybe that is the patient population we're talking about.

DR. DIMICK-SANTOS: I believe those were patients who were intolerant. But, Linda, I will allow you all to answer that question.

DR. RAUFMAN: Can I also ask, if you could tell us what percentage of these patients are

intolerant and what is the nature of the intolerance?

DR. ROBERTSON: Yes. Dr. MacConell, could you come up to speak to, within the 301 study, which patients were intolerant and what the nature is. And then we can also speak to the 201 study.

DR. MacCONELL: Yes. So in the phase 3 study, there had to be evidence in the patient's medical history that they had at one time been on UDCA. And then, of course, they could not have been on UDCA for a given period of time before study entry. In the phase 2 study, it was a little different. Patients were not to have been on UDCA for the prior 3 months prior to enrollment, but we didn't actually collect information as to why they were not on UDCA.

DR. DIMICK-SANTOS: But I believe intolerance is mostly gastrointestinal intolerance and sometimes weight gain.

DR. RAUFMAN: Maybe Dr. Jones could comment on intolerance.

DR. JONES: I think there were some really important points made about decision-making and patient choice. Intolerance, in our experience, is usually GI

disturbance. So it is a sense of sickliness with the tablets. And as the doses of UDCA have gone up with an optimal of 13 to 15 milligrams per kilogram, so pill burden has gone up with that, it's a bile acid, and bile acid at a fairly high dose, and they are gastric irritants.

So for most people, it's also bile habit or a sense of sickliness that never quits settles down. And you can adjust dosing and help people with that, but some people never get over that.

Hair loss we do see in a small number of people. That's a relative minority, and amongst women in particular, that could be an issue, and then weight gain, we often see. But the people who are unable to take the tablet, it is usually because of GI disturbance. Now, the reality is people will make a decision about whether to take it based on their perceived value from it.

So intolerance is associated with the perception it's not working because people don't feel that there is a trade off. So this will be a question which will crop up as time goes by. And I have been

asked that question before around pill burden, that if I've been in a trial -- and I think of a patient in the 301 trial who had a normalization of LFTs on the trial, whereas previously had no benefit whatsoever with UDCA, I ask the question why am I still taking 15 tablets a day when you tell me it doesn't work?

So I think that question will come up in practice. And we were advocates of the monotherapy trial at the beginning, and I think it is an important area. But it's mainly GI disturbance in the context of patients perceiving they're not benefiting, in my experience.

DR. RAUFMAN: Thank you. Dr. Lipman?

DR. LIPMAN: Could you just, Dr. Jones, clarify how many patients are able to tolerate, however you define tolerance, but don't have a response, however you want to define response?

DR. JONES: Sorry. I didn't quite catch that.

DR. LIPMAN: How many patients are tolerant to UDCA, however you want to define tolerance, but do not have a clinical response to UDCA, however you want to -- an outcome benefit or a surrogate outcome

benefit, however you want to define that? What is the percentage? I mean, is it 4 percent or is it 50 percent?

DR. JONES: In my experience, the people who have no benefit that's measurable at all -- and I take the point absolutely about variable benefit -- it is around 10 percent of patients that have no change biochemically, and then about 20 to 30 percent of patients have an improvement. But it's not at the level that we've defined as response.

The issue that worries me is that that vast pattern of no response at all is very characteristic of the younger patients, and that's the concern.

DR. LIPMAN: Isn't it appropriate to study this population with -- I mean, again, my question is why continue a drug that doesn't seem to work, and shouldn't that population be studied with a monotherapy of OCA? Yes?

DR. JONES: Scientifically, yes, I think that's a very important question.

DR. MARATHE: I have an important point to make here. Actually, the UDCA was approved with

clinical outcomes, betterment in clinical outcomes. So based on something that we have seen in just ALP response, it will be very difficult to suggest to the patient that you can abandon UDCA and just go on taking this new drug, which may or may not have long-term outcome consequences. I think that's a very important point to make.

DR. RAUFMAN: Dr. Proschan?

DR. PROSCHAN: I mean, it's always hard to be able to say, well, does it work in this subgroup or that subgroup. But the FDA's slide number 36 sure does look consistent. I mean, it's 38 percent responders versus 4 percent in the monotherapy. And in the combination, it's 41 percent versus 5 percent.

So that's about as consistent as you can get. It doesn't prove anything, but there's no evidence to suggest that the effect is differential, depending on whether they're also receiving UDCA.

DR. RAUFMAN: Please?

DR. ELLENBERG: I would certainly say that further study is needed in the monotherapy as well as the other indication. But an obvious way to study the

question that Dr. Lipman raises is to include somewhere a randomization after a certain period of time of people who are not responding to either continue or not continue. And then you would be able to see whether there might be something worthwhile.

DR. RAUFMAN: Again, if I could bring this discussion to conclusion, what I'm hearing -- and the question was raised to the FDA earlier about whether we should consider before or after approval. I think what I'm hearing is that the panel feels that there is sufficient evidence to go ahead with monotherapy, but that it does need to be studied and also in stratified populations those that don't respond as well as those that are intolerant to urso.

Does that seem like a reasonable consensus?

(No response.)

DR. RAUFMAN: So discussion question 4, discuss the adequacy of the data to support the use of OCA in moderately advanced and advanced stages of PBC. Include in your discussion whether the applicant should be required to further study the use of OCA in moderately advanced and advanced stages of PBC.

Dr. Sjogren?

DR. SJOGREN: So my answer to this question is that in the trials, people with advanced liver disease were not included. Therefore, it's kind of hard to come up with a decision, say, use it, even though later on, we saw that there were doses, weekly doses or biweekly doses, in people with advanced liver disease.

I shudder to think that I would do that without good evidence that I was not going to get in trouble and the patients were going to be hurt, especially because there were side effects with bigger doses, with 50 milligrams. But in one year spent, to go from early or moderate PBC to bleeding varices, to encephalopathy, to major decompensation, what was the mechanism of action for that? I think we need data to be able to really justify using it in advanced cases.

DR. RAUFMAN: Dr. Silveira?

DR. SILVEIRA: Marina Silveira. So I think there are a couple of issues here. One is that there is data, but there's a little bit of discrepancy between the nomenclature used by the applicant and by the FDA. So there are a couple different criteria.

The biochemical criteria, also known as Rotterdam criteria, is what's alluded to in this question, the moderately advanced and advanced stages of PBC, and that's where my earlier question came from.

So for the FDA, about 10 percent of the patients in the phase 3 study were at least moderately advanced. None of them were advanced stages of PBC. So there's limited data that support, but there is some data. It seems like these patients did respond just like the early biochemical stages of disease.

There's also different criteria used by the applicant, where they included advanced disease patients. They quoted that as about 30 percent, and that was predominantly based on transient elastrography and other clinical aspects of classifying the patients. Again, data there is more limited, but in 30 percent of the patients, they did seem to show adequate response with the treatment was in that one year and long-term extension.

There's really very, very limited data if you're looking at cirrhotic patients with moderately advanced disease, meaning Child-Pugh score B and

advanced disease score C. Those were not included in the phase 3 study. They were only included -- patients were included in a phase 2 trial. The data was not presented. And those patients were not patients with PBC. They were patients that had alcoholic cirrhosis, portal hypertension. So that is the population where those studies were limited for advanced liver disease by different criteria for what this question is asking.

DR. RAUFMAN: Dr. Conjeeveram?

DR. CONJEEVERAM: I think we're very clear about the terminology, and I think when you use the word "advanced, moderately advanced," in general as clinicians, most people think they start that once you have cirrhosis. Obviously, that's not what we are talking about here. You're talking about biochemical data.

So I think whatever the recommendation is, you need to be very clear that these are cirrhotic versus non-cirrhotic patients. Otherwise, I think it's going to be very, very misleading because we really don't have much data at all on cirrhotic and moderate and advanced cirrhotic patients to make any recommendation

at this time.

So I think we need to be very, very clear on it. We're talking about patients where most of them are not cirrhotic. Clearly, that needs to be studied. I think the question is any of these drugs. We use Ursodiol in patients who already have developed cirrhosis with the hope that it may delay progression. Clearly, that needs to be studied with this drug as well, so I think it's important.

Even the assumptions that the FDA made is really based on assumptions. The whole thing about twice a week, three times a week, I think we need to be very careful when we make these recommendations. We're making recommendations based on, really, not much data that we have. So I would be a bit cautious. But the data that's been shown so far based on the biochemical data, although small numbers, at least a trend seems to be very similar to "the way we think of very mild disease."

DR. RAUFMAN: Dr. Lipman, I think you had your hand up.

DR. LIPMAN: I think that we ought to at least

keep in the background the real-world scenario, is that if this drug is approved, it's going to be used in all-comers. It doesn't matter what requirements are suggested or the limitations are suggested. It's going to be widely used.

So I think that to answer this question, there is really very limited data in moderately advanced or advanced disease, and the applicant should be required to provide more data because if it gets approved, it's going to be used widely. And I think it's going to be very difficult to get the data after it's approved.

DR. DIMICK-SANTOS: Dr. Raufman, the FDA does have the option of putting a limitation of use in a labeling, which would tend to make insurance companies not let you have it. So we could take an option of putting the limitation of use for patients with cirrhosis. So my question to the panel would be, would you recommend that we limit patients with cirrhosis from getting this drug except under a clinical trial?

DR. LIPMAN: I would certainly agree with that.

DR. RAUFMAN: I think that's the consensus I'm

hearing, too.

MS. CRYER: I prefer to leave it to the discretion of physicians and patients. But I wanted to answer an earlier point.

My initial comments, which Dr. Assis actually cleared up so well in terms of the scope of the data used and the difference between the percentage of moderate and severely ill patients in the larger registry versus in some of the trial data, I think that Dr. Chang and Dr. Vos made really fantastic points throughout this meeting about the need to be able to look at the different effects stratified by severity, including hepatic impairment and hepatic toxicity.

So I would say that we do need additional study on moderately advanced and advanced stages of PBC patients.

DR. RAUFMAN: Dr. Silveira?

DR. SILVEIRA: Again, I think this comes back to nomenclature because even patients with cirrhosis, there's a spectrum, so there's compensated or early stage cirrhosis, which are typically the Child A cirrhosis, and then there's what we're calling

moderately advanced cirrhosis, Child B, and then advanced cirrhosis, which is Child C.

So I think to put a limit on all cirrhosis might not be the right answer here. This phase 3 study did include patients who had a histologic diagnosis of cirrhosis. Those were about 10 percent of the patients. And actually, in fact, it was a greater number than patients with monotherapy, and we just all agreed that we don't need to limit those patients with monotherapy because there was enough evidence.

Plus, there it did show data that some other patients that they classified clinically as having cirrhosis, that makes sense even though they didn't have a biopsy. So it does seem like they have about 15 percent of the patients that were enrolled that had early stage cirrhosis and had a response just like the rest of the earlier non-cirrhotic patients.

So I disagree with limiting it to all cirrhotics, but again, once again, I emphasize that there was no data on the decompensated cirrhosis or the Child B and C for PBC.

DR. RAUFMAN: Dr. Robertson?

DR. ROBERTSON: I thought it might be interesting and useful to show some of the data we have in cirrhotic patients. It is limited, as you said, but it might be useful in your deliberation.

I'd like to start with the safety first because I think that's probably the most concerned. Dr. Hooshmand-Rad?

DR. HOOSHMAND-RAD: As my colleague has mentioned, the data that we have is somewhat limited. However, it might be of value for the committee to see these pieces of information.

First, I'd like to start with a summary of the serious adverse events that have occurred in patients with cirrhosis. Slide 3 up, please. Indeed, what we have observed is that patients who have had cirrhosis have continued, it appears during the course of the study, to progress. And the serious adverse events that they have experienced appear to be also indicative of the progression of disease.

As I mentioned earlier during the core presentation, we have not observed elevations, critical elevations, of ALT and AST that are typically

associated with hepatotoxicity, and there was only a single patient in that trial, in that arm, that experienced such elevations.

Slide down, please.

DR. RAUFMAN: Before you take it down, just a point of clarification. These are episodes -- are these separate patients? In other words, we don't have a patient here who developed both edema and upper GI bleeding?

DR. HOOSHMAND-RAD: So for example, in the titration arm, there were only two patients who experienced such adverse events. One patient experienced both ascites, hepatic encephalopathy, and edema. And this was subsequent to a cruise, during which she acquired an infection and subsequently decompensated. The other is a patient who had an upper GI hemorrhage due to a variceal bleed.

Slide down, please. I thought it also useful to show a little bit of the efficacy also as a balance. And I'd like to follow with Dr. Hirschfeld to give his clinical perspective, too, on these patients since he has treated patients in practice.

DR. MacCONELL: Slide 2 up, please. So given it was a relatively small sample size about 9 percent of the overall patient population exhibited cirrhosis, and that cirrhosis is based on their initial diagnostic biopsies taken as part of the inclusion/exclusion criteria, rather than summarizing the data, I'm showing individual patient profiles given the small sample size. And this is the alkaline phosphatase over time for these patients.

So albeit a small sample size, the efficacy profile, based on these spaghetti plots, does appear to be similar in the subgroup of cirrhotic patients relative to the overall PBC population with clear improvement in their alkaline phosphatase levels in these patients.

DR. RAUFMAN: Thank you. So we'll get back to the discussion now. Thank you.

DR. HOOSHMAND-RAD: Okay.

DR. RAUFMAN: Dr. Assis?

DR. ASSIS: Just a quick point. I do think that getting the label, the type of terminology correct is very important, because as others have mentioned,

the clinical use quickly far exceeds what often people are familiar with. And I know those of us who are familiar with the Rotterdam criterion, and others might be quite knowledgeable about that, I think an average clinician in a hepatology or GI clinic will know about compensated/decompensated cirrhosis.

From a strictly personal point of view, I think in the absence of other data, I would be very hesitant to prescribe this to a decompensated patient. I think a compensated patient, more data would be necessary, but I would feel a little uncomfortable prescribing it to a patient with preexisting decompensation.

DR. RAUFMAN: Dr. Sjogren?

DR. SJOGREN: It was striking to me in the table that was shown that all these side effects of decompensation were people on drug, and they were zero on the placebo. The numbers are smaller and may be skewed, but it raises a question to me what's going on with these patients on the drug.

DR. CONJEEVERAM: I think we need to put things in perspective. We're talking about two

patients. That doesn't mean it's not concerning, but there's a natural history of cirrhosis as well, which these are patients -- if they were diagnosed with cirrhosis 10 years ago or 5 years ago, at some point, a certain percent every year will decompensate.

So I don't think we have enough data to say that the drug pushed it or it's safe at this time. We know most compensated cirrhotics actually do well with most drugs that we use, and we watch them, but it doesn't really stop us from doing it.

So I do agree with the others that if you have a well compensated cirrhosis, you should be able to use it. Once it gets into decompensated, we may have to define that, then there's really no data because this really doesn't address that. But compensated cirrhosis, I think it should be okay.

DR. RAUFMAN: Dr. Silveira, and then Dr. Lipman.

I thought you had your hand up. Dr. Lipman?

DR. LIPMAN: You've got a sample size of 11 patients treated. That's not enough to make any conclusions. I think all you can say is it needs

studying, and I personally think we're -- it's not productive to talk about complications, or efficacy, or anything else in this small sample size.

DR. RAUFMAN: Dr. Khurana, last, and then maybe I can bring it to closure.

DR. KHURANA: I agree with Dr. Lipman. I think the sample size is too small, and I think it should not be used in cirrhosis unless it's further studied.

DR. RAUFMAN: So I'll let that stand as the consensus because that's what I'm hearing, is that regarding the first point here, the data are inadequate at present, based on the small sample size, to support the use of OCA in moderately advanced and advanced stages of PBC. Hence, this should be studied further.

Comments?

(No response.)

DR. RAUFMAN: So we're half way through the questions, et cetera. Maybe we can take a 10-minute break, and then we'll finish up. So it is now 3:05. Let's resume at 3:15. And again, no discussion about this outside of the room.

(Whereupon, at 3:05 p.m., a recess was taken.)

DR. RAUFMAN: Let's reconvene. We just had some discussion, and it may be that we were actually answering question -- or discussing question 5 when we thought we were discussing question 4.

Question 5 is discussed whether the available evidence supports the FDA's proposed dosing of OCA in PBC patients with moderately advanced and advanced cirrhosis. I think what we were just discussing basically is that there is insufficient data to support treating these patients.

So if we go back to question 4, the issue here is was moderately advanced and advanced stages of PBC, which is a different question. Specifically, although it's not put here, it's not in the discussion point, it was the Rotterdam criteria that I think were being raised here.

Does anybody on the panel want to opine specifically now about moderately advanced and advanced stages of PBC? And after that, we'll go to question 6. We've answered question 5.

Dr. Silveira?

DR. SILVEIRA: Again, I reiterate what I said earlier. When talking about biochemically moderately advanced, I think there is sufficient data to support the use of the drug. It was a smaller population, but they were included in the study. No significant signals in terms of safety concerns, and they did appear to have a response.

Again, so moderately advanced would be the patient that has either abnormal bilirubin or abnormal albumin. And the advanced stage of PBC, based on biochemical criteria as in this question, would be the patient who had abnormal albumin and abnormal bilirubin. And there did not seem to be a large population of those number of patients included in the studies with that, who met that criteria.

DR. RAUFMAN: To rephrase that, you believe there are adequate data to support treatment of moderately advanced, but not advanced --

DR. SILVEIRA: Correct.

DR. RAUFMAN: -- stages of PBC.

Any discussion there? Does everybody generally agree with that?

DR. VOS: I'm not sure I saw enough to differentiate between those, given the small numbers of the both moderately advanced and advanced. To me, advanced is cirrhosis, which we just discussed. And I was concerned about --

DR. SILVEIRA: That's exactly why we're clarifying this. These criteria do not necessarily apply to compensated and decompensated cirrhosis. This is biochemical response. It's very specific to PBC patients. So it's defined as patients -- so early disease are patients with a good prognosis who have both normal bilirubin and albumin regardless of their histologic stage.

So some patients might have cirrhosis and might have both parameters to be normal and are considered early stage biochemically. So this is what these criteria are about. It doesn't necessarily mean cirrhotic or not cirrhotic, or advanced cirrhotic and early cirrhotic. It's just biochemical.

That's why I think there's a difference between this question and the next question. The breakdown was about 10 percent patients with moderately

advanced biochemical criteria, and they did not have any patients with biochemically advanced stage disease in this study.

DR. RAUFMAN: Dr. Conjeeveram, then Dr. Sjogren.

DR. CONJEEVERAM: And I think we also need to keep in mind that these patients, the way we're defining on this -- quite a few -- I don't know what percent, an overall small percent can be Child's class A cirrhotic. When we use the word "cirrhosis," all we know, based on all the information that was presented is where they had a biopsy that's documented cirrhosis.

I think it's important for us to recognize that just because it doesn't say cirrhosis, that they actually do not have cirrhosis, could well be this group may well include whatever the percent is -- we think it's small, but it's definitely patients who have Child's class A cirrhosis. Child class A cirrhosis, you can have a normal appearing liver, normal platelets, and that's well documented.

So I think when we're making decisions based on cirrhosis or no cirrhosis, I think we have to be

very cautious. The next question obviously addressed B and C, which is very obvious. And I think earlier in the discussion, we were talking about Child's class A, which could well be this. So I think we need to keep that in perspective.

DR. RAUFMAN: Dr. Sjogren, then Dr. Lipman.

DR. SJOGREN: So my plea to the FDA is to use nomenclature that we use in clinic. We use cirrhosis or non-cirrhosis. We use Child's criteria. Because to me, moderately advanced may mean one thing, and to Dr. Silveira, it may mean another thing, and to Dr. Conjeeveram would mean something else. So I think we need to be very clear based on what is in the literature and give guidance to the sponsor of these trials in terms of what patients should be studied.

This day and age, Fibroscan and other modalities to diagnose cirrhosis, that I think has to come into play as well if we are concerned about -- there patients that look absolutely compensated, but they have cirrhosis. So it needs a little bit more for sure to recommend one way or another. But I think we need to start with making a

uniform distinction of these patients based on the nomenclature.

DR. LIPMAN: I assume we're talking to question 5, not 4. We're on question 5, not 4, or we're back in 4?

DR. RAUFMAN: The sense was that we hadn't really addressed question 4; we had addressed question 5 previously. So I just wanted to --

DR. LIPMAN: Well, I still feel quite strongly that -- or think quite strongly that we're talking about a set of -- the data set of 11 patients, which is insufficient to draw any conclusions, yay or nay, despite what people think in clinical practice. We're advising the FDA based on the data that's presented to us, and the data is insufficient to draw any conclusions.

DR. RAUFMAN: Dr. Silveira, you were in favor of treating moderately advanced. Did you want to --

DR. SILVEIRA: What I would like to comment with regard to that is not all of the patients will have biopsy in clinical practice. It's not required for a diagnosis of PBC. So we will frequently see

patients who are cirrhotic that don't have a biopsy, and all we have to go by is their biochemical information.

Like we all know, some patients with compensated cirrhosis will have normal albumin levels and will have normal bilirubin levels. So it is more than possible that some of these patients who, again, are on other slides that showed response and tolerated this with no safety issues, were cirrhotics but were just not diagnosed with that biopsy.

So I think it's harder to restrict that population of patients based on 9 patients who had a biopsy. There's other criteria that are used in clinical practice for diagnosis.

DR. RAUFMAN: Dr. Dasarathy?

DR. DASARATHY: You know, even if you don't have a biopsy, if you suspect cirrhosis, we still are obligated to do screening endoscopies. We're obligated to do screening for hepatocellular carcinoma. So there has to be some way to say whether they are cirrhotics or not because it's not just treating for the OCA or anything else. It's also managing cirrhosis, which is

standard practice.

DR. SILVEIRA: Oh, no, absolutely. Patients with cirrhosis should be treated differently. What I was trying to say is that there are some patients that have normal scans, so you can get a CT scan, and they have a normal appearing liver. They have an endoscopy for a GERD reason, and then you know they don't have varices. And their albumin is normal and bilirubin is normal, but if you got a biopsy, you'd find out they're cirrhotic.

So I'm just saying that there are some patients who have completely normal markers, and it's just an unsuspected cirrhotic patient that you might have in front of you.

DR. RAUFMAN: Let me see if I can now bring this to consensus on 4 and 5. Regarding Child's B and C cirrhosis, I think there is a consensus that there's insufficient data and that more studies are needed. Go back to 4 for a second. Regarding moderately advanced and advanced stages of PBC, I think there is some controversy around the table. There were some that feel that there is sufficient data to treat moderately

advanced but not advanced. There are other members of the panel who feel that there is insufficient data to treat either moderately advanced or advanced.

Is that a fair consensus, summary?

DR. DASARATHY: I'm sorry, Jean-Pierre. I'm still confused. What is advanced? Is it fibrosis? Is this biochemical advancement? Are you going advanced as MELD, going advanced by Child? This question is a little odd.

DR. RAUFMAN: Again, it's Rotterdam criteria. It would be nice to have the Rotterdam criteria in front of us.

DR. SILVEIRA: The Rotterdam criteria, the early stage, biochemical stage, are patients who have both normal bilirubin and albumin levels. The moderate stages would be patients who have either bilirubin or abnormal albumin. And the advanced stage would be patients who have both abnormal albumin and bilirubin.

DR. DASARATHY: How would you classify Child's class A --

DR. SILVEIRA: That's a difference -- again, if your Child A has a normal albumin and a normal

bilirubin, that would be an early biochemical stage within Rotterdam criteria.

DR. EGAN: Amy Egan from the FDA. Just to clarify, Rotterdam criteria were prespecified in the protocol that the sponsor submitted for staging of the disease. It was also part of their statistical analysis plan. It is also part of the Lammers paper that uses Rotterdam criteria for staging of PBC. So that's why we have used these criteria.

DR. RAUFMAN: Go ahead.

DR. MARATHE: I would like clarify regarding question 5. Actually, this addresses hepatic origin not biliary origin. For example, from chronic viral infections or abuse of alcohol, Wilson's disease, hemochromatosis, or fatty liver. And that's the population that we are looking at when we are talking about question 5, not really biliary origin.

DR. RAUFMAN: I think we've addressed -- I'd like to see question 6.

(Laughter.)

DR. RAUFMAN: Discuss the pros and cons of continuing OCA treatment in patients who do not

demonstrate reduction in alkaline phosphatase after 6 months of treatment on a maximally tolerated dose. Take into consideration the risk of alterations in lipid profile versus the potential for benefit.

Dr. Lipman?

DR. LIPMAN: Could I ask for some data from the applicant? Because we basically have mean data, and we don't have any individual data. So I'd like to know are there any patients who show response after 6 months. If they're not, then it doesn't make sense to continue, like I think it doesn't make sense to continue UDCA if there's not a response. If they're patients who respond after 6 months -- or who respond between 6 months and 12 months, then we need to see that data.

DR. ROBERTSON: Dr. MacConell, could you speak to the data we have around patients who did not have a response at 6 months and subsequently responded?

DR. MacCONELL: I can, and it's sort of a complicated question and answer because it depends on what type of response you're looking for at 6 months. So we did this in a variety of ways. If you

specifically look at patients that showed absolutely no response in terms of alkaline phosphatase lowering, so no change from baseline in alkaline phosphatase at month 6, they still had a 35 percent likelihood of a 15 percent improvement in alkaline phosphatase by 12 months.

DR. LIPMAN: Is that 35 percent of patients or 35 percent probability? I'm looking for actual patient numbers rather means.

DR. DIMICK-SANTOS: And is that the titration arm, or the 10-milligram arm, or a combination of both?

DR. MacCONELL: That was the titration arm, and that's a 35 percent probability. And that's based on observed data in the study.

DR. DIMICK-SANTOS: So is that the patients who titrated up from 5 to 10 milligrams?

DR. MacCONELL: Those are patients -- all the patients -- yes, that's correct. No. I'm sorry, no. Those are the patients that remained on 5.

DR. DIMICK-SANTOS: Okay.

DR. ELLENBERG: How many patients are there in that group?

DR. MacCONELL: We might need to pull the statistician up because this is a probability analysis based on the observed data. So we don't actually have subject numbers.

DR. SJOGREN: So are you suggesting that maybe 12 months is a better time to make the decision whether to stop the drug or not, to give a chance to those patients?

DR. MacCONELL: That is exactly what we're suggesting, yes.

DR. MARATHE: If you can pull up my slide 21? Yes, the presentation. There are those patients who were on 10-milligram OCA, that is after titration. After 6 months of titration, you see that some of those patients have change in ALP from baseline or just 5 percent. One patient actually has increase in ALP from baseline as compared to -- at 12 months. That means at 6 months on the maximum tolerated dose. So there are some individuals actually who do not respond ALP-wise.

DR. RAUFMAN: Summarize the bottom line on this slide for me.

(Laughter.)

DR. MARATHE: So what I'm showing is that there are some subjects who in spite of up-titrating to 10-milligram dose, they do not show enough ALP response. The ALP response is very marginal.

DR. CHANG: I think you have to look at the red open diamonds. And if you take the X-axis, you go to zero, between zero and anywhere less than 15, minus 15, and you look up, the people that actually have some reduction at 12 months, that's the people who didn't respond at 6 months but did respond 7 months -- 12 months. And there's a handful. It's not that many, but there are some.

You don't have a circle around it. That's probably where I would have put the circle. You know what I'm saying? So the X-axis is your change at 6 months, and Y is at 12 months.

DR. MARATHE: Right.

DR. CHANG: You can see the people at zero or less than minus 15. And if you go up, you'll see the people that are below zero. So the people under the line are the people that actually improved at 12 months that didn't improve at 6 months.

DR. RAUFMAN: So in using these data, are you arguing that there is insufficient benefit to going longer than 6 months?

DR. MARATHE: What I'm suggesting is that there are subjects who may not improve in terms of ALP in spite of having 12 months on therapy with 6 months of maximal dose. They will not show response of ALP.

DR. RAUFMAN: Dr. Ellenberg?

DR. ELLENBERG: So one thing about surrogate endpoints is that you worry that they may be showing a benefit that is really not there. But the other thing that can happen is that they may not reflect a benefit that's there. There may be some other mechanism of the drug that's causing something that's not modulated through the surrogate. And there are examples of that less fewer than the other way, but there are some.

So I don't know what the mechanisms are here, but if there's any plausibility to the possibility that even if they don't get a nice ALP response, they might still be benefitting, then it would seem reasonable -- I think we talked about this before -- to actually study to see whether it's worthwhile. You

could randomize people at 6 months if they haven't had a response and randomize them to either continue treatment or stop and see whether there's a difference. That would really be the only way to see whether there could be benefit.

DR. DIMICK-SANTOS: Alternatively, you could compare them to the placebo arm.

DR. MEHROTRA: Nitin Mehrotra, team leader, Division of Pharmacometrics, OCP. I just wanted to clarify the question we are asking. We are not saying treat the patient on OCA for 6 months and discontinue. What we are saying is you treat a patient on OCA for 3 months, and then if it needs up-titration, then you will additionally treat a patient for 6 more months on a stable dose. Then if the patient does not respond, should we continue or discontinue?

I think that's the question. It a 6-month treatment on a stable dose, which will mostly likely be the higher dose.

DR. RAUFMAN: But isn't that what these data address? Isn't that what we're looking at, 5 for 3 months and then 10 for 6 months?

DR. MEHROTRA: This data is suggesting that it is premature to discontinue patients earlier than 6 months on their stable dose. What we are asking is if a patient is not responding even after 6 months, after titration, should we continue patient further? I think that's the question.

DR. RAUFMAN: Dr. Silveira?

DR. SILVEIRA: I have a few comments, and I'd like to echo Dr. Ellenberg's comments. We're using a surrogate marker, and we agreed with alkaline phosphatase because most of these patients have early stage, but there can be beneficial effects on bilirubin and other markers and other mechanisms of improvement.

So I think that as long as the patients are tolerating the drug and are not having any safety issues, it might be premature to discontinue after 6 months of not having an effect. The data that they showed, some patients who remained on 5 milligrams without dose change still had further improvement after more than 6 months.

Looking back at the urso studies, even though also most of the patients respond with weeks, months,

most of which will be between 6 and 9 months, their data came later on, that patient's going to continue to improve up to 2 years and even up to 5 years while continuing on urso despite a suboptimal response initially.

So if you look at the criteria for response -- for example, one of the first ones, Mayo 1 or by Dr. Angulo, was based on 6 months of therapy, but some of the Toronto criteria are based on 2 years of therapy. So that can be something that we won't find out until later. It might be really premature right now to recommend discontinuation of drug after 6 months of therapy.

Again, it comes to that consensus of what is the criteria for response. We looked at how several small improvements in alkaline phosphatase for an individual patient might reduce their risk of having important clinical outcomes. So even though there's this nice discussion about 1.67 times or 2 times, if you look at the PBC Global study data, almost any level of alkaline phosphatase will change -- changes in alk-phos levels for every threshold can lead to different

clinical outcomes. So it would be also hard to premature, to just pick a random threshold for non-response and discontinue within 6 months.

DR. RAUFMAN: I'm reading this question as no reduction in alkaline phosphatase, not a small reduction, but no reduction. And I'd ask you, would you stop at 12 months if there was no reduction in alkaline phosphatase?

DR. SILVEIRA: Again, I think that's tricky because of it's a patient who had a normal bilirubin and continues to have a normal bilirubin, or if it was a patient who had an abnormal bilirubin and has a normal bilirubin but their alk-phos is the same, it would be really hard for me to discontinue that drug even without a marked improvement in the alk-phos.

But I think we're also talking as a group here, we're talking about how we need more data, long-term use of this drug. I think it's hard to be encouraging. And again, in an individual patient if they're having safety -- if there's any concern about safety or they're not tolerating the drug, that's completely different. But I think if we want to gather

long-term data of treatment, it will be important to have these patients continue on therapy.

DR. RAUFMAN: Dr. Conjeeveram, and then Dr. Lipman.

DR. CONJEEVERAM: I think as we try to answer this question, there are two issues. One is the stopping rules that we are talking about, and I don't think we have data to go either way, but for now continue. But keep in mind, the older studies, they all had biopsy endpoints, so we do have that information.

So on one side, we don't want to assume that if there's no biochemical response, some of them will have it, but it definitely needs to be studied. So I think when we try to answer this question, if we don't have a stopping rule, we have to say we do need the answer for it, how do we measure, really, a non-response. And I think it comes back to the sponsor to define that at some point.

We don't have enough data now to say that we can stop it because some of these patients may be having benefit. As long as they're tolerating it, we

can argue to continue it. But at the same time, you still need an answer to the question, when do you actually stop for refractory, and that needs to be clearly studied. And I'm assuming, everyone is calling it the same thing, but we're kind of talking about it in different ways.

DR. RAUFMAN: Dr. Lipman, and then Dr. Proschan.

DR. LIPMAN: I would just repeat, we're dealing with a study that's dealing with surrogate outcomes. And at least from my view, it's a candidate surrogate outcome. I would also point -- and I think that there's data that the company has that they should be able to provide. If not now, then later to the FDA, which may help inform this decision. And I would also point out the risk of alterations in lipid profile is just another surrogate outcome. It's not a clinical outcome.

DR. RAUFMAN: Dr. Proschan?

DR. PROSCHAN: A couple of points. It seems like, first of all, the HDL effects are probably going to take a long time to have any consequences, I would

think. And you'll be able to measure their HDL on individual patients. So maybe you take that into consideration along with the change in ALP to make an individual decision seems logical. I mean, if there's no decrease in HDL, then maybe you would continue them on it. If there's a dramatic decrease in HDL, maybe you'd say, well, no, it's not worth it.

MS. CRYER: Dr. Victor Montori speaks beautifully on minimally disruptive health care. And as a patient who's surprised that she doesn't rattle when she walks, I really want us to think about not being cavalier about keeping patients on medications when there's no clear benefit that they're working.

I agree that we should try to find if there is some benefit at 6 months or 12 months, but we do need a real stopping rule. And if we are concerned about a patient's lipid profile, perhaps a statin or some other drug is more appropriate. But just to keep a patient on a drug for some hoped for benefit that we haven't defined really doesn't do the patient a great service and I don't believe is in the best practice of medicine.

DR. SJOGREN: So it weighs my mind that there are patients that are helped in the second 6 months. So I couldn't stop the drug then knowing that I haven't given them the entire chance of responding. And given that the side effect profile of the 10 milligrams, 5, 10 milligrams is acceptable, I would favor continuing on and stopping at 12 months if indeed there is no -- unless, of course, if something else intervenes and the patient decompensates or something else happens, then it's always that I have to stop. But other than that, I think I would like to give them the benefit of the second 6 months and see then, at the end of the year, if I need to stop or not.

DR. RAUFMAN: Perhaps we can then take that as a near consensus. I think there were some people around the table that may not agree, but I've heard a few people now use 12 months as a trial period, and that if there's no response by the end of 12 months, then the drug should be discontinued.

Is that fair?

(No audible response.)

DR. RAUFMAN: So the next one is the voting

question, I believe. We'll be using an electronic voting system. Once we begin the vote -- and the buttons are on your microphones -- the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote and well until I read the question before you vote.

If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner. Well, there's only one voting question.

Any questions about that before I read the question?

(No response.)

DR. RAUFMAN: This is question 7. Taking into

account the risks and benefits of OCA and the populations studied, is there substantial evidence to support accelerated approval of OCA for the proposed indication, based on its effect on alkaline phosphatase?

So please vote yes, no, or abstain.

(Vote taken.)

DR. HONG: Question 7, we have 17 yeses, zero noes, and zero abstain.

DR. RAUFMAN: Okay. Let's go around the room. I think Dr. Proschan, you're the first voting member on that side.

DR. PROSCHAN: Yes. I voted yes. I do have a concern about using surrogate endpoints, and it would be better if we had more data like if the observational studies had both people who were taking OCA and people who weren't, that would have strengthened it. But I think we don't have that obviously.

So to me, I was persuaded that the evidence was strong enough, and I'm relying on the medical experts as well to convince me that it has an impact.

DR. KUMAR: So there isn't a negative safety

signal here. The disease condition warrants something, a therapy, given the long-term sequelae of this condition, which is fairly morbid and has a high mortality that warrants approval. So the pros and cons balance out.

DR. RAUFMAN: Please remember to state your names when you --

DR. KUMAR: Atul Kumar.

DR. RAUFMAN: Thank you.

DR. SJOGREN: Maria Sjogren. I welcome this drug in the clinic, and I think it would be a great addition to many patients. I just have a caveat that we have discussed at length about the people with cirrhosis that needs to be studied further. But other than that, I'm in agreement.

DR. SILVEIRA: Marina Silveira. I think there's an unmet need. Alkaline phosphatase is reasonably likely to predict clinical benefit, and there's no significant safety or tolerability concerns with the current dose proposed. I do think that there are more studies that are going to be needed to be carried out before full approval.

DR. CONJEEVERAM: Hari Conjeeveram. I voted a yes as well, based on all the information that was presented, all the discussion we had, with the hope and faith that -- I think this is just the beginning of much more work to be done with this drug because I think we're kind of limiting to what it's being used for, but it may have other potentials and also at the same time long-term safety issues as well, which we don't want to ignore. And hopefully that will be studied.

MS. LUPOLE: Patricia Lupole. I voted yes. There's potential here for patients who haven't had much hope, and I look forward to more safety data to expand its use.

MS. CRYER: Donna Cryer, patient representative. I voted yes. I'm certainly grateful for the innovation here that had not been present in almost a quarter century since I was diagnosed initially with this condition and look forward to additional innovation and study, and certainly thank the FDA and the chair for so well incorporating the patient voice in this process.

DR. FEAGINS: Linda Feagins. So I voted yes. And just considering all the data that we've discussed today and weighing the risks and benefits of the medication, especially in the setting of patients with PBC, which have limited treatment options, I think it's very reasonable to go forward, especially since we're going to have phase 4 data coming out as well. That helps make me more comfortable to vote yes.

DR. LIPMAN: Tim Lipman. I did vote yes because I think it meets FDA's requirements based on rare disease, difficult disease. And a use of the surrogate outcome, I think that this is a candidate surrogate outcome at best.

DR. CHANG: Lin Chang. I voted yes, and I agree that it fulfills an unmet need. I can definitely hear what the patients were saying today, this afternoon. I appreciate that. This drug shows efficacy over placebo, whether you use the applicant's primary endpoint, use the FDA's proposed stratified endpoint, or the risk score. So I think it definitely showed efficacy.

DR. RAUFMAN: Jean-Pierre Raufman. I voted

yes for all the reasons you just heard.

DR. KHURANA: Sandeep Khurana. I voted yes. Obviously, my recommendation to FDA would be, clarified earlier, regarding its use in cirrhosis and the monitoring of HDL.

MS, BELL-PERKINS: Elizabeth Bell-Perkins, consumer rep. I voted yes for all of the reasons that both clinicians and patient representatives pointed out. I think it meets all the criteria, that specific question of going forward with accelerated approval. Thanks.

DR. VOS: Miriam Vos, and I also voted yes for all the reasons that have been stated.

DR. ASSIS: David Assis. I voted yes. This is a rare disease, and I think accelerated approval is appropriate in this case. I would definitely put the onus on the applicant and the FDA to publicize in addition to perform the subsequent studies so that researchers and clinicians can help to define the cohorts that will benefit the most. And I think education will be very key in looking for safety and efficacy signals moving forward.

DR. DASARATHY: Dasarathy. I voted yes because the data that was reanalyzed, where the FDA showed the same conclusion, that it's effective.

DR, ELLENBERG: Susan Ellenberg. I voted yes, although I want to say it was not just because of the effect on alkaline phosphatase. I feel like we could have seen that effect and seen other things that might have made us more cautious. It seems to me that the potential benefit here, which remains to be established clinically, would outweigh the potential risks that we see. So I look forward to hearing about the results of future studies.

DR. RAUFMAN: Thank you. So we have one more discussion point. This is the last discussion point. Discuss what, if any, changes in the enrollment criteria or design of the postmarketing confirmatory trial would be necessary to obtain any additional information that you think is necessary for full regular approval of OCA for the treatment of PBC. Alternatively, discuss what additional postmarketing studies you think would be necessary to obtain any data or information that has not been provided.

Go ahead.

DR. PROSCHAN: I think in the description -- this is Mike Proschan. In the description of the postmarketing study, it wasn't mentioned that they're going to be combining some historical control data with the regular control data. It wasn't mentioned here today I don't think. It was in the briefing materials. That gives me great concern. I think that almost always is disastrous to try and rely on historical control data. So I have a lot of concern about that postmarketing design.

DR. RAUFMAN: Dr. Ellenberg?

DR. ELLENBERG: Yes. I'm not sure I exactly understand what the status of -- I thought I understood from the applicant that this study started in February 2015, but then I heard from the FDA that the design of the study hasn't been firmed up yet. So I don't really understand what the status of this study is. And if it's been ongoing for over a year, what are the possibilities of suggesting changes.

DR. ROBERTSON: So the study was indeed started in 2014, however, it's a Global study. We

needed to get concurrence with the EMA about the study design as it will be satisfying a confirmatory -- a conditional approval in the EU, and it's across many different countries. There's 170 sites globally across 28 countries. That takes quite a while to start.

So we have started the study. Seventy-three patients have been randomized during screening. But as FDA mentioned, we are in discussions with FDA, and that's the reason this question is here, about is there a modified design, are there protocol amendments we could make to make it a stronger post-approval commitment study.

MS. CRYER: Well, since there are 5,000 patients in the Global PBC study, how closely are -- it seems like FDA in the past has encouraged the sponsor to work very closely with that group to boost enrollment and to diversify the number and type of patients in that study. How closely are they working with that group moving forward?

DR. DIMICK-SANTOS: That has to be answered by the sponsor.

DR. ROBERTSON: Perhaps we can talk a little

bit about the work that's been done to date and the design of the study. I'd like to have Dr. Bettina Hansen speak a little bit to the PBC study group. But she's the late investigator there, and she can talk about how we've been working together in terms of the historical control.

I would like to clarify that the study is designed with the placebo control, and it's only in the event that placebo cannot be maintained are we looking to multiple controls.

DR. HANSEN: Yes. The design indeed for the phase 4, of course is on discussion, that's for sure. But we did decide in that sense that they discuss with me and Global PBC study group members.

Can I have slide 2 up, please? Just to show you the slide that was also shown to the core presentation, these are all the centers that are involved in the Global PBC study group. And of course, these data are retrospective, and that means that they go long back. And these patients, some of them have been diagnosed in '85, so really a long time ago, and they are retrospectively in the data sets.

What we do have very well described in the database is of course the clinical endpoints and also decompensation and HCC [ph]. We also have all the lab values across all visits in the database as well. And we hope with the database like this today -- and also we are increasing the database at the moment and also collecting extra additional data to calculate the MELD score and the Mayo score.

We hope that we are able to generate an historical control with this population. And in case that is necessary, that we could use this historical control with sort of weighting -- the probability of treatment weights, that we could use these in the case that it's not possible to do the phase 4 trial. Thereby it says also that Intercept does not have our database, but the FDA does have the database. So I think it would be something that we would talk with the FDA about as well.

DR. ROBERTSON: As a point of clarification, it was clear before, but because of confidentiality with the different study sites involved in the PBC study group, the sponsor was not privy to the database

but was party to the analyses. FDA, we were able to negotiate getting access to the actual database through work from Dr. Bettina Hansen.

The other study group, as you were interested, I think it's important to note that a UK-PBC group is also quite involved, and obviously they have an interesting historical database that's both prospective and retrospective.

DR. JONES: The question was about how we can all work together to boost recruitment. Global PBC is a historic data set to find out what happened to people in the past, whereas UK-PBC is a prospective study and a trials platform with something like 7,000 patients consented to be approached about participating in studies. And it was designed to precisely allow us to do stratified therapeutic studies by making people within that cohort aware of the trials and then to give information to allow people to come into the study if they're interested based on their baseline characteristics.

So we know within the UK who potentially meets the criteria for enrollment to a particular trial

design. It's been established and funded by the MRC in the UK to precisely allow us to do that.

There is also a move in Europe for a structure, a series of structures called European in reference networks, which take that model out on a Europe-wide basis to develop centers that will identify people and characterize and phenotype them, ready to be recruited into studies. So we set UK-PBC up for fortuitously to allow us to do these sorts of trials prospectively.

DR. DIMICK-SANTOS: I just want to make a comment that the FDA does not have access to all of the data sets from the Global PBC study group. We don't have the original source data sets, but we have the analysis data sets. But we had enough to work with to do this analysis that we did.

DR. RAUFMAN: Dr. Lipman?

DR LIPMAN: As a clinician who is very interested in clinical study methodology, I am very concerned about the possible risk of bias. I think that certainly, as was mentioned down here, the use of historical controls is a non-starter, and that makes

that a low-quality study if that's what we're talking about.

Two, changes in protocol as the study goes on are always problematic. And three, I'd be concerned that the fact if the medicine is approved, which I assume it will be, then I think there's going to be a disincentive to people to participate in clinical trials, especially in which there's a placebo arm. And that's going to be very difficult to recruit patient because I think that -- I mean, we've already heard around the room that clinicians are looking forward to the drug so they can use it in all their patients. I don't think that there's going to be an incentive to randomize patients to clinical trials. So that does then limit us to historical controls.

DR. DIMICK-SANTOS: So the FDA is always concerned about this issue. When we use accelerated approval, this is one of the biggest drawbacks to using accelerated approval, is the retention of patients in a placebo-controlled trial after approval.

DR. RAUFMAN: Dr. Proschan?

DR. PROSCHAN: If the reason for not having a

placebo-controlled trial is an ethical concern because you've shown an effect on this surrogate, you could possibly have a lower dose versus a higher dose. I don't know whether that's here, 2 and a half instead of 5.

DR. DIMICK-SANTOS: So the FDA does not consider it an ethical concern because we have not proven clinical benefit.

DR. PROSCHAN: Okay.

DR. DIMICK-SANTOS: I do know that the applicant is doing a multi-country trial, and the first country that this will be approved in is in the United States, if it is approved, and then it will be approved in the EU, is the second application they have. They do also have it in several countries where it probably will be many years yet before approval is obtained. So hopefully, at least some placebo patients can be maintained.

DR. RAUFMAN: Dr. Assis?

DR. ASSIS: I'm not sure whether this fits the discussion in terms of a trial that's already underway, but I think it was raised a few times, the desire and

perhaps the need to study OCA monotherapy. And I would recommend that that be built in to this for patients who have no response whatsoever to Ursodiol, it that could be considered even in a subsequent evaluation.

DR. DASARATHY: I didn't see anything about this postmarketing study. I still am pretty concerned about this reduction in HDL. And the Framingham score is just a score. It doesn't tell -- cardiovascular events are not going to happen one year, two years. This is something that we have learned from other drugs that they all come with a lot of fanfare, that everybody wants them to be approved, and then five years down the road, you start seeing that they have cancers, osteoporosis, and all kinds of bad things start happening.

So I don't see anything, any discussion or incentive for anyone to study long-term clinical cardiovascular events, not biochemical events. And also, just to mention, HDL alone may not be the best way. Right now, what can be done is there are methods to study HDL function in terms of [indiscernible] transport, which are much more reliable and robust in

predicting long-term clinical outcomes. And those don't require too much effort or resources. And they could be done fairly easy.

One can never say what will happen 10 years down the road, but this is a much more robust method than just measuring HDL numbers. And the LDL numbers that we have been shown is only a 12-month follow-up, that it goes up and then it comes back down. So we don't know whether it's a cyclical event, is it something that's going to happen to the LDL when they're followed up for longer periods of time or in a much larger population?

Those are the kind of postmarketing studies on lipid profile, HDL function, and clinical cardiovascular events, which should be probably measured.

DR. RAUFMAN: Dr. Dimick?

DR. DIMICK-SANTOS: Could you put up from my slides the inclusion criteria, slide number -- 13. If the panel could comment on the acceptability of the inclusion criteria or any changes you'd like to see, because this trial has only really enrolled a very

small amount of patients. It's not too late to broaden the population. Additionally, we could ask for other trials to be performed if you didn't want to change the design of this particular trial.

DR. RAUFMAN: But this again is without a control group. This is people on drug.

DR. DIMICK-SANTOS: No. This is the phase 4 trial, which is designed as a placebo-controlled trial.

DR. RAUFMAN: Then you're going to get subjects who volunteer for this trial.

DR. DIMICK-SANTOS: I'm not confident we will get that in the United States or in -- if the drug is approved -- I'm sorry; I have to caveat -- post-approval, yes. You know, how many people are going to want to be in a placebo-controlled trial when they can go and get their drug? So this is always a major issue for the FDA on approving drugs under accelerated approval.

So yes, will we have it in this country? I certainly doubt that. May we get it from some of the other countries where the drug is not approved yet? I would think so, but what the percentage will be, I

don't know.

DR. RAUFMAN: Dr. Chang?

DR CHANG: Well, there are patients who probably don't have insurance or that it's too expensive. I'm sure it's going to be expensive when it comes out, and they may want to take the risk; although, this is a really long study. I would just try to gather all the data of questions that we had here today. For example, they're including patients who are not taking UDCA, so you'd probably want to get the information of whether they've been on it, did they tolerate it but it wasn't effective, answering some of the questions because it's going to be a monotherapy -- there are going to be a group of patients that will be monotherapy, and will be nice to know what they have.

Then I saw that the primary objectives are really liver related outcomes, liver transplant, death. So you're not really using any biochemical endpoints. But I'm assuming that you're going to collect those data for the secondary endpoints, and then try to look at the endpoints that you thought were important,

whether it's a risk score or this proposed stratified criteria.

That would be helpful. And then you're going to also get a wider range of patients of disease severity so it's your opportunity to look at a different biochemical endpoints and determine.

Then I would also get blood levels because you still don't know, in patients with more advanced disease, if they don't tolerate it as much, and that you'd have to use lower doses. So you take an opportunity to do that because it's a long study.

DR. DIMICK-SANTOS: So if you look at the biochemical criteria being and/or, I can tell you that we're unclear what patients would be enrolled. So could you comment on that?

DR. ROBERTSON: Yes, we could speak to the patients that have enrolled to date, and maybe a little bit more definition of the study. Dr. MacConell, could you come up to speak to this?

A little bit, too, that this is a delicate balance between trying to find a study design in which we can confirm clinical benefit in a timely fashion,

but also make sure it's a patient population that we can actually have an effect in. So it's been a lot of discussions to get to this point with a potential study design.

Dr. MacConell?

DR. MacCONELL: So let me just quickly remind you of the study design since we didn't talk into much detail about it. Slide 2 up, please. So the study design is presented here, and again was finalized based on extensive dialog with the FDA regarding the trial design and analysis plan. It was a very difficult conversation because we agree with your assessments around the feasibility concerns with this study, but we did implement several design elements very carefully in which we thought were the best way to address some of these feasibility concerns.

In the current ongoing phase 4 studies, we are enrolling, targeting a total of approximately 350 patients with PBC. These do represent a more advanced population, so that will address in many ways the concerns that have been raised here today regarding the current phase 3 study and the relative limited data set

in terms of more advanced patients. But this more advanced patient population will also enable us to accrue the needed number of events that's required to ultimately confirm clinical benefit in these patients.

So these patients will be randomized to one of two arms, the placebo control. So again, as Dr. Robertson noted, that is the prespecified control arm here is placebo control as the best scientific evidence or obeticholic acid. And consistent with what we've learned in the phase 3 study, these patients would be employing the titration strategy, so initiating on the lower 5 milligram dose and titrating up to 10 milligrams. And then we do have a historical control prespecified as well in place.

The primary composite endpoint -- it's a time to event assessment. The primary composite endpoint is death. That's all-cause mortality, liver transplant, or events related to end stage liver disease, based on a desired total number of 121 events. Based on our analysis of the Global PBC database, that will provide us with 80 percent power approximately to demonstrate statistical significance with a hazard ratio of 0.6.

With respect to our ability to assess patients with obeticholic acid delivered as monotherapy, that's also very important. They will indeed be enrolled in the study. Based on the current enrollment to date, we have approximately 17 percent of patients actually with obeticholic acid as monotherapy. And we do indeed collect precisely the information that you are suggesting exactly, their past history with UDCA, namely the intolerance behind it.

DR. RAUFMAN: Dr. Ellenberg?

DR. ELLENBERG: For all the reasons discussed about the potential difficulties of carrying out a full-fledged placebo-controlled trial, I would really encourage you to consider continuing to accrue, not limiting yourself to two years of accrual. The more patients you accrue and the longer the accrual period is in the period of the whole study, the shorter the whole study will have to be, and the less problem you're going to have with dropouts. You surely will be having some, but again, you want to minimize that.

DR. ROBERTSON: Yes, completely agree, and we will be monitoring accrual on a regular basis

throughout the study.

DR. RAUFMAN: I think we're also hearing that we'd like to see some cardiovascular and lipid endpoints there as well because of the concern about the fall in HDL levels.

DR. ROBERTSON: Yes, I can speak to that a little bit. We will be assessing cardiovascular events, and they will be actually adjudicated. And they're handled separately from the adjudication of the primary endpoint for the study, which is the liver related endpoints. We will be also carefully assessing CV safety, and there's going to be an integrated analysis of aggregate data, including abnormal vital signs, changes in lipids, abnormal ECGs, ECG related adverse events, and incidence of CV adverse events.

DR. DIMICK-SANTOS: However, the study is not powered to analyze for cardiovascular events --

DR. ROBERTSON: Correct.

DR. DIMICK-SANTOS: -- so if a signal is seen, then an actual cardiovascular events trial would need to be performed to assess that.

DR. KUMAR: So given these concerns about

cardiovascular safety, how does having a post-approval, if the drug gets approved, registry help address that issue?

DR. DIMICK-SANTOS: Are you asking me?

DR. KUMAR: Yes.

DR. DIMICK-SANTOS: Well, that's a good suggestion. A registry could be done to help us gather more data for patients who are not in a clinical trial.

Donna, you look like you have something to say about that. No?

I still am concerned that the biochemical criteria for entry into this trial is either a total of bilirubin or an elevated alk-phos, so that while the patients won't be as early stage as the ones in the phase 3 clinical trial -- so for one, we have concern that we won't really have clinical benefit outcome on the same patients that were in the phase 3 trial, and two, we still may have for the most part early stage and maybe moderate stage. And cirrhosis is an exclusion criteria, so we won't have data on cirrhotic patients unless we perform separate trials in these patients.

DR. CONJEEVERAM: I think it's a wonderful opportunity, given the commitment, to really expand on the inclusion criteria. I think we're limiting ourselves and may not be able to do a bigger study or another study, especially if you're committing yourself to a long-term study, not only look at efficacy but also safety as well. I'm not sure why cirrhotics are being excluded. You can stratify them in a well compensated cirrhosis. We're not talking about decompensated, especially if you already had some in your earlier study. To me, this is a great opportunity to actually look at cirrhotic patients, can we actually delay time to decompensation.

The other thing is also from a cardiovascular standpoint, we're looking at an event. As Dr. Dasarathy talked about, there are other ways to -- better ways beyond the HDL and LDL. There's an opportunity to look at are there signals which are going to predict an event. That might be very useful as well, rather than just looking at the levels. Again, this is going to be a wonderful opportunity to do so.

DR. RAUFMAN: Dr. Silveira, and then Dr. Lipman.

DR. SILVEIRA: I have a few comments. Like Dr. Dimick was mentioning, I agree that the current enrollment criteria might still lead to a majority of patients with early stage liver disease just because of the or. So they could end up with what is considered high-risk patients with alkaline phosphatase levels above 3, but without true advanced liver disease, so normal bilirubin. And I think it was a consensus here that a lot of us are concerned about the lack of data in actual cirrhotic patients, particularly decompensated cirrhotics.

I didn't see exclusion criteria for cirrhotics. If they are included with a MELD less than 12, it would be compensated cirrhotics.

DR. ROBERTSON: If I could clarify, we're not excluding cirrhotic patients.

DR. SILVEIRA: I don't see it either, but anyway -- so again, with the inclusion being and/or alk-phos above 3 versus bilirubin between 1 and 3 and other inclusion criteria, we might still end up with

early stage disease. So I was wondering whether one of the things that could be established is that a certain proportion of patients would have to meet the criteria of bilirubin and/or other criteria rather than risk most of the patients being enrolled based on the criteria of alkaline phosphatase.

The other comment that I have, sometimes to facilitate enrollment, it sounds like it's proposed a one-to-one randomization scheme. So it would offer 2 to 1 or something like that, where the patients might perceive higher chances of being on drug rather than placebo. That might also be an incentive for enrollment.

The last comment that I have, I agree that it has to be taken very seriously, the signal with HDL and all of this data, and cardiovascular events have to be collected and reported. But I would like to add that cholestatic liver disease, dyslipidemia, may be a little bit different than dyslipidemia to the general population; 75 percent to 95 percent of the patients with chronic cholestatic liver disease have dyslipidemia. That might be associated with a

mechanism of disease rather than the regular run-of-the-mill dyslipidemia, even to allude to tests that can be altered by other things.

For example, dyslipidemia and chronic cholestasis can be influenced by the presence of lipoprotein X, which is more common in patients with PBC and other chronic cholestatic liver diseases that might lead to abnormally elevated or decreased LDL and HDL on tests, which are not real. If you do further testing, sometimes it's just a laboratory error because of the presence of LPX in the serum of patients with PBC. So the decrease in the HDL might actually be demonstrating treatment of the cholestasis rather than a true -- rather than something more concerning from cardiovascular sampling.

DR. LIPMAN: Dr. Lipman. Just one comment and one facetious question. The comment is, however you do it, I think you have to have more advanced patients in this clinical trial. However, it's defined, I think it has to be expanded.

My facetious question to my colleagues who treat PBC is how many of you would actually encourage

your patients to be randomized into an eight-year clinical trial in which they might get placebo? I think that's going to be very difficult. I don't expect anybody to answer it in public, but I think this is the issue that is of very great concern. Somebody else's patients, fine; my patients, no.

DR. ELLENBERG: I have a quick comment on that.

DR. RAUFMAN: Dr. Assis?

DR. ASSIS: Sure. Just to reiterate very briefly, I think, number one, I would hope that the design could be modified, if possible, to include enough compensated cirrhotics so that by the end of the trial, like this multiyear trial, we do have enough information about safety and tolerability, and perhaps decreased risk of decompensation. So if the study design allows and could be including enough compensated cirrhotics, that would be very desirable.

Number two, I would say that there is an ongoing concern about the clinical meaning of hypercholesterolemia in these patients, but this would be the perfect opportunity I think to do longitudinal

studies to look at the modulation of this and cardiovascular risk. There has never been a large enough study to really draw any conclusions, and this would be very helpful for other cholestatic diseases as well.

DR. RAUFMAN: Dr. Ellenberg, then Dr. Vos.

DR. ELLENBERG: I would be a little concerned about the signal that a 2 to 1 randomization would send to patients. It may make it seem more attractive in the beginning, but those who get randomized -- well, of course I guess they won't know. But I think a better incentive might be some possible crossover mechanism based on, I don't know, maybe a big increase in ALP or something happening to the bilirubin, something short of the clinical endpoints that are there. But telling people it's a 2 to 1 kind of tells them that you really, really think it's going to work, and I would be a little worried about that.

DR. DIMICK-SANTOS: I have a question for you all. If we enroll primarily patients with more advanced disease in the clinical trial, you will not answer the question of the patients with early phase

disease, was there a clinical benefit for them.

Would you be comfortable if you proved clinical benefit, in the patients with more advanced disease that you could interpret that it worked for patients with early stage disease based on that?

DR. RAUFMAN: Dr. Vos?

DR. VOS: So before you even asked that, I was starting to wonder if we were putting too much on one trial; if maybe there are several questions that need to be asked in studies specifically designed for that question.

In the later stage disease, just to echo the comments of my colleagues, I think that's a particularly concerning group who really need a focus study, possibly a dose-ranging study given the concerns about pharmacokinetics and clearance and that population. So it might be able to be something shorter that would specifically answer some of those safety and dose efficacy questions.

DR. RAUFMAN: Ms. Cryer?

MS. CRYER: Donna Cryer. Now, I love redesigning trials, particularly ones that I'm not

responsible for paying for.

(Laughter.)

MS, CRYER: I have a multitude of thoughts, but I think that probably the most productive take-away to the sponsor and to FDA is, as Dr. Chang mentioned, to take the list of questions that we have asked throughout the course of today and to prioritize them, and to figure out what is most feasible.

Certainly, one of the things that I -- two of the things that I have heard that I would not want to be lost is the effect on early rather than advanced patients. But also to the question that you raised about if this were to be approved and what would happen in the real world, is there an opportunity to have more of an extension of what we've seen so far? So placebo versus urso, versus monotherapy with OCA perhaps, so that there were real-world options for patients in addition to placebo versus drug.

DR. SILVEIRA: I have a comment about the early and the advanced. I think those are indeed two separate questions, is it effective in patients with

early stage disease versus is it a drug that's effective in late stage disease. That's why I was wondering potentially a proportion of patients being advanced liver disease versus another proportion of early stage but high-risk patients, which with an alk-phos above 3 will enroll, but not necessarily the bilirubin.

The other comment that I have about the eight-year study is I saw their quarterly visits. That's going to make it very hard to recruit, too.

DR. RAUFMAN: Are there any other comments from FDA about this question? I mean, there's been a lot that's been proposed. Any specific issues? Is that satisfactory then?

DR. EGAN: Amy Egan, FDA. No, I don't think we have anything more to add. We take your comments very seriously, and we really appreciate the thought that you have given. The design of this trial, we still have some more thinking to do ourselves and number crunching to do to see if we can come up with the best design and to be able to answer as many questions as are feasible to answer.

I will take this opportunity to thank Dr. Raufman and all the members of the committee for your very thoughtful comments, and also to thank the patients who spoke during the open public hearing. It's always important for us to hear the patient perspective, and it reminds us of why we are all here.

I also want to thank Intercept for their excellent presentations and my FDA colleagues, the OCA review team, for their extraordinary efforts and presentations today. Thank you.

Adjournment

DR. RAUFMAN: Panel members, please take all personal belongings with you, as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop of your name badges at the registration table on your way out so they may be recycled.

We will now adjourn the meeting. Thank you.

(Whereupon, at 4:31 p.m., the meeting was adjourned.)