FDA Briefing Document

NDA# 212833

Drug name: Obeticholic Acid (OCA)

Applicant: Intercept Pharmaceuticals

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting

05/19/2023

Division of Hepatology and Nutrition/Office of Immunology and Inflammation

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought obeticholic acid (OCA) 25 mg oral tablets, submitted by Intercept Pharmaceuticals, Inc., for the treatment of pre-cirrhotic liver fibrosis due to nonalcoholic steatohepatitis to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	Advisory Committee
AE	Adverse Event
BD	Briefing Document
BRF	Benefit-Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CMH	Cochran–Mantel–Haenszel
CV	Cardiovascular
DILI	Drug-induced Liver Injury
ELF score	Enhanced Liver Fibrosis Score
FDA	Food and Drug Administration
MELD	Model for End-stage Liver Disease
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic Steatohepatitis
NIDDK	National Institutes of Diabetes, Digestive, and Kidney Diseases
NIH	National Institutes of Health
IA	integrated assessment
REMS	risk evaluation and mitigation strategy
RPM	Regulatory Project Manager
SAP	Statistical Analysis Plan
SD	standard deviation
TEAEs	Treatment Emergent Adverse Events
TZD	Thiazolidinedione
T2D	Type 2 Diabetes Mellitus
ULN	Upper Limit of Normal

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The FDA is convening this Advisory Committee meeting to discuss the benefits and risks of obeticholic acid (OCA) 25 mg for treatment of non-alcoholic steatohepatitis (NASH) with fibrosis.

1.2 Context for Issues to Be Discussed at the AC

The estimated prevalence of NASH is around 5% in the US and is projected to almost double by 2030. Of the 16.8 million patients[1] with NASH about 5.7 million people in the USA are expected to have NASH with advanced fibrosis (stage F2 and F3) (Estes et al. 2018). NASH is the second leading cause of liver transplant in the US and remains the fastest growing indication for liver transplantation (Burra et al. 2020).

There are no pharmacologic treatments approved for NASH in the US. Weight loss is currently the most effective intervention. However, the durability of response is low across clinical trials attempting lifestyle intervention, and long-term outcomes are lacking.

Bariatric surgery (Mummadi et al. 2008; Lassailly et al. 2020) is another option to improve weight loss. Studies have shown improvement in fibrosis and resolution of NASH in the majority of patients up to 5 years following the procedure. However, bariatric surgery is a high-risk procedure and is not a recommended treatment for NASH.

Pharmacological treatment for NASH remains an unmet medical need.

1.3 Brief Description of Issues for Discussion at the AC

In the pivotal trial, OCA 25 mg compared to placebo met one of the two prespecified primary endpoints "improvement in fibrosis of at least 1 stage with no worsening of NASH" at Month 18. The risk difference was modest, 8.6% (95% CI 4.2, 13.0). The OCA 25 mg dose failed to meet the second prespecified primary endpoint of "NASH resolution with no worsening of fibrosis" at Month 18. The OCA 10 mg dose failed to meet either of the prespecified primary endpoints. "Improvement in fibrosis by one or more stage with no worsening of NASH" has been accepted by the FDA as one of the two acceptable surrogate endpoints in this population (FDA 2018).

The adverse reactions experienced with OCA 25 mg suggest that treatment with this dose exacerbates co-morbidities or creates new ones for a patient population at risk for metabolic syndrome and its manifestations. Specifically, OCA 25 mg-treated subjects[2], relative to placebo-treated subjects, experienced:

- Hepatotoxicity: cases adjudicated by drug-induced liver injury (DILI) experts identified a serious signal for DILI in the OCA 25 mg-treated subjects.
- Excess risk of cholecystitis and bile duct stones/sludge and related life-threatening complications and surgical interventions.

[1] The term 'patient' refers to an individual receiving medical care according to normal clinical practices.

[2] The term 'subject' refers to a participant in an interventional or observational study.

- Excess risk of new onset prediabetes/diabetes requiring new treatment or poor glycemic control in diabetic subjects that required additional anti-diabetic therapies.
- Substantial excess risk of dyslipidemia that required new treatment with statins or increased dose/intensification of statins.
- Substantial excess risk of severe pruritus leading to treatment-interruptions, administration of antipruritic agents/bile acid binding agents/corticosteroids, or drug discontinuations.
- Excess risk of developing acute kidney injury.

1.4 Draft Points for Consideration

NASH requires life-long drug therapy. Trial results for obeticholic acid indicate it causes multiple off-target effects making it challenging to develop and implement effective risk mitigation. The Committee will be asked to discuss whether the available efficacy data for OCA 25 mg on a single histologic endpoint are sufficient to justify/counterbalance the observed risks in the proposed population. The Committee will be asked to opine on the following:

1. Discuss the available efficacy data on the histopathologic endpoints and whether treatment with OCA 25 mg is reasonably likely to confer clinical benefit in NASH patients with stage 2 or 3 fibrosis.
2. In Trial 747-303, NASH subjects were selected for treatment based on a liver biopsy obtained at baseline to identify the presence of "definite NASH with Stage 2 or 3 fibrosis", a subset of the NASH patient population. Discuss the acceptability of obtaining liver biopsy in the general NASH patient population to identify suitable patients for OCA treatment in clinical practice outside a clinical trial.
3. Based on the data presented concerning cholestatic drug-induced liver injury (DILI) in OCA-treated patients, discuss whether periodic liver enzyme monitoring could mitigate the risk of DILI in clinical practice.
4. As presented in the clinical trial, pharmacological treatments were required to manage treatment-emergent adverse reactions of dyslipidemia, dysglycemia, and pruritus associated with OCA treatment. Comment on the adequacy of adding pharmacological treatments in clinical practice, outside a clinical trial, to mitigate these adverse reactions in the NASH subjects who frequently have preexisting cardiovascular (CV) risk factors and/or preexisting comorbid conditions, at baseline, e.g., type 2 DM.
5. Given the available efficacy and safety data, do the benefits of OCA 25 mg outweigh the risks in NASH subjects with Stage 2 or 3 fibrosis?
6. Clinical outcome events in subjects in Trial 747-303 will continue to be captured for a future regulatory submission. At this time, do you recommend approval of OCA 25 mg via the accelerated (approval) pathway based on a surrogate histologic marker?

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

NASH is a severe form of nonalcoholic fatty liver disease (NAFLD). Differentiating NAFLD, which represents bland steatosis in the liver, from NASH is of paramount importance because patients with NASH are at increased risk of progressive fibrosis and ultimately, cirrhosis and its complications. NASH is associated with other comorbidities such as obesity, type 2 diabetes mellitus (T2D), dyslipidemia, hypertension, and hypertriglyceridemia. The prevalence of NASH is higher in subjects with these metabolic disorders (NHLBI 2022).

NASH is a diagnosis of exclusion; as other causes of fat in the liver (Rinella et al. 2023) such as significant alcohol consumption, must be excluded. NASH is characterized by the presence of inflammation and hepatocyte ballooning, a manifestation of severe inflammation.

NASH may not be associated with hepatic fibrosis, but with disease progression, patients can develop significant liver fibrosis, including bridging fibrosis. Fibrosis is the strongest predictor of mortality (Sanyal et al. 2021), and staging is performed to assess degree of fibrosis. Over time NASH can progress to compensated cirrhosis in which patients usually do not have clinically significant portal hypertension. However, clinically significant portal hypertension heralds the onset of decompensated cirrhosis and hepatic decompensation can result in patients requiring liver transplantation or death from complications of cirrhosis. The complications of the metabolic diseases that are frequently associated with NASH (cerebral vascular accidents (stroke), myocardial infarction, T2D and its complications) are significant contributors to morbidity and mortality in patients with NASH (Sanyal et al. 2021).

Although noninvasive biomarkers and imaging potentially can assist in selecting a high-risk NASH population, currently there are no tests, or panel of tests, established to accurately diagnose and stage NASH. In the pivotal phase 3 trial conducted by the Applicant, liver biopsy was utilized at various intervals to gauge treatment effect and disease progression.

The Brunt-Kleiner staging and grading system was used for assessing liver histopathology in this clinical trial (Kleiner et al. 2005). The NAFLD activity score (NAS)[3] is an unweighted multicomponent measure of fat, lobular inflammation, and ballooning degeneration scores. The population enrolled in the pivotal trial conducted includes subjects who met histologic criteria for steatosis and significant inflammation (NAS ≥4) and established fibrosis (fibrosis stage 2 or 3).

2.2 Pertinent Drug Development and Regulatory History

Obeticholic acid (OCA) is a synthetic bile acid, with a 6α-ethyl group added to chenodeoxycholic acid (CDCA). CDCA is a primary bile acid and an endogenous bile acid in humans. OCA and its conjugates are farnesoid X receptor (FXR) agonists, a nuclear receptor that regulates bile acid biosynthesis, and has been demonstrated to mediate inflammatory, fibrotic, and other metabolic pathways. FXR is expressed at high levels in liver, intestine, kidney, and adrenal glands and is critical in maintaining bile acid homeostasis (Sinal et al. 2000). Ultimately FXR activation decreases de novo bile acid synthesis from cholesterol via inhibiting expression of cholesterol-7alpha-hydroxylase (CYP7A1), the key enzyme of bile acid synthesis (Gupta et al. 2001).

Nonclinical animal models demonstrate FXR agonism improves liver inflammation and fibrosis in diet-induced fatty liver disease in mice.

OCA has higher hydrophobicity compared to endogenous primary bile acids, and in vitro studies have demonstrated that OCA increases the bile acid hydrophobicity index, thereby affecting micellar formation, rendering the bile less polar (in liver and intestines). The concentrations of bile acids and cholesterol necessary to form micelles depend on the composition of endogenous bile acids in patients with chronic liver disease (Wang et al. 2009) In addition to increasing bile hydrophobicity, OCA also promotes bile saturation with cholesterol, which increases the risk of gall stone formation (Al-Dury et al.

[3] Disease grading: NAFLD activity score (NAS) for grading of disease activity. Grading includes assessment of fat, inflammation, and ballooning. Staging disease: Fibrosis stages are classified in 5 categories, no fibrosis = F0, stage 1 fibrosis = F1, stage 2 fibrosis = F2, stage 3 fibrosis = F3, and stage 4 fibrosis = F4. Fibrosis stages 2 or 3 are categorized as advanced fibrosis and stage 4 fibrosis is cirrhosis.

2019). Because OCA has a higher hydrophobicity index compared to endogenous primary bile acids, OCA potentially increases the risk of liver injury (van Golen et al. 2018).

2.2.1 Brief Regulatory History

OCA was granted accelerated approval in 2016 for the treatment of primary biliary cholangitis (PBC) at doses of 5 – 10 mg daily with lower doses for patients with advanced cirrhosis. The product label was later amended to include both a boxed warning and a contraindication, to decrease the risk of hepatic decompensation in PBC patients with decompensated cirrhosis or compensated cirrhosis with evidence of portal hypertension. These safety labeling changes are the FDA's strongest warnings for patients and healthcare providers.

An IND for OCA for the treatment of NASH was initially submitted in 2010 by the National Institutes of Diabetes, Digestive, and Kidney Diseases (NIDDK). The current Applicant became the IND sponsor on December 9, 2014. On January 28, 2015, OCA received Breakthrough Therapy Designation[4] for the treatment of non-alcoholic steatohepatitis with liver fibrosis based on the results of the phase 2 FLINT trial.

Dose Selection for Phase 3 NASH Trial

The Applicant's selection of the 10 mg and 25 mg once daily doses for the pivotal phase 3 study, 747-303, was informed by histologic and biochemical data from two randomized, double-blind, placebo-controlled phase 2 studies: one conducted in the US (FLINT) and the second conducted in Japan (Trial D8602001).

In trial D8602001, NASH subjects were administered doses of OCA 10 mg (n=51), OCA 20 mg (n=51), and OCA 40 mg (n=50), or placebo (n=50). Most subjects were males (~70%) with a mean BMI 28 kg/m^2. Improvement in NAS ≥2 points with no worsening of fibrosis was observed in 20.0% (n=10/50) in the placebo group; 22.0% (n=11/50) in the 10 mg dose group; 28.0% (n=14/50) in the 20 mg dose group; and 38.0% (n=19/50) in the 40 mg dose group. Although the 25 mg dose was not studied, a dose-dependent improvement in NAS ≥2 was observed between 20 mg and 40 mg dose groups. A dose-dependent increase in the incidence of pruritus and drug-induced liver injury (DILI) was also observed.

In the phase 2 trial conducted by the NIDDK (Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT)), NASH subjects were randomized to either OCA 25 mg (n=141) or placebo (n=142). Most subjects were white, 66% were female, and the mean BMI was 34.6 (SD = 6.3). About 80% of subjects had definite histologic criteria for NASH and 58% had stage 2 (27%), or stage 3 (31%) fibrosis. Subjects with stage 0 and stage 1 fibrosis were also enrolled, i.e., 40% of the enrolled population in FLINT had a lower degree of fibrosis than the population enrolled in the phase 3 trial (747-303). In addition, two percent of enrolled subjects in FLINT had cirrhosis (stage 4 fibrosis). Therefore, the population of the FLINT study was different compared to study 747-303.

Per the Applicant, the FLINT trial was stopped early for efficacy based on a planned interim analysis, which demonstrated that the primary endpoint of the trial ("no worsening of the fibrosis score and an improvement in NAS ≥2 points") had been met; therefore, many subjects did not complete the trial as planned and did not have the end-of-treatment (EOT) biopsy performed. In a paper published by the NASH clinical research network (CRN) (Neuschwander-Tetri et al. 2015), the Drug Safety Monitoring Board raised concerns associated with the long-term risk with chronic OCA use, due to increases

[4] In the modified intent to treat (mITT) population, greater percentage of OCA-treated subjects [50 (45%) out of 110 subjects] compared with placebo [23 (21%) out of 109 subjects] had "no worsening of the fibrosis score and an improvement in NAS ≥2 points" following 72 weeks of treatment (p=0.0002, Relative Risk [95% CI]: 2.2 [1.4 to 3.3].

observed in LDL cholesterol (LDL-C). In the FLINT trial there was no strategy in place to manage the increased LDL-C with statin therapy during the study. Subjects in FLINT did meet the threshold for reduction of NAS ≥2 points, but this histologic finding did not cross the threshold from a diagnosis of definite/borderline NASH to non-NASH on EOT liver biopsy.

The Applicant used a modified intention to treat (mITT) population, defined as all subjects in the ITT population except those who did not have an EOT biopsy due to protocol modification after stopping criteria were met, to analyze FLINT's primary endpoint. A greater percentage of 25 mg OCA-treated subjects (45% [50/110] subjects) compared to placebo (21% [23/109] subjects) had "no worsening of the fibrosis score and an improvement in NAS ≥2 points" following 72 weeks of treatment (p=0.0002, Relative Risk [95% CI]: 2.2 [1.4 to 3.3]). Key AEs observed in FLINT included DILI, increased LDL, and pruritus.

The AE profile from FLINT and D8602001 were consistent with the observed dose-dependent increase in pruritus and drug-induced liver-injury (DILI) in subjects with primary biliary cholangitis (PBC) treated with doses ranging between 5 mg and 10 mg.

Original NDA Review (2019 to 2020)

Study 747-303, served as the pivotal trial for the current NDA submission. The Applicant had a pre-NDA meeting with the Agency on April 30, 2019 and submitted an NDA on September 26, 2019. A priority review was granted with an action goal date of March 26, 2020. The goal date was extended to June 26, 2020, due to the need for adjudicated data on the risk of DILI – a key safety concern for OCA 25 mg. The adjudicated DILI findings, based on an agreed upon adjudication charter and conducted by DILI experts, provided a more thorough assessment of DILI to inform the benefit-risk assessment.

For the OCA 25 mg treatment group relative to placebo, a statistically significant treatment difference of 11.1% (95% CI: 5.3%, 17.0%) was demonstrated for the histopathological assessment endpoint of one stage or more improvement in fibrosis stage and no worsening of NASH at Month 18. OCA 25 mg failed to meet the second accepted endpoint of "resolution of NASH with no worsening of fibrosis." Using the statistical testing procedure for the Month 18 interim analysis described in Figure 13, the OCA 10 mg dose was then evaluated for both endpoints. The OCA 10 mg dose failed to meet either of these primary endpoints. Based on the December 2018 draft guidance (FDA 2018) and the pre-specified statistical analysis plan, demonstrating statistical significance on only one of the two Month 18 primary endpoints was considered acceptable for accelerated approval. However, there was poor to moderate inter- and intra-reader concordance in the histopathology readings which added uncertainty to the results.

Specific safety concerns included the risk of serious DILI events, gallbladder disease and related complications (including cholecystitis), pruritus (in some cases severe requiring treatment discontinuation), increased LDL-C requiring new treatment or intensification of treatment, as well as new onset T2D or worsening glycemic control requiring addition of new anti-diabetic drugs in subjects with existing T2D. The Agency concluded that while DILI events were more frequent in the 25 mg OCA treatment arm compared to the 10 mg OCA treatment arm, the DILI events were not preventable using protocol prespecified monitoring, and in some instances were potentially serious, including one subject who required a liver transplant for rapidly progressive liver failure.

In the Complete Response (CR) letter issued on June 26, 2020, the Agency "determined that the potential serious risks associated with OCA 25 mg outweigh the efficacy findings based on a surrogate histopathologic endpoint." The CR letter detailed the Agency's safety concerns described above in the context of modest efficacy on a surrogate endpoint. The Agency went on to recommend, "that the long-term extension phase of study 747-303 should be continued and evaluated for efficacy, based on clinical

outcomes and additional planned histopathology evaluations, and for longer-term safety to provide for a comprehensive assessment of the benefits and risks of OCA for the treatment of NASH with fibrosis."

NDA Resubmission Review (2022 to Present)

The NDA resubmission contains results of biopsy reads on a larger number of subjects and additional data for safety. This additional interim analysis of histopathologic surrogate endpoints (using the ITT_histology analysis population defined in Section 3.1.1) was not pre-specified prior to the CR letter resulting from the original NDA review. Clinical outcome data have not been submitted; these results remain blinded to maintain the integrity of the ongoing trial to evaluate clinical benefit.

2.2.2 Clinical Pharmacology

Upon oral absorption, OCA undergoes extensive metabolism and is primarily excreted through biliary secretion. At steady-state systemic exposure (AUC_{0-24}) of two major active conjugates, glyco-OCA and tauro-OCA is 12- to 14-fold higher than compared to unconjugated OCA. In vitro pharmacological activity of glyco-OCA and tauro-OCA are similar to that of OCA.

Similar to endogenous bile acids, OCA undergo enterohepatic recirculation primarily as conjugates. OCA and its conjugates utilize similar processes for uptake, conjugation, and biliary secretion as endogenous bile acids, e.g., tauro-OCA is a substrate of the bile-salt export pump (BSEP) localized on the canalicular membrane of hepatocytes and glyco- and tauro-OCA are substrates of apical sodium-dependent bile acid transporter (ASBT; also known as ileal bile acid transporter [iBAT]) in the lieum.

In a study using radiolabeled OCA, OCA related materials were detectable in feces for a prolonged period of time ranging from 20 days to as long as 48 days, following a single 25 mg dose in healthy subjects.

Following multiple-dose administration of OCA 5, 10, and 25 mg once daily, systemic exposures of OCA increase dose proportionally while exposures to glyco-OCA and tauro-OCA, and total OCA (the sum of OCA and its two active conjugates) increased more than proportionally with dose. At steady-state systemic exposure (AUC0-24h) achieved on Day 14, total OCA systemic exposure (AUC0-24h) was 4.2-, 6.6-, and 7.8- fold the systemic exposure achieved on Day 1 after 5, 10, and 25 mg once daily dosing, respectively. The systemic exposure to OCA and its major conjugates have moderate inter-individual variability with the coefficients of variation (CV%) of 50% to 70% in healthy subjects as well as in NASH subjects with fibrosis.

OCA and its conjugates can induce BSEP expression via FXR activation. On the other hand, in vitro OCA, glyco-OCA and tauro-OCA inhibited transport of taurocholic acid via BSEP in a concentration-dependent manner. The net effect on bile acids export via BSEP modulation with chronic OCA administration is likely to vary among subjects. Potential accumulation of bile salts in the liver due to inhibitory effects on BSEP cannot be completely ruled out.

In subjects with mild to severe renal impairment (eGFR 15 - 90 mL/min/1.73 m2 by MDRD[5]), the total OCA exposure was 1.4- to 1.6-fold the exposure in subjects with normal renal function.

Hepatic impairment significantly increases systemic exposure of total OCA.

In subjects with moderate hepatic impairment (Child-Pugh B cirrhosis) due to primary biliary cirrhosis (PBC), mean AUC_{0-24h} for total OCA increased in a dose proportional manner from OCA 5 mg once weekly, 5 mg twice weekly, and 10 mg twice weekly in subjects with PBC and Child-Pugh B cirrhosis. PBC

[5] Modification of Diet in Renal Disease (MDRD)

subjects with severe hepatic impairment (Child-Pugh C) were not dosed with OCA, therefore, data for dose exposure are not available.

In a hepatic impairment study, the mean AUC of total OCA increased by 1.1-, 4- and 17-fold, respectively, in subjects with mild, moderate, and severe hepatic impairment (Child-Pugh A/B/C respectively mainly secondary to viral hepatitis) compared to subjects with normal hepatic function following a single dose of 10 mg OCA.

In another hepatic impairment study, total OCA systemic exposure (AUC) at steady-state were substantially higher in NASH subjects with cirrhosis (Child-Pugh A class) than in healthy subjects; by 8 to 9-fold after receiving a 10 mg daily dose and 2.3 to 2.8-fold following once daily dosing of 25 mg (Figure 1). In a cross-study comparison, mean GGT, ALP, total bilirubin, and direct bilirubin levels in NASH subjects with Child-Pugh A cirrhosis were about 1.7 to 2.7-fold higher compared to the subjects with mild hepatic impairment (Child-Pugh A) due to other etiologies (i.e., mainly secondary to viral hepatitis).

After once daily dosing of 100 mg OCA for 5 days, there was no significant effect on the QT interval to any clinically relevant extent.

As for effects of other drugs on OCA, OCA is not metabolized by major CYP enzymes in vitro. Concomitant drugs that inhibit BSEP or iBAT may affect the disposition of major metabolites of OCA.

Bile acid binding resins may reduce the absorption, systemic exposure, and efficacy of OCA. OCA should be administered at least 4 hours before or 4 hours after taking the bile acid binding resin.

In a drug-drug interaction study, concomitant administration of 20 mg omeprazole (an acid-reducing agent) once daily with 25 mg OCA once daily resulted in 20% and 12% increase in steady-state Cmax and AUC of OCA, respectively. Cmax and AUC of glyco-OCA are increased by 22% and 25%, respectively. Cmax and AUC of tauro-OCA are increased by 28% and 33%, respectively.

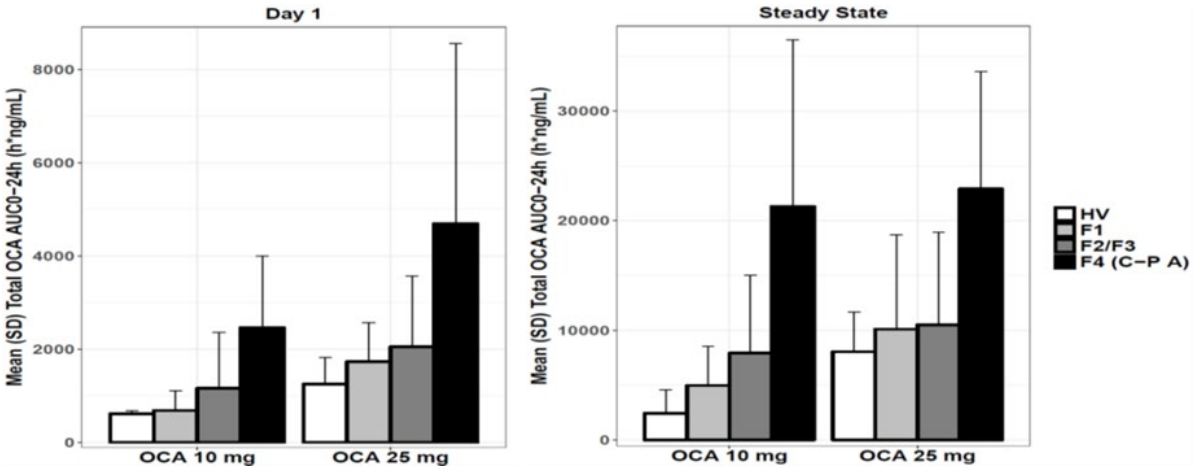
Multiple doses of 25 mg OCA increases the systemic exposure to caffeine by 65% and omeprazole by 37%. Single dose of 25 mg OCA increases the systemic exposure to rosuvastatin by 30% and midazolam by 26%.

2.2.2.1 Effect of Fibrosis on OCA Hepatic and Plasma Exposure – Results from Hepatic Impairment Trial

Systemic Exposure by Fibrosis Stage

In a cross-study comparison, systemic exposure of total OCA tended to be higher in subjects with NASH with fibrosis. In Study 747-117, an increasing trend in plasma total OCA exposure was observed with a higher fibrosis stage in NASH subjects (Figure 1). NASH subjects with fibrosis can progress to cirrhosis during OCA treatment. In a cross-study comparison, total OCA systemic exposure was substantially higher in NASH with F4 fibrosis (cirrhosis, Child-Pugh A) compared to NASH subjects with F2/F3 fibrosis.

Figure 1. Mean Plasma Exposure of Total OCA on Day 1 and at Steady State by Fibrosis Stage Following Administration of 10 mg and 25 mg OCA Once Daily

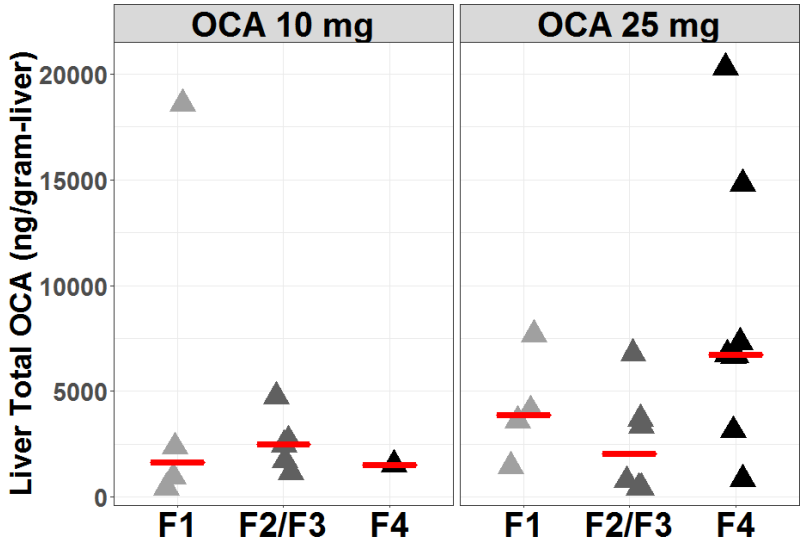


Source: FDA reviewer's graph generated based on data from: Study 747-117: F1 – F3: NASH subjects with F1 (10 mg N=5; 25 mg N=8) or F2/F3 (10 mg N=9; 25 mg N=11); Study 747-118: heathy controls (HV: 10 mg N=4; 25 mg N=4) and NASH subjects with Child-Pugh A (F4 (C-P A); 10 mg N=8; 25 mg N=8)

Liver Exposure by Fibrosis Stage

The concentration of total OCA (both conjugates) in the liver were measured in biopsied liver samples. Total OCA concentration consisted of glyco-OCA and tauro-OCA in the liver largely overlapped across fibrosis stages in NASH subjects within each dosing group (Figure 2). Unconjugated OCA was not detected in the liver. However, these data should be interpreted with caution due to a small sample size with a large variability.

Figure 2. Total OCA Concentration in the Liver at Steady State by Fibrosis Stage Following Administration of 10 mg and 25 mg OCA Once Daily in Subjects With NASH



Source: FDA reviewer's graph generated based data from: Study 747-117: all F1 – F3 data (N=8 for F1; N=11 for F2/F3) and F4 (N=1 for 10 mg; N=1 for 25 mg); Study 747-118: F4 (N=7)

In the current NDA resubmission, the Applicant provided safety triggered PK data collected from the ongoing clinical trial, Study 747-303. A single PK blood samples were collected from a total of 45 subjects after the onset of an SAE, or progressed to cirrhosis, or discontinued OCA due to cirrhosis or

hepatic injury. Overall, the mean total OCA concentrations of these safety triggered PK samples appear to be within the range of mean C_{trough} to C_{max} values observed at steady-state (Month 18) in Study 747-303 (i.e., mean total OCA C_{max} and C_{trough} was 194 and 52.5 ng/mL for 10 mg, respectively and 557 and 257 ng/mL, respectively for 25 mg dose). The interpretation of these concentrations is limited by the unknown time lapse from the last dose while a PK sample was to be collected as long as seven days after a qualified safety event per protocol; therefore, plasma concentrations could have been higher than the observed in those subjects.

Of note, one subject (Subject 1, see Section 3.2.3.2.3) who discontinued OCA 25 mg one day after experiencing an SAE of hyperbilirubinemia had significantly high total OCA concentration of 3950 ng/mL at four days after OCA was discontinued (i.e., which is approximately seven-fold higher than the mean C_{max} at Month 18 in the same study). Total OCA concentration prior to the SAE is unknown in the subject. Refer to Section 3.2.3.2.3. for more details.

3 Summary of Issues for the AC

3.1 Overview of Study 747-303

The efficacy and safety evaluation will be based primarily on the results available from ongoing Study 747-303.

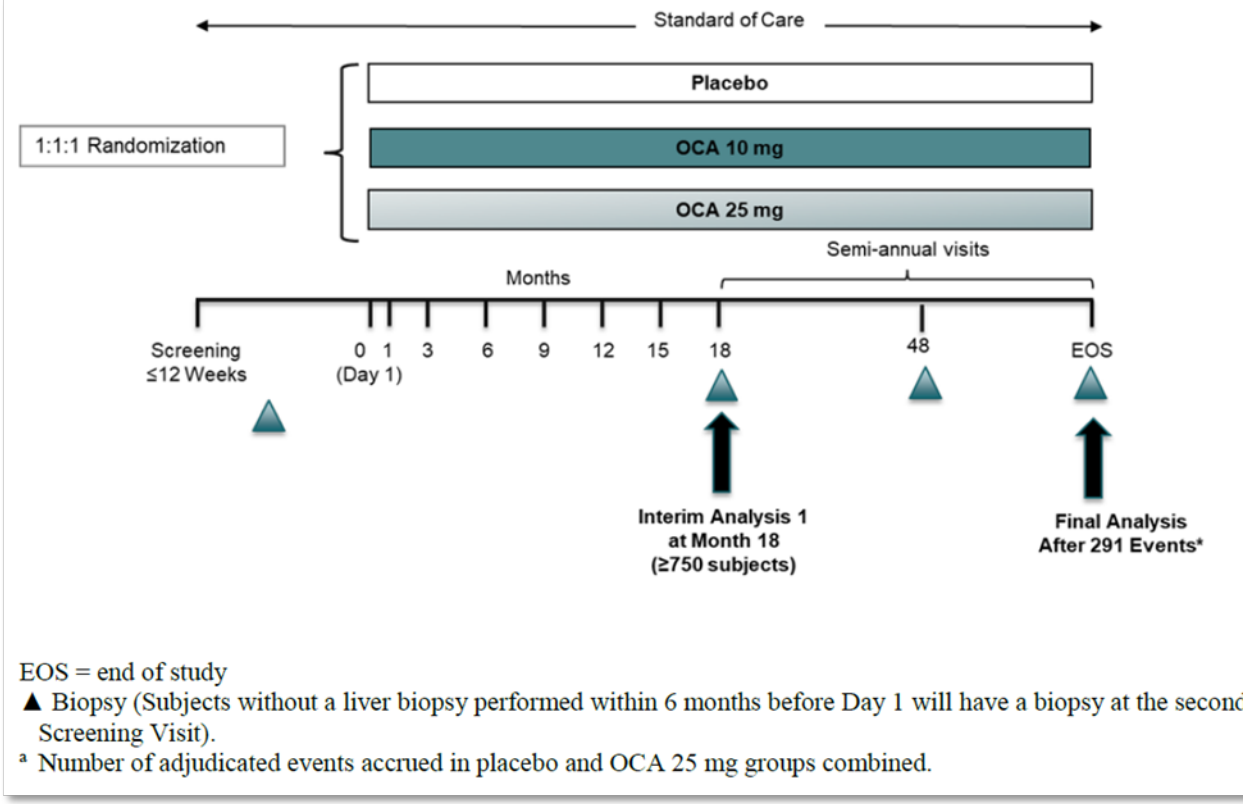
In accordance with draft guidance published December 2018 (FDA 2018), efficacy was assessed based on surrogate endpoints that are considered reasonably likely to predict clinical benefit. With reasonably likely surrogate endpoints, there is uncertainty about how the magnitude of changes observed on these surrogate endpoints may translate to meaningful changes in clinical outcomes.

Although OCA 25 mg demonstrated superiority to the placebo on one of two primary endpoints, the treatment effect on this surrogate endpoint was modest. The main issue for the Advisory Committee to consider is weighing the modest treatment effect on a surrogate endpoint that is reasonably likely to predict clinical benefit against the substantial risks identified with use of OCA.

During the original NDA review, the Agency was concerned about the reliability of the central reading method for histopathologic interpretation (liver biopsy reads) in producing scores for the surrogate primary endpoints. The NDA resubmission contains results of biopsies from a larger number of subjects evaluated by using a new consensus reading method (refer to Section 6.7.2). The overall conclusions regarding the treatment effect based on the new consensus reading method in the NDA resubmission are generally consistent with conclusions about the treatment effect based on the biopsy data in the original NDA submission.

3.1.1 Design and Efficacy Analysis of Study 747-303

Figure 3. Study 747-303 Design Schematic



EOS = end of study
▲ Biopsy (Subjects without a liver biopsy performed within 6 months before Day 1 will have a biopsy at the second Screening Visit).
[a] Number of adjudicated events accrued in placebo and OCA 25 mg groups combined.

Source: Figure 1 of Applicant's Protocol 747-303 Version 8.0 (January 8, 2019)

Study 747-303 is an ongoing phase 3, double-blind, randomized, long-term, placebo-controlled, multicenter study of OCA 10 mg daily and OCA 25 mg daily versus placebo. An interim analysis of surrogate endpoints at Month 18 was intended to support an accelerated approval. The study is ongoing to evaluate clinical benefit outcomes intended to support a traditional approval. Study 747-303 was initiated on December 9, 2015. Figure 3 (above) depicts the overall study design.

The main inclusion criteria include:

- Histologic evidence of definite NASH upon central read of a liver biopsy obtained no more than six months before Day 1 defined by presence of all three key histological features of NASH (ballooning, inflammation, steatosis) with a score of at least 1 for each and a combined NAS of 4 or greater out of a possible 8 points based on NASH CRN criteria.
- Histologic evidence of fibrosis stage 2 (perisinusoidal and portal/periportal) or stage 3 (bridging fibrosis) as defined by the NASH CRN scoring of fibrosis. An exploratory cohort included subjects with histologic evidence of fibrosis stage 1a or stage 1b (mild or moderate, zone 3 perisinusoidal) as defined by the NASH CRN scoring of fibrosis if accompanied by ≥1 of the following risk factors:
  - Obesity (body mass index [BMI] ≥30 kg/m2)
  - T2D diagnosed per 2013 American Diabetes Association criteria (hemoglobin A1c [HbA1c] ≥6.5%, fasting plasma glucose ≥126 mg/dL, two-hour plasma glucose ≥200 mg/dL during oral glucose tolerance test (OGTT), or random plasma glucose ≥200 mg/dL)
  - ALT >1.5× upper limit of normal (ULN)

- Stable dose of vitamin E and antidiabetic medications for at least 6 months prior to entry.

Table 1 presents the NASH CRN scoring system used to determine eligibility at enrollment and for assessment of the histological endpoints.

Table 1. NASH CRN Scoring System for Histological Assessment

NAFLD Activity Score (NAS)		Fibrosis Staging	
Parameter	Scoring Criteria	Parameter	Staging Criteria
Steatosis	0 = <5% 1 = 5% - 33% 2 = >33% - 66% 3 = >66%	Stage 0	No Fibrosis
Lobular Inflammation	0 = No Foci 1 = <2 Foci per 200 × field 2 = 2-4 Foci per 200 × field 3 = > 4 Foci per 200 × field	Stage 1 Stage 1a Stage 1b Stage 1c	Perisinusoidal or Periportal Mild, zone 3, persinusoidal Moderate, zone 3, perisinusoidal Portal / periportal
Ballooning	0 = None 1 = Few balloon cells 2 = Many cells / prominent ballooning	Stage 2	Perisinusoidal and portal / periportal
		Stage 3	Bridging fibrosis
		Stage 4	Cirrhosis

Source: Applicant's Table 7 on page 91 of protocol 747-303 (Version 9.0: July 29, 2019)

Key exclusion criteria included:

- Evidence of other forms of liver diseases (active hepatitis C, primary biliary cholangitis, autoimmune hepatitis etc.)
- Histologic presence of cirrhosis
- Body weight increase by >10% in 3-months prior to enrollment
- HbA1c >9.5 within 60 days prior to enrollment
- Total bilirubin >1.5 mg/dL (if subject has Gilbert's syndrome, then conjugated bilirubin <1.5x ULN); ALT/AST ≥10x ULN; international normalized ratio (INR) ≥1.4, or serum creatinine ≥1.5 mg/dL; Creatine phosphokinase >5x ULN; Platelet count <100 000/mm3.
- Other medical conditions that may diminish life expectancy to <2 years, including known cancers
- BMI >45 kg/m2 with at least one of the following comorbidities:
  - Blood pressure ≥140/90 if <60 years; ≥150/90 if ≥60 years or on anti-hypertensive medications
  - Hyperlipidemia defined as LDL cholesterol ≥160 mg/dL, total cholesterol ≥200 mg/dL, or on lipid lowering medication
  - T2D

Eligible subjects were randomized in a 1:1:1 ratio to receive OCA 25 mg, OCA 10 mg, or matching placebo once a day for the duration of the study, in conjunction with local standard-of-care (SOC). Randomization of subjects with fibrosis stage 2 or stage 3 was stratified by the presence of T2D at enrollment (yes/no) and use of thiazolidinediones (TZDs)/glitazones or vitamin E at baseline (yes/no). Investigational product was taken orally, with water, once daily.

Under protocol version 8 (08 Jan 2019) as in earlier versions, liver biopsies were planned at Month 18, Month 48, and end of treatment. Subjects who discontinued study drug were encouraged to remain in the trial through study closure.

A Month 18 interim analysis was planned after a minimum of 750 randomized subjects with fibrosis stage 2 or stage 3 reached their actual/planned Month 18 visit and liver biopsy (including subjects who discontinued before reaching the planned Month 18 visit). The database lock for the 18-month interim analysis occurred on October 26, 2018. In protocol version 9 (29 Jul 2019), the requirement for Month 18 biopsies was removed because the study shifted focus from the interim analysis to clinical outcome events.

The focus of the efficacy evaluation for this Advisory Committee meeting is on the pre-specified Month 18 interim analysis of surrogate endpoints that are considered reasonably likely to predict clinical benefit. This interim analysis was planned to support an accelerated approval. Subjects continue to be followed in the study to capture events that comprise the composite clinical benefit endpoint (refer to Section 6.7.1), which is intended to support a traditional approval.

Schedule of Assessment

Subjects were followed to assess vital signs (heart rate, blood pressure, temperature); body weight; laboratory tests (serum chemistry, hematology, coagulation, HbA1c, pregnancy test); adverse events, Model for End-stage Liver Disease (MELD score, and concomitant medication use; DILI or liver decompensation events at baseline (Day 1), month 1, month 3, and then every 3 months until month 18 and then every 6 months.

Hepatobiliary ultrasound was performed at baseline (Day 1), and then semi-annually thereafter. Liver biopsy was performed at baseline and then at month 18 and month 48. After 2019, the month 18 liver biopsy was optional.

Prespecified safety monitoring included:

- Triggers for DILI: The prespecified DILI algorithm was based on liver tests (AST, ALT, TB, DB, ALP), imaging, and clinical findings (symptoms consistent with clinical hepatitis). The triggers for close monitoring, treatment interruption, and study drug discontinuation for suspected DILI were prespecified in the protocol. Hepatic safety adjudication committee (HSAC) members performed blinded adjudication of potential liver injury events.
- Triggers for progression to cirrhosis and liver decompensation: The protocol's prespecified algorithm to identify subjects was based on clinical (liver decompensation) events, laboratory evaluation (liver tests, liver stiffness by transient elastography, FIB-4, APRI, NFS, platelet count, elevated INR, low albumin, elevated bilirubin), and histology, or imaging (nodular liver, splenomegaly) findings for detecting progression to cirrhosis. The Hepatic Outcomes Committee (HOC), consisted of hepatologists, who adjudicated all deaths and potential liver-related clinical events including progression to cirrhosis and hepatic decompensation events.
- Kidney and cardiac monitoring
  - Cardiac Adjudication Committee, members consisting of cardiologists, adjudicated all potential major adverse cardiac events (MACE) including death and hospitalization events.
  - Kidney Adjudication Committee members, expert nephrologists, adjudicated potential events of acute kidney injury.
- The protocol included prespecified algorithms for monitoring and management of dyslipidemia and dysglycemia, which included the following:

- Monitor lipids during the trial. If LDL-C elevations (≥15% relative to baseline value) were identified. Alerts were sent to the principal investigator, who then added pharmacotherapy (statins were added or intensified).
- A treatment algorithm for adding anti-diabetic agents, as well as monitoring, detecting, and managing the following:
  - poor glucose control in diabetic subjects,
  - progression to T2D from prediabetes,
  - progression to prediabetes from normoglycemia.

- In addition, a Data Monitoring Committee (DMC) reviewed the data for safety during the clinical trial.

Endpoints

The following pre-specified primary endpoints for the Month 18 interim analysis were evaluated in subjects with fibrosis stage 2 or stage 3 at baseline:

- Improvement of fibrosis by ≥1 stage AND no worsening of NASH (no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis).
- Resolution of NASH by global interpretation and NAS of 0 for ballooning, 0-1 for inflammation AND no worsening of fibrosis.

These histological endpoints are considered by the Agency to be surrogate endpoints that are reasonably likely to predict clinical benefit (FDA 2018). Use of these endpoints was supported by retrospective and prospective published data that show F2 and F3 fibrosis is associated with higher mortality (Angulo et al. 2015; Ekstedt et al. 2015; Sanyal et al. 2021). Although these are reasonably likely surrogate endpoints likely to predict clinical benefit, there is uncertainty about the magnitude of effect on the surrogate endpoints that may translate into a assessing a meaningful effect on the endpoints for clinical benefit.

Several secondary endpoints based on histology and liver biochemistry were proposed to be assessed at Month 18. Multiplicity adjustments for these endpoints were not pre-specified and therefore, these endpoints are considered exploratory. Exploratory outcomes, including those evaluating biomarkers and noninvasive tests, were also specified, but these endpoints were not included in the multiplicity adjustment.

Histopathology Readings and Analysis Populations

In the review of the original NDA submission, the Agency found poor to moderate inter- and intra-reader concordance in the histopathology readings using a central read method, adding uncertainty to the observed results. For the NDA resubmission, the Applicant reassessed the histopathology slides using a consensus read method. Refer to Section 6.7.2 for the details of these two histopathology read methods.

For the original NDA submission, the efficacy analysis population (N=931) was defined as all fibrosis stages 2 or 3 subjects (central method) who were randomized by July 15, 2017 and received at least one dose of investigational product (IP).

The NDA resubmission contains data from additional subjects in Study 747-303 who were planned to have a Month 18 biopsy but were not planned to be included in the pre-specified interim efficacy analysis due to their later randomization date. The NDA resubmission defines several efficacy analysis

populations.[6] Efficacy analyses will be presented for the following analysis populations, defined in the Statistical Analysis Plan Addendum 2 (April 25, 2022):

- ITT_old: This population includes all of the 931 subjects that made up the efficacy analysis population in the original submission; liver biopsy readings for this population will be presented using both 1) the original central method, and 2) the new consensus method, allowing a comparison of the two methods.
- ITT_histology: This population includes all 1607 subjects who were randomized, received at least one dose of investigational product, have original eligibility baseline fibrosis stage 2/3 (central method), and who had or were expected to have completed a Month 18 visit (including the Month 18 biopsy) per protocol Version 8 (08 Jan 2019) or earlier. Liver biopsy readings for this population will be presented using only the new consensus reading method. ITT_old is a subset of the ITT_histology population.

The interim analyses of the Month 18 primary endpoints in the ITT_old population were pre-specified and accounted for in the method to control the overall type I error rate. P-values are provided for the ITT_old analysis population for both the central method and consensus method for evaluating histopathology slides, as the consensus method for evaluating the ITT_old analysis population can be considered a re-measurement of the pre-specified Month 18 primary endpoints.

The analysis of the ITT_histology analysis population is considered a separate interim efficacy analysis that was not pre-specified, and this analysis was not accounted for in the method to control the overall type I error rate. The results for ITT_histology are considered exploratory, and p-values and discussion of statistical significance are not applicable for ITT_histology. Results are presented for the ITT_histology population to provide additional precision in the estimation of the magnitude of the treatment effect.

Statistical Analysis and Type I Error Control

The pre-specified primary efficacy analysis method for the Month 18 Interim Analysis was a Cochran–Mantel–Haenszel (CMH) test stratified by baseline Type 2 Diabetes Mellitus (T2D) status (yes/no) and baseline thiazolidinediones (TZDs)/vitamin E use (yes/no) to separately compare OCA 25 mg to placebo and OCA 10 mg to placebo. Subjects without a liver biopsy at Month 18 were considered non-responders. Refer to Section 6.7.5 for additional details on the methods for handling missing data.

The overall type I error rate was controlled at the two-sided alpha =0.05 significance level with alpha of 0.02 allocated to evaluate histological endpoints for the 18-month interim analysis and alpha of 0.03 allocated to the clinical outcome endpoint at the end of study. At the 18-month interim analysis, the testing hierarchy started with the comparison of OCA 25 mg to placebo. A truncated Hochberg procedure (See Section 6.7.4 for detail) was used to test the two Month 18 primary endpoints. If at least one of the two Month 18 primary endpoints demonstrated statistical significance in the OCA 25 mg arm, the two Month 18 primary endpoints were to be subsequently tested (also based on a truncated Hochberg procedure) for the comparison of OCA 10 mg to placebo. Refer to Figure 13 in Section 6.7.4 for a depiction of this methodology and for details of the statistical testing procedure for the Month 18 interim analysis.

[6] Traditionally, intent-to-treat (ITT) is defined to include all randomized subjects. The Applicant used a different definition. For ease of comparison of documents for this advisory committee meeting, we are using the Applicant's nomenclature in this document.

3.1.2 Baseline and Efficacy Summary

Efficacy is primarily supported by a single adequate and well-controlled investigation, Study 747-303. NASH can be potentially life-threatening or severely debilitating and is an area of unmet medical need, so additional flexibility may be warranted when considering how to meet the statutory standard of substantial evidence of effectiveness. This document will not discuss potential confirmatory evidence.

3.1.2.1 Demographics and Baseline Characteristics

Table 2 presents the baseline demographic information for all subjects randomized into Study 747-303 who have received at least one dose of investigational product up to the data cutoff on December 31, 2021. Demographics for the ITT_old and ITT_histology populations are similar. The demographics were generally balanced across the treatment groups.

Table 2. Baseline Demographics, Study 747-303 (All Subjects Randomized and Treated With at Least One Dose by December 31, 2021)

Characteristic	OCA 10 mg N=825	OCA 25 mg N=827	Placebo N=825
Sex, n (%)			
Female	475 (57.6)	494 (59.7)	478 (57.9)
Male	350 (42.4)	333 (40.3)	347 (42.1)
Age, years			
Mean (SD)	55.3 (10.8)	55.3 (11.7)	54.4 (11.2)
Median (minimum, maximum)	56 (20, 78)	57 (18, 83)	55 (19, 79)
Age group, years, n (%)			
<65 years	655 (79.4)	644 (77.9)	663 (80.4)
≥65 years	170 (20.6)	183 (22.1)	162 (19.6)
Race, n (%)			
American Indian or Alaska Native	5 (0.6)	8 (1.0)	6 (0.7)
Asian	47 (5.7)	43 (5.2)	29 (3.5)
Black or African American	14 (1.7)	20 (2.4)	12 (1.5)
Native Hawaiian or Other Pacific Islander	4 (0.5)	4 (0.5)	2 (0.2)
White	679 (82.3)	674 (81.5)	685 (83.0)
Missing	76 (9.2)	78 (9.4)	91 (11.0)
Ethnicity, n (%)			
Hispanic or Latino	129 (15.6)	149 (18.0)	147 (17.8)
Not Hispanic or Latino	620 (75.2)	594 (71.8)	592 (71.8)
Not reported	2 (0.2)	7 (0.8)	4 (0.5)
Unknown	4 (0.5)	6 (0.7)	3 (0.4)
Missing	70 (8.5)	71 (8.6)	79 (9.6)
Region of participation, n (%)			
Europe	211 (25.6)	212 (25.6)	200 (24.2)
North America	572 (69.3)	581 (70.3)	582 (70.5)
Rest of world	42 (5.1)	34 (4.1)	43 (5.2)

Source: Clinical data Scientist's analysis of adsl.xpt; Software: R (Ver 4.1.0)
Abbreviations: OCA, obeticholic acid; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Table 3 presents the baseline histopathology characteristics for the ITT_histology population based on both the central method and consensus method for reading liver biopsies. Baseline histopathology characteristics were similar for the ITT_old population (Table 26 in Section 6.7.3). There are subjects included in the main efficacy analyses of the Month 18 primary endpoints who at baseline had fibrosis

Stage 2 or 3 according to the central method but did not have fibrosis Stage 2 or 3 according to the consensus method.

Table 3. Baseline Histopathology Characteristics (ITT_histology)

ITT histology	OCA 10 mg N=532 n (%)	OCA 25 mg N=539 n (%)	Placebo N=536 n (%)
Baseline fibrosis stage (central method)			
Stage 2	219 (41)	238 (44)	223 (42)
Stage 3	313 (59)	301 (56)	313 (58)
Baseline fibrosis stage (consensus method)			
Stage 0	0	1 (<1)	1 (<1)
Stage 1	17 (3)	17 (3)	23 (4)
Stage 2	135 (25)	142 (26)	136 (25)
Stage 3	223 (42)	216 (40)	227 (42)
Stage 4	69 (13)	66 (12)	70 (13)
Not evaluable	9 (2)	3 (<1)	5 (1)
Missing	79 (15)	94 (17)	74 (14)

Source: Statistical reviewer's analysis of adsl.xpt.
Abbreviations: ITT, intention-to-treat; OCA, obeticholic acid

3.1.2.2 Subject Disposition in Trial 747-303

Table 4 presents the disposition for all subjects randomized into Study 747-303 who have received at least one dose of investigational product up to the data cutoff on December 31, 2021. Subject disposition for the ITT_old and ITT_histology populations are similar.

During the trial, 40.5% of OCA 25 mg-treated subjects and 32.2% of placebo-treated subjects discontinued the investigational agent.

A higher percentage of OCA 25 mg-treated subjects (185/827, 22.4%) compared to placebo-treated subjects (99/825, 12.0%) discontinued the study drug due to TEAEs.

Unlike the investigational agent discontinuation rates, the study discontinuation rates were balanced for all treatment arms with approximately 25% of subjects in each arm discontinuing the trial. The primary reason for study withdrawal is due to withdrawal by subject (13.2% OCA 25 mg and 12.4% placebo) followed by adverse event (5.9% OCA 25mg and 3.9% placebo). While the level of study discontinuation can complicate the estimation of risk for a given treatment arm, the balance of study discontinuation across treatment arms allowed for appropriate comparisons of risks between OCA 25 mg and placebo.

Table 4. Subject Disposition, Study 747-303 (All Subjects Randomized and Treated With at Least One Dose by December 31, 2021)

Disposition	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)	Placebo N=825 n (%)
Randomized	825	829	826
ITT_old	312	308	311
ITT_histology	532	539	536
Safety population	825	827	825
Discontinued study drug	277 (33.7)	335 (40.5)	267 (32.2)
Adverse event	103 (12.5)	185 (22.4)	99 (12)
Lost to follow-up	23 (2.8)	20 (2.4)	33 (4)
Noncompliance with study drug	3 (0.4)	4 (0.5)	0 (0)
Physician decision	12 (1.5)	13 (1.6)	9 (1.1)
Protocol violation	3 (0.4)	1 (0.1)	3 (0.4)
Site terminated by sponsor	8 (1)	2 (0.2)	1 (0.1)
Withdrawal by subject	78 (9.5)	72 (8.7)	77 (9.3)
Death	2 (0.2)	2 (0.2)	2 (0.2)
Pregnancy	0 (0)	0 (0)	2 (0.2)
COVID-19 non-AE related issues	1 (0.1)	0 (0)	1 (0.1)
Other	44 (5.3)	36 (4.4)	40 (4.8)
Discontinued study	199 (24.2)	219 (26.5)	203 (24.6)
Adverse event	20 (2.4)	49 (5.9)	32 (3.9)
Lost to follow-up	30 (3.6)	25 (3)	34 (4.1)
Physician decision	9 (1.1)	10 (1.2)	9 (1.1)
Protocol violation	1 (0.1)	1 (0.1)	2 (0.2)
Site terminated by sponsor	8 (1)	3 (0.4)	2 (0.2)
Withdrawal by subject	108 (13.1)	109 (13.2)	102 (12.4)
Death	8 (1)	10 (1.2)	9 (1.1)
Noncompliance with study drug	3 (0.4)	0 (0)	0 (0)
Other	12 (1.5)	12 (1.5)	13 (1.6)

Source: Clinical data Scientist's analysis of adae.xpt; Software: R (Ver 4.1.0)
Treatment-emergent adverse events defined as any AEs that newly appear, increase in frequency, or worsen in severity following treatment up to 30 days from last dose of permanent investigational product discontinuation up to new data cutoff.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; COVID-19, coronavirus disease 2019; ITT, intent-to-treat; OCA, obeticholic acid

3.1.2.3 Efficacy Results

Table 5 and Table 6 contain the results of the primary endpoints for the Month 18 interim analysis. For details on the amount of missing data, refer to Section 6.7.5.

Given the method for controlling the overall type I error rate accounts for multiple testing across the interim and final analyses, two doses, and two primary endpoints, p-values are not compared to the standard 0.05 threshold and the 95% confidence intervals cannot be used to interpret whether an endpoint has achieved statistical significance.

Statistical significance can only be discussed for the pre-specified interim analysis of the ITT_old analysis population (refer to Section 3.1.1). The OCA 25 mg arm demonstrated superiority to placebo on the primary endpoint evaluating improvement of fibrosis and no worsening of NASH and failed to achieve statistical significance on the primary endpoint evaluating resolution of NASH and no worsening in fibrosis. The OCA 10 mg dose failed to achieve statistical significance on either primary endpoint. The conclusions about the statistical significance are the same regardless of histopathology slide read method, central method, or consensus method.

The estimated risk difference (95% confidence interval) comparing OCA 25 mg to placebo on the endpoint of improvement of fibrosis and no worsening of NASH ranged from 8.6% (4.2%, 13.0%) to 12.8% (7.0%, 18.5%) across the different analysis populations and histopathology read methods. Risk difference is the summary measure presented in Table 5 and Table 6 because the statistical analysis plan (SAP) specified the null hypothesis in terms of evaluating the "percentage of subjects" who were responders, and the risk difference is clinically meaningful and easily interpretable. Efficacy results using the odds ratio as the summary measure are presented in Table 29 and Table 30 in Section 6.7.3.

Table 5. Study 747-303 Month-18 Interim Analysis Primary Endpoint Results—Improvement of Fibrosis and No Worsening of NASH (ITT_old and ITT_histology)

	OCA 10 mg	OCA 25 mg	Placebo	Risk Difference 10 mg-Placebo (95% CI)	Risk Difference 25 mg-Placebo (95% CI)	P-Value 10 mg	P-Value 25 mg
ITT_old							
Central method (original results)	N=312	N=308	N=311				
N (%)	55 (17.6)	71 (23.1)	37 (11.9)	5.7 (0.2, 11.3)	11.1 (5.3, 17.0)	0.0446	0.0002*
Consensus method	N=312	N=308	N=311				
N (%)	44 (14.1)	69 (22.4)	30 (9.6)	4.5 (-0.6, 9.5)	12.8 (7.0, 18.5)	0.0863	<0.0001*
ITT_histology							
Consensus method	N=532	N=539	N=536				
N (%)	86 (16.2)	113 (21.0)	66 (12.3)	3.8 (-0.4, 8.0)	8.6 (4.2, 13.0)	N/A	N/A

Source: Statistical analyst's analysis of adsl.xpt, admi.xpt, and adbx.xpt datasets; same as Applicant's results. P-values calculated using CMH test stratified by randomization strata (diabetes at enrollment [yes/no] and use of TZDs or vitamin E at baseline [yes/no]). The Mantel-Haenszel method was used to construct the CIs.
* denotes statistical significance.
Note: 95% confidence intervals cannot be used to determine statistical significance.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; N/A, not applicable; OCA, obeticholic acid

Table 6. Study 747-303 Month-18 Interim Analysis Primary Endpoint Results—Resolution of Nash and no Worsening of Fibrosis (ITT_old and ITT_histology)

	OCA 10 mg	OCA 25 mg	Placebo	Risk Difference 10 mg-Placebo (95% CI)	Risk Difference 25 mg-Placebo (95% CI)	P-Value 10 mg	P-Value 25 mg
ITT_old							
Central method (original results)	N=312	N=308	N=311				
N (%)	35 (11.2)	36 (11.7)	25 (8.0)	3.1 (-1.4, 7.7)	3.6 (-1.0, 8.3)	0.1814	0.1268
Consensus method	N=312	N=308	N=311				
N (%)	19 (6.1)	20 (6.5)	11 (3.5)	2.5 (-0.8, 5.9)	3.0 (-0.5, 6.4)	0.1377	0.0926
ITT_histology							
Consensus method	N=532	N=539	N=536				
N (%)	34 (6.4)	39 (7.2)	19 (3.5)	2.8 (0.2, 5.4)	3.7 (1.0, 6.4)	N/A	N/A

Source: Statistical analyst's analysis of adsl.xpt, admi.xpt, and adbx.xpt datasets; same as Applicant's results. P-values calculated using CMH test stratified by randomization strata (diabetes at enrollment [yes/no] and use of TZDs or vitamin E at baseline [yes/no]). The Mantel-Haenszel method was used to construct the CIs.
Note: 95% confidence intervals cannot be used to determine statistical significance.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; N/A, not applicable; OCA, obeticholic acid

An Agency-requested post-hoc sensitivity analysis evaluated all randomized subjects who had or were expected to have completed Month 18 visit (including Month 18 biopsy) under protocol version 8 or earlier and who were determined to have a baseline fibrosis stage 2 or 3 based on the consensus method (Table 27). The estimated risk differences and 95% confidence intervals are generally consistent with those estimated based on the subjects with baseline fibrosis stage 2 or 3 based on the central method (Table 5 and Table 6).

3.1.3 Efficacy Uncertainties

While OCA 25 mg demonstrated superiority to the placebo on one of two primary endpoints, there was a modest treatment effect on this surrogate endpoint. There is uncertainty how the magnitude of changes in these surrogate endpoints may translate to meaningful changes in clinical outcomes.

The main issue for the Advisory Committee to consider is weighing the modest treatment effect on a reasonably likely surrogate with the risk considerations.

3.2 Safety Issues

3.2.1 Sources of Data for Safety

The first review cycle for this NDA application was conducted between 2019 and 2020 and encompassed data from 20 phase 1 and clinical pharmacology studies; two phase 2 trials (FLINT Trial and D8602001), and one phase 3 trial (Trial 747-303). Data from 1968 subjects who had completed EOT (month 18 visits) were available for review from Trial 747-303: OCA 10 mg (n=653), OCA 25 mg (n=658), and placebo (n=657).

The Agency has summarized results from Trial 747-303 in this background document. Results from Phase 2 trials (FLINT and D8602001) were not pooled with Trial 747-303. When the NDA submission was reviewed in 2019-2020, the Agency identified several safety issues across the phase 2 trials and phase 3 trial. These safety issues are described in detail below. With the addition of 509 subjects since the original NDA submission, the safety profile of OCA has not changed. With data from the original submission and from additional subjects that were enrolled in Trial 747-303, the number of AEs has increased and the confidence intervals around those event incidences has narrowed.

The current resubmission included data from 1968 subjects in the original submission plus 509 additional subjects who completed the month 18 visit in Trial 747-303, with a data cut-off date of December 31, 2021. A total of 2,477 subjects had been randomized to OCA 10 mg (n=825), OCA 25 (n=827), and placebo (n=825). The safety review in this document is based only on the updated data from Trial 747-303 because this provides the best representation of long-term controlled safety data to characterize the safety profile of OCA 25mg.

The safety issues identified during the previous review cycle remain the focus of the safety review in this cycle. The analyses of safety outcomes are focused on the proposed to-be marketed dose of OCA 25 mg in trial 747-303. Because the OCA 10 mg dose did not demonstrate a benefit on the primary endpoints, the safety of the OCA 10 mg arm will not be discussed, except in the context of evaluating potential dose-response associations with adverse events.

3.2.2 Safety Summary

3.2.2.1 Approach to Safety Review

General adverse event reporting was based on coding verbatim terms to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. The following Adverse Events of Special Interest (AESI) were pre-specified in the study protocol and are discussed in this document: hepatotoxicity/DILI, gallstone and bile duct stones/sludge and related complications, dyslipidemia, dysglycemia, and

pruritus. The Applicant implemented adjudication committees to adjudicate potential hepatic safety/DILI events, renal/AKI events, and cardiovascular events.

Analyses of safety outcomes are summarized based on two follow-up windows:

- On-treatment plus 30 days. This follow-up window includes time from randomization until the earliest of last dose of treatment + 30 days, death, study discontinuation, or data cutoff date. Analyses of treatment emergent adverse events, dyslipidemia, and pruritus were conducted based on this follow-up window.
- On-study. This follow-up window includes time from randomization until the earliest of: death, study discontinuation, or data cutoff date. Analyses of deaths, adjudicated DILI, gallstones, and bile duct stones and sludge were conducted based on this follow-up window.

Incident AE outcomes (i.e., first event) were estimated using incidence rates (IR) for within-arm estimates and incidence rate differences (IRD) for comparing OCA to Placebo. The incidence rate for an adverse event of interest was calculated by dividing 100 x the number of subjects who experienced the event by the total number of patient-years of follow-up based on the follow-up windows defined above. The incidence rate difference was calculated by subtracting the IR of events observed in the placebo arm from the IR of events observed in the corresponding OCA arm. The IR, IRD and their corresponding 95% confidence intervals were calculated using the Poisson model.

3.2.2.1.1 Extent of Exposure

At the time of the data cutoff, 616 (74.5%) OCA 25 mg-treated subjects and 667 (80.9%) placebo-treated subjects had achieved at least eighteen-months duration of exposure (Table 7). This exposure was calculated considering drug holidays and reduced dosing frequency.

The mean (SD) duration of treatment was 1065.8 days (618.4) for OCA-25 mg-treated subjects and 1171.7 days (571.7) for placebo-treated subjects.

The total exposure was 2413.1 person years (PY) for 827 subjects on OCA 25 mg, 2584.7 PY for 825 subjects on OCA 10 mg, and 2646.6 PY for 825 subjects on placebo. The total person-years of exposure are calculated by summing the time of exposure, measured in years, for each subject treated in the trial (time from first dose to last dose in the trial for each subject, taking into account drug holidays and reduced dosing frequency).

Table 7. Duration of Exposure, Study 747-303

	OCA 10 mg N=825	OCA 25 mg N=827	Placebo N=825
Duration of treatment, days			
Mean (SD)	1144.3 (564.6)	1065.8 (618.4)	1171.7 (571.7)
Median (Q1, Q3)	1177 (760, 1642)	1125 (524, 1611)	1238 (839, 1662)
Minimum, maximum	2, 2197	1, 2201	1, 2200
Total exposure (person years)	2584.7	2413.1	2646.6
Subjects treated, by duration, n (%)			
>0 days	825 (100)	827 (100)	825 (100)
≥6 months	773 (93.7)	714 (86.3)	768 (93.1)
≥12 months	713 (86.4)	663 (80.2)	723 (87.6)
≥18 months	659 (79.9)	616 (74.5)	667 (80.9)
≥48 months	299 (36.2)	274 (33.1)	305 (37.0)

Source: Statistical reviewer analysis based on Applicant submitted data adexsum.xpt.
Abbreviations: OCA, obeticholic acid; SD, standard deviation

3.2.2.1.2 Overview of Treatment-Emergent Adverse Events (TEAE) in Trial 747-303

Overall, mild AEs were balanced across all the treatment arms; see Table 8.

However, more subjects in the OCA 25 mg treatment arm experienced severe and worse AEs, and AEs leading to dose modification (drug interruption or dose reduction) or permanent discontinuation than subjects in the placebo arm (257 (12.1%) versus 191 (8.1%), with incidence rate (IR) difference of 4.0 per 100 PY (95% CI 2.2, 5.9)). There was an imbalance in the moderate AEs, with higher event rates in the OCA 25 mg-treated subjects; see Table 8.

AEs leading to permanent drug-discontinuation occurred in higher number of OCA 25 mg-treated subjects compared to the placebo-treated subjects (179 (7.3 per 100 PY) versus 93 (3.4 per 100 PY), IR difference 3.8 per 100 PY (95% CI 2.6, 5.1)); see Table 8.

Higher numbers of OCA 25 mg-treated subjects required dose modification (treatment interruption and dose reduction) relative to placebo-treated subjects; see Table 8. Number of fatal outcomes in this Table occurred secondary to SAE. In Table 9, we discuss all deaths that occurred after the subject was enrolled in the trial, that is the reason for differences in the number of deaths noted in Table 9 and Table 10.

Table 8. Overview of Adverse Events, Study 747-303

Event Category	OCA 10 mg N=825 n (%) Events (IR)	OCA 25 mg N=827 n (%) Events (IR)	Placebo N=825 n (%) Events (IR)	OCA 25 mg vs. Placebo IR Difference (95% CI)
SAE	204 (8.8)	216 (10.2)	181 (7.5)	2.6 (0.9, 4.4) *
SAEs with fatal outcome	9 (0.3)	10 (0.4)	8 (0.3)	0.1 (-0.2, 0.4)
Life-threatening SAEs	12 (0.5)	7 (0.3)	9 (0.3)	-0.1 (-0.4, 0.2)
AE leading to permanent discontinuation of study drug	102 (3.8)	179 (7.3)	93 (3.4)	3.8 (2.6, 5.1) *
AE leading to dose modification of study drug	265 (12.4)	331 (18.4)	229 (10.0)	8.3 (6.0, 10.7) *
AE leading to interruption of study drug	245 (11.2)	314 (16.9)	214 (9.2)	7.7 (5.4, 9.9) *
AE leading to reduction of study drug	34 (1.3)	52 (2.2)	22 (0.8)	1.4 (0.7, 2.1) *
Any AE	795 (312.3)	807 (442.3)	766 (202.0)	240.2 (206.5, 273.9) *
Severe and worse	203 (8.8)	257 (12.1)	191 (8.1)	4.0 (2.2, 5.9) *
Moderate	445 (29.9)	436 (32.7)	441 (28.2)	4.5 (0.5, 8.5) *
Mild	147 (6.4)	114 (5.2)	134 (5.7)	-0.5 (-1.9, 0.8)

Source: Clinical Data Scientist's analysis of adae.xpt; software, R (Ver 4.1.0).
*, Rows where the 95% confidence interval excludes zero.
Treatment-emergent adverse events defined as any AEs that newly appear, increase in frequency, or worsen in severity following treatment up to 30 days from the last dose of permanent investigational product discontinuation up to new data cutoff.
Mean duration is approximately 39 months, including 976 subjects with long-term exposures >4 years.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; IR, incidence rate per 100 PY; IR Difference, incidence rate difference per 100 PY; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; PY, patient-years

3.2.2.1.3 Deaths

There was a numerical imbalance in deaths across trial 747-303 and the NASH drug development program. More subjects dosed with OCA 25 mg died compared to the placebo arm (14 versus 10 in trial 747-303; 17 versus 10 across all NASH studies conducted by the Applicant- see Table 9). Although the Applicant presented only deaths occurring in subjects on active treatment and up to 30 days after treatment discontinuation, for completeness, the Agency is reporting deaths occurring in subjects on active treatment, as well as those occurring in subjects who remained in the study ("on study follow-up") following discontinuation of active treatment.

Table 9. Deaths Across OCA Drug Development Program

Trial	OCA 10 mg N=917	OCA 25 mg N=1009	Placebo N=1017
747-303*	11	14	10
747-209 including LTSE	1	1	0
DS8602001	0	0	0
FLINT Trial	0	2	0
Total number of deaths in NASH drug development program	12	17	10

Source: Statistical reviewer analysis based on Applicant submitted data adsl.xpt and the supporting document number 001 (Applicant submitted on September 26, 2019).
*On-Study Analyses up to cutoff date of 12/31/2021.
*One subject in OCA 25 mg died after the cutoff date was included in the analysis.
Abbreviations: LTSE, long-term safety extension; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid

Trial 747-303 was designed to exclude subjects with significant comorbidities who were at high risk of non-hepatic and hepatic death. The risk of liver-related death is generally low in a non-cirrhotic population. One subject (Subject 2) in the OCA 25 mg arm died of acute on chronic liver failure. Table 25 describes the causes of death for subjects across the three treatment arms, as noted in Section 6.5.

3.2.2.1.4 SAEs

Most SAE's were captured within the AESI, see Section 3.2.3 for details.

3.2.2.1.5 Treatment Interruptions Secondary to Pruritus

Most treatment interruptions were secondary to pruritus. There was an imbalance in treatment interruptions across treatment arms, with the maximum number of treatment interruptions occurring in the OCA 25 mg arm, followed by the OCA 10 mg arm, with fewer interruptions in the placebo arm (Table 10). Triggers for treatment interruptions were prespecified in the protocol as to when subjects experienced grade 3, or severe, or sustained pruritus events.

Table 10. Treatment Interruption Due to Pruritus, Study 747-303

	OCA 10 mg N=825	OCA 25 mg N=827	Placebo N=825
Duration of exposure* (years)	2584.7	2413.1	2646.6
Subject with at least one treatment interruption due to pruritus	37	162	15
Lasting 1-5 days	7	25	4
Lasting 6-10 days	9	41	2
Lasting >10 days	21	96	9

Source: Statistical reviewer analysis based on Applicant submitted data adexsum.xpt.
* Duration of exposure excluded the days on drug holiday, missed dose, or treatment interruption.
Abbreviation: OCA, obeticholic acid

3.2.2.1.6 Postmarketing Experience

Experience of OCA-Related Hepatoxicity in the Postmarketing Setting in the PBC Population

Ocaliva (obeticholic acid) tablets was approved on May 27, 2016 under the accelerated approval pathway for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults who are unable to tolerate UDCA. About 90% of the subjects in the trial used to support accelerated approval had early stage PBC; however, the approval was for all PBC patients. The rationale for approving OCA in a wider spectrum of disease severity was that PBC is a rare disease, and the mechanism of action of OCA includes reduction in fibrosis. The postmarketing trials required to confirm clinical benefit included patients with more advanced PBC and patients with cirrhosis.

Following approval, deaths and liver decompensation events were reported to the FDA adverse event reporting system (FAERS). Most, but not all, cases were due to higher than recommended OCA dosing, specifically, doses approved for noncirrhotic patients were administered to PBC patients with decompensated cirrhosis. On February 1, 2018, the FDA added a Boxed Warning highlighting the need to follow the recommended dose reduction for patients with advanced cirrhosis.

Following the 2018 addition of the boxed warning to the labeling, FDA continued to receive reported cases of serious liver injury leading to liver decompensation or liver failure associated with use of OCA (Ocaliva), despite appropriate dosing in PBC patients with cirrhosis. In May 2021, based on an evaluation of these cases FDA added a contraindication for use of Ocaliva in all PBC patients with decompensated cirrhosis or compensated cirrhosis with evidence of portal hypertension. Discussion of the hepatotoxicity in these PBC patients with advanced liver disease was also added to the Warnings and Precautions section of labeling. These significant labeling changes were disseminated in an FDA Drug Safety Communication on May 26, 2021.[7]

3.2.3 Safety Issues in Detail

3.2.3.1 Hepatotoxicity – Drug-Induced Liver-Injury (DILI)

Issue

OCA can cause liver injury in two primary ways. A cholestatic DILI attributable to OCA was identified in subjects with NASH. OCA also causes biliary sludge and stone formation that can lead to cholangitis, an indirect liver injury of concern discussed separately in Section 3.2.3.2.

Background

OCA is a synthetic, hydrophobic bile acid. It does not exist naturally in humans. OCA and OCA conjugates (glyco- and tauro- OCA) absolute levels and levels relative to other bile acids increase in the liver due to enterohepatic circulation and reduction in endogenous bile acid synthesis because OCA suppresses bile acid biosynthesis. Hydrophobic bile acids are considered more toxic to the liver compared to hydrophilic ones. Dose-dependent DILI from OCA has been observed in both the NASH and PBC populations, as well as in healthy volunteers.

Phase 1 Healthy Volunteer Studies

The pattern of OCA-related hepatoxicity included cholestatic, hepatocellular, or mixed, with elevations observed in aminotransferases, ALP, or a mix of both.

OCA Hepatoxicity in the Premarketing Setting in the PBC Population

A dose-dependent hepatotoxicity with a cholestatic pattern of injury was identified across the PBC drug development program.

NASH Drug Development Program

During the review of the original NDA submission for NASH, a cholestatic liver injury pattern was predominant, although hepatocellular and mixed injuries were also observed. Hepatotoxicity was observed both with single high-dose OCA administration as well as with multiple OCA dose administration. The injury was reversible in most cases (i.e., with OCA discontinuation, the elevations in

[7] https://www.fda.gov/drugs/drug-safety-and-availability/due-risk-serious-liver-injury-fda-restricts-use-ocaliva-obeticholic-acid-primary-biliary-cholangitis

liver enzymes normalized). However, rapid progression and irreversible injury was observed in three OCA 25 mg-treated subjects in three phase 2 trials (747-209, FLINT, and D8602001).

The Applicant also completed a trial assessing safety and efficacy of OCA 25 mg in subjects with compensated cirrhosis (Anon 2018) due to NASH. OCA failed (2022) to meet its primary endpoint of one stage reduction of fibrosis, and the Applicant is no longer pursuing drug development in this population.

Key Findings From Pivotal Phase 3 Trial 747-303

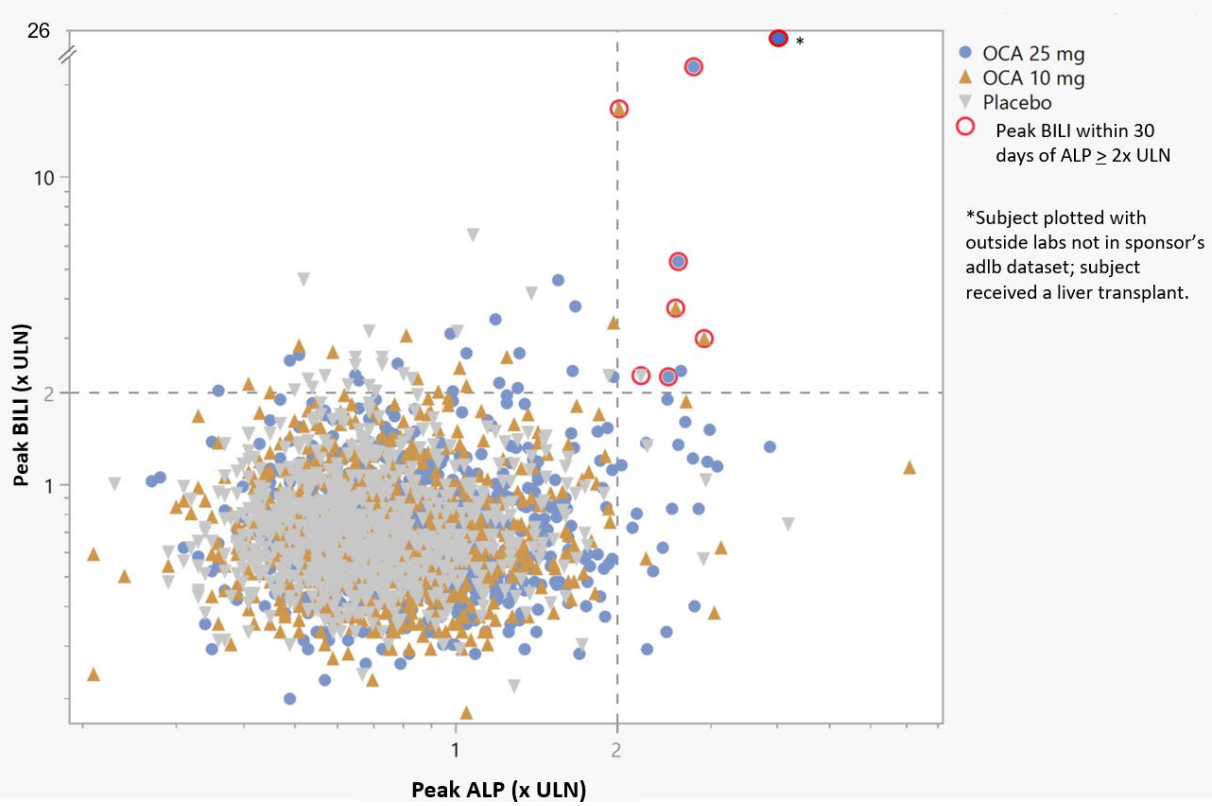
Trial 747-303 data establishes a DILI risk that is concerning for OCA approval. The risk is discussed in the following four key findings.

3.2.3.1.1 Cholestatic DILI Risk

ALP and TB levels increased more in subjects on OCA arms compared to those on placebo arm, leading to a higher incidence of ALP ≥2x ULN and ALP ≥2x ULN with jaundice (TB ≥2x ULN) suggesting clinically important cholestatic DILI risk.

A cholestatic scattergram (Figure 4) plots peak total bilirubin (TB) versus peak alkaline phosphatase (ALP) with both analytes expressed as times upper limit of normal (log scale). The table inside the figure provides counts and crude incidence rates for subjects having ALP ≥2x ULN with TB ≥2x ULN (right upper quadrant), ALP <2x ULN with TB ≥2x ULN (left upper quadrant) and ALP ≥2x ULN with TB <2x ULN (right lower quadrant).

Figure 4. Cholestatic Scattergram Plotting Peak Total Bilirubin (TB) Versus Peak Alkaline Phosphatase (ALP)



Quadrant	OCA 25 mg (N = 827)	Placebo (N = 825)
ALP≥2x ULN & TB≥2x ULN	5 (0.6%)	1 (0.1%)
ALP<2x ULN & TB≥2x ULN	17 (2.1%)	19 (2.3%)
ALP≥2x ULN & TB<2x ULN	20 (2.4%)	4 (0.5%)

Source: Reviewer using the ADaM datasets.

Thus, the ALP and TB elevations between arms suggest a potential cholestatic DILI. Attribution of these analyte elevations to DILI requires case level assessments, which is discussed next.

3.2.3.1.2 Case Level Assessment

The blinded case level assessments of liver injury events by the Applicant's independent Hepatology Safety Adjudication Committee (HSAC) suggests OCA causes DILI. The HSAC used the Drug-Induced Liver Injury Network (DILIN) methodology (Fontana et al. 2009) to score cases as 1=definite, 2=highly likely, 3=probable, 4=possible, or 5=unlikely DILI, and was blinded to study arm. A higher proportion of subjects treated with OCA 25 mg had possible, probable, or highly likely DILI compared to those on placebo (Table 11).

Table 11.Trial 747-303, Blinded HSAC DILI Assessments for Liver Injury Events

Blinded HSAC Assessment Score	Study Arm			
	OCA 25 mg	(% Within Arm)	Placebo	(% Within Arm)
1 = Definite	0	(0)	0	(0)
2 = Highly likely	1	(0.5)	0	(0)
3 = Probable	7	(3.5)	1	(0.6)
4 = Possible	57	(28.6)	11	(6.8)
5 = Unlikely	134	(67.3)	150	(92.6)
Total	199	(100)	162	(100)

Source: Reviewer generated from data submitted by the Applicant; blinded HSAC DILI assessments for liver injury events (numbers and percentages within arm) in the OCA 25 mg/day and placebo arms.
Abbreviations: DILI, drug-induced liver injury; HSAC, Hepatic Safety Adjudication Committee; OCA, obeticholic acid

However, the liver injury pattern, latency, and severity of DILI cases adjudicated by the HSAC remained unclear. FDA readjudicated twelve cases of interest in an unblinded manner (Table 12) and using the same DILIN methodology for causality assessment already referenced (i.e., 1=definite, 2=highly likely, 3=probable, 4=possible, or 5=unlikely DILI) (Fontana et al. 2009). These twelve cases included, eleven moderate to severe liver injuries, causality was considered as at least "possible" OCA related hepatotoxicity (25 mg or 10 mg) by the HSAC; and one fatality that was considered "possible to probable" OCA related liver injury by FDA, but was considered as "unlikely" related to OCA by the HSAC. Definitions of severity level follow:

- Mild: ALT/ALP reaching criteria for DILI but TB <2xULN.
- Moderate: Elevated ALT or ALP with TB >2x ULN (i.e., jaundice) or >2x baseline if baseline elevated.
- Severe: Moderate criteria met and at least one of the following
  - INR >1.5 (>1.5x baseline if baseline elevated)
  - Ascites and/or encephalopathy, disease duration <26 weeks, and absence of underlying cirrhosis
  - Other organ failure considered to be due to DILI.
- Fatal / Liver transplantation: Death or transplantation due to DILI.

FDA and HSAC causality scores were similar. All but one subject had cholestatic injury with a median R-value[8] of 0.9 (range 0.5 to 11.7). Median exposure (days) between initiating OCA and the onset of DILI was 307 days with a wide range (28 to 912 days). One subject with baseline F2 fibrosis required liver transplant for cholestatic liver injury 187 days after OCA start (Table 12, #1; Subject 3). Another subject had a TB of 19.9 mg/dL but recovered (Table 12, #2, Subject 4). Significant gallstone disease was not seen in either of these two cases. One subject with cirrhosis died of acute on chronic liver failure (Table 12, #10, Subject 2).

[8] R-value = (ALT/ULN) ÷ (ALP/ULN); values ≤2 are cholestatic, 2-5 are mixed and ≥5 hepatocellular.

Table 12. Twelve Subjects on OCA With Moderate To Severe Liver Injury Assessed as at Least Possible DILI by FDA or the HSAC

#	OCA dose (mg/d)	Unblind FDA Score*	Blinded HSAC Score*	Alternate diagnosis	Fibrosis at baseliine	Age (yr)	Fatality	Days OCA start to injury onset	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak	Notes
1	25	3 ←	4	Not applicable	F2	63	Yes	150	139	233	399	28.9	1.1	Liver transplant Day 187
2	10	3	3	Not applicable	F3	49	No	28	135	168	304	19.9	1.4	
3	25	3	3	Not applicable	F3	63	No	28	50	100	234	5.2	0.7	
4	25	3 or 4 ←	5	Gallstone disease progression	F3	60	Yes	530	57	108	294	37.4	0.6	ACLF; new porcelain GB
5	25	4	4	De novo gallstone disease	F1b	70	No	912	399	375	104	11.7	11.7	ERCP pancreatitis
6	25	4	4	Fracture; cephalosporin liver injury	F2	68	No	408	90	116	529	3.6	0.5	
7	25	4	4	De novo gallstone disease; other DILI	F3	65	No	461	108	80	218	11.9	1.5	ERCP x 3
8	10	4	4	Gallstone disease	F2	59	No	833	62	93	407	2.2	0.5	
9	25	4 →	3	Unknown	F3	57	No	28	196	130	297	2.7	2.0	
10	25	4	4	Disease progression	F3	64	No	176	38	84	249	2.8	0.5	
11	25	5 →	4	Unknown	F2	59	No	363	150	66	197	0.9	2.3	
12	25	5 →	4	AM/CL liver injury	F3	68	No	251	100	119	393	6.4	0.8	
					Mean	***62***		***347***	***127***	***139***	***302***	***11.1***	***2.0***	
					Std dev	*5.5*		*287*	*94*	*83*	*110*	*11.3*	*3.0*	
					Median	***63***		***307***	***104***	***112***	***296***	***5.8***	***0.9***	
					Min	*49*		*28*	*38*	*66*	*104*	*0.9*	*0.5*	
					Max	*70*		*912*	*399*	*375*	*529*	*37.4*	*11.7*	

Source: FDA DILI Team
R-value = (ALT/ULN) ÷ (AP/ULN); R > 5: hepatocellular; R 2 to 5 mixed; R <2 cholestatic; if peak enzyme was below the ULN, the ULN was imputed for R-value calculation.
* 1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely. ** ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL.
~~ Initial biopsy F3; biopsy on Day 470 showed cirrhotic nodules formation with F3 fibrosis.
Abbreviations: Abx, antibiotics; ACLF, acute on chronic liver failure; ALT, alanine aminotransferase; AM/CL, amoxicillin/clavulanate; AP, a kaline phosphatase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ERCP, endoscopic retrograde cholangiopancreatography; fatality, death or need of liver transplant; GB, gallbladder; HSAC, Hepatology Safety Adjudication Committee; NA, not available or not applicable; OCA, obeticholic acid; ULN, upper limit of normal

FDA has concluded that OCA can cause significant DILI. The pattern of injury was predominantly cholestatic, had a wide latency range, and two of twelve with at least moderate injury had fatal outcomes. Overall incidence rates of at least moderately severe DILI based on OCA exposure is discussed below.

3.2.3.1.3 Incident Rates of Moderate to Severe DILI

Based on the HSAC adjudications and incidence rate differences (IRD), approximately 2.4 additional moderate to severe DILI events, at least possibly due to OCA, are expected for every 1000 patients treated with OCA 25 mg for one year that would not be observed if patients received placebo (IRD of 0.24 per 100 PY). Similarly, 11.1 additional mild DILI events are expected for every 1000 patients treated with OCA 25 mg for one year that would not be observed if patients received placebo. The observed IR for mild DILI events in Trial 747-303 was approximately 4.3-fold as high in the OCA 25 mg arm than on placebo (IR 1.45 versus 0.34 per 100 PY).

Table 13. Hepatoxicity Adverse Events of Special Interest, Study 747-303

Adverse Events of Special Interest	OCA 25 mg N=827 n [IR]	Placebo N=825 n [IR]	IR Difference (95% CI) per 100 PY
Adjudicated DILI (Possible/prob/highly likely causality and ≥moderate severity)	8 [0.28]	1 [0.03]	0.24 (0.04, 0.45)
Adjudicated DILI (Possible/prob/highly likely causality and ≥mild severity)	41 [1.45]	10 [0.34]	1.11 (0.62, 1.60)

Source: Statistical reviewer analysis based on Applicant-submitted data adtte2i4.xpt.
* On-Study Analyses up to cutoff date of 12/31/2021.
Abbreviations: DILI, drug-induced liver injury; IR Difference, incidence rate difference between OCA and placebo; [IR], incidence rate per 100 PY; OCA, obeticholic acid; PY, patient-years of follow-up until the earliest date of study discontinuation, loss of follow-up, cut-off date, first event, or death

3.2.3.1.4 Rate of Fatality due to DILI

The DILI fatality (death or transplant) rate of one in 827 subjects exposed to OCA is 18-fold higher than the rate that typically raises Agency's concerns for drug approvability by the Agency (FDA 2009).

Concerns for approvability arise if there are one or two cases of hepatocellular DILI with jaundice in large registry trials (e.g., 3000 subjects exposed to study drug). This rate is anchored on Hy's Law which says hepatocellular DILI with jaundice has a 10% mortality risk. Since the early 2000's, when the Agency incorporated this threshold for DILI risk concern, no drug has been removed from the market for severe DILI, and retrospective analyses of drugs previously removed suggested they had breached this threshold in clinical trials. The intent of incorporating Hy's Law was to ultimately reduce the risk of liver-related fatality risk due to drugs. Therefore, in applying this threshold to OCA translates to just 0.2 fatalities in 3000 exposed (10% mortality risk for two subjects with hepatocellular jaundice).

While there is no Hy's Law equivalent to use as a surrogate marker predicting fatality with cholestatic DILI, Trial 747-303 had a DILI fatality stepping over the need for a surrogate. The subject (Subject 3) who needed transplant completed the outcome to be avoided, thereby setting the fatality rate without the need for a Hy's Law-like predictor. Even if the Agency's threshold of concern is relaxed by 10-fold (i.e., 2 DILI fatalities in 3000 exposed), the rate seen in study 747-303 is still 1.8-fold higher. The threshold of concern for fatal hepatocellular DILI should also apply to cholestatic DILI because fatality avoidance is the ultimate goal. If the DILI fatality rate is defined by a registry trial, that rate should be held to the usual Agency's DILI fatality rate of concern, regardless of injury pattern.

Therefore, the DILI fatality rate in study 747-303 depended on the adjudication of the subject that required liver transplant. FDA discusses this case in detail below.

3.2.3.1.5 Subject 3

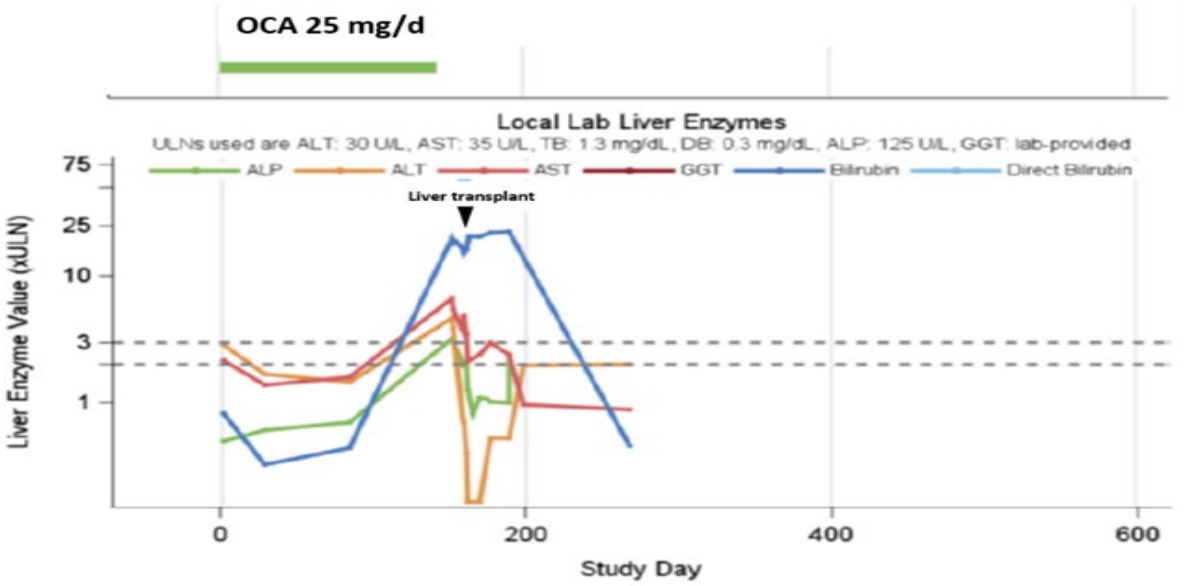
Summary:[9] This is a 63-year-old black man who was noted to have an acute cholestatic injury with jaundice 150 days after starting OCA at 25 mg.

At baseline he had Stage 2 fibrosis on biopsy. ALT, AST, ALP, and TB were 116 U/L, 94 U/L, 63 U/L and 1.13 mg/dL respectively. He had a history of gout since 2014, obesity, hypertension, and dysplipidemia. His medications included allopurinol since 2014, diclofenac since Sep 13, 2016, amlodipine, colchicine since 2014, and acetaminophen + hydrocodeine since 2014, i.e., to prior to enrollment in the trial. There was no mention of herbal/dietary supplement or alcohol use.

He started OCA 25 mg on Day 1. He developed pruritus around Day 70. ALT, AST, and TB declined through Day 83 to 44 U/L, 56 U/L and 0.58 mg/dL, respectively, but ALP rose modestly to 88 U/L. On Day 129, he had a vesicular rash, nausea, vomiting, dizziness, diarrhea, and dark urine, but no fever. He self-discontinued the OCA on Day 142. Labs were drawn on Day 150. ALT, AST, ALP, and TB were 139 U/L, 233 U/L, 399 U/L, and 25.7 mg/dL, respectively (Figure 5). Ultrasound and MRI imaging showed a "small dependent gallstone" without ductal dilation. Liver biopsy suggested "obstruction to bile flow or possible drug injury" with increased fibrosis but no mention of cirrhosis. Dermatology diagnosed the rash as "folliculitis" with staph aureus infection and "purigo nodules… thought to be secondary to methicillin-sensitive Staphylococcal aureus bacteremia." Liver enzymes then improved, but hyperbilirubinemia was unrelenting with development of ascites and encephalopathy. He was evaluated and listed for transplant on Day 160. By Sep 2, 2017, his "bacteremia was also noted to be resolved" with subsequent negative blood cultures. He was discharged on Day 175 with a MELD-Na of 31 (TB 28.5 mg/dL). "On Day 187, the subject was hospitalized and underwent liver transplant" by standard piggy-back caval anastomosis from a deceased donor. There was no mention of needing choledochoenterostomy. MELD-Na at transplant was 39 (TB 28.9 mg/dL). No explant histology information was provided. On Day 267, his liver analytes had returned to baseline.

[9] All phrases in quotations are from the case narrative. NDA212833 (212833 - 0098 - (105) - 2023-01-26 - ORIG-1 /Clinical/Response To Information Request) - 747-303 Related-Liver Events Narratives 25Jan2023 (#6)

Figure 5. Liver Analytes Over Time For Subject 3

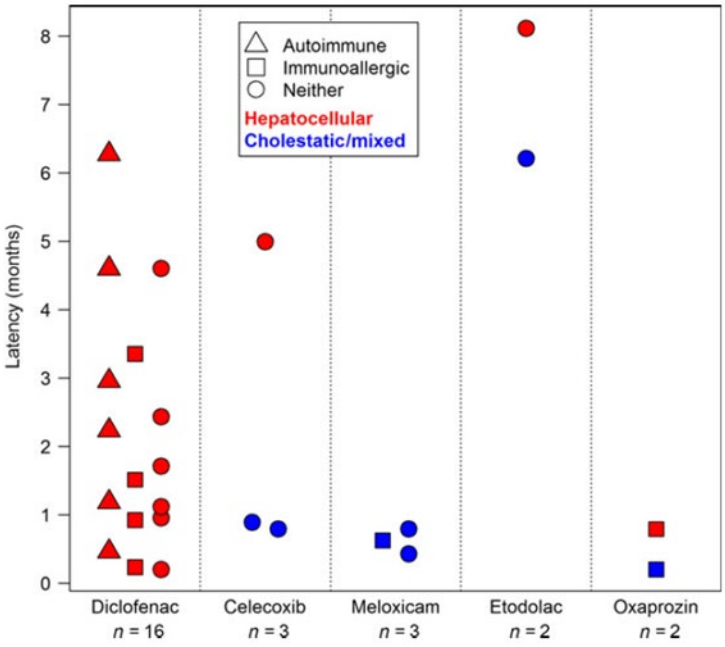


Source: Adapted from NDA Information Request #01 NDA212833 (212833 - 0098 - (105) - 2023-01-26 - ORIG-1 /Clinical/Response To Information Request) - 747-303 Related-Liver Events Narratives 25Jan2023 (#16)

HSAC Assessment(s): The HSAC consider this possible DILI due to OCA. Each of the reviewers' reports and comments are attached.

FDA's Assessment: The FDA assessed this case as at least probable DILI due to OCA. The liver biopsy suggested biliary obstruction or DILI. However, biliary obstruction was ruled out by MRI, ultrasound, and presumed bile duct examination by laparotomy at transplant. Typically, surgeons do a careful examination of the bile duct for suitability to proceed with the transplant. Moreover, there was no mention of transplant needing choledochoenterostomy, suggesting the bile duct was suitable for duct-to-duct anastomosis. Thus, DILI remains the most likely diagnosis based on pre-transplant histology. Cholestasis due to sepsis may have contributed to jaundice early in the course, but persistence of cholestasis after resolution of infection and hospital discharge to the point of requiring transplant twelve days later is unlikely, and cholestasis of sepsis is not an indication for transplant. The subject was admitted and transplanted on the same day, so FDA suspects he was called in for transplant in stable condition without recurrent sepsis. The subject did not have cirrhosis, so acute on chronic liver failure and NASH disease progression are unlikely. Above all, transplant evaluation for causes of acute liver failure is typically exhaustive and did not reveal other etiologies. The Agency concluded DILI became the probable diagnosis once bile duct obstruction, ongoing sepsis, and diseases infiltrating the liver were considered but became less-likely causes. FDA felt diclofenac was unlikely because the 10.6-month latency and cholestatic injury pattern were inconsistent with diclofenac hepatotoxicity. Diclofenac injury typically occurs within six months of drug start and is "almost exclusively hepatocellular" (Figure 6).

Figure 6. Latency and Pattern of Injury (Hepatocellular Versus Cholestatic/Mixed) for Nonsteroidal Anti-inflammatory Agents Including Diclofenac Reported by the Drug-Induced Liver Injury Network (DILIN)



Source: Schmeltzer et al. (2016)

By comparison, the five-month latency for OCA and cholestatic pattern of injury are consistent with OCA hepatotoxicity in published data (Eaton et al. 2020), postmarket reports, and other subjects with DILI in study 747-303.

FDA concludes alternate etiologies were adequately addressed which left FDA to conclude DILI as the most likely cause of the liver injury. Both latency and liver injury pattern were consistent with OCA injury while they were inconsistent with diclofenac injury.

Assessment of Key Issues

There is pathophysiologic plausibility for liver injury due to OCA's hydrophobicity (Al-Dury et al. 2019; Wei et al. 2020). OCA-related liver injury, particularly cholestatic injury, was seen in healthy volunteers, and in early phase trials for both PBC and NASH subjects, as well as from cases reported to FAERS in the postmarketing period in PBC patients. Study 747-303 confirms OCA can cause cholestatic DILI that can be severe. Increased ALP and TB levels in subjects on OCA compared to placebo, case adjudication implicating OCA, and incidence rates for moderate to severe DILI provide firm evidence of an important DILI risk.

The transplanted subject (Subject 3) creates a DILI fatality rate (1 in 827) that exceeds by several fold the rate which typically raises substantial concerns for approvability. Moreover, there was one additional fatality due liver failure (Subject 2) that the HSAC deemed unlikely DILI, but the FDA hepatologists were split between 3 (probable) and 4 (possible).

Therefore, OCA must have clear and substantial benefit that outweighs the rate of moderate to severe DILI (2 in 800 treated for one year). This risk assessment includes the chance of fatalities occurring in the larger post-market population which exceeds the Agency's typical threshold of concern for approvability. Before OCA is approved for NASH with fibrosis, the following should be considered

- Progression to cirrhosis should lead to drug discontinuation both because of increased risk of liver injury and lack of efficacy, as demonstrated by the failed trial in NASH subjects with compensated cirrhosis. (Trial 747-304).
- Monitoring for liver injury will need to be prolonged and adherence may decline.
- Postmarket interventions to include enhanced pharmacovigilance; prospective cohort and/or controlled studies may be necessary.

3.2.3.1.6 Conclusion

FDA has substantial concerns about moderate to severe DILI occurrence with OCA use. Risk mitigation is unlikely to eliminate this risk because of need for long term monitoring and potential for increasing risk in patients who progress to cirrhosis. Therefore, the committee is asked to discuss whether the available efficacy data on one of the histopathologic endpoints for OCA 25 mg dose are sufficient to justify/counterbalance the observed risk/harm of DILI in the proposed population.

3.2.3.2 Gallstone and Bile Duct Stones/Sludge Disease and Related Complications

3.2.3.2.1 Issue

Increased incidence of gallstone or bile duct stones/sludge and related complications were observed in the OCA-treated subjects relative to placebo. Events of gallstones and bile duct sludge/stones led to more invasive procedures including cholecystectomy and endoscopic retrograde cholangiopancreatography (ERCP) in the OCA-treated subjects relative to placebo-treated subjects.

3.2.3.2.2 Background

The overall prevalence of gallstones and cholecystitis in obese patients is higher than the general population (Stinton and Shaffer 2012). In the United States, annually 893,000 cholecystectomies are performed for gallbladder disease and related complications (Figueiredo et al. 2017).

In a published clinical report (Al-Dury et al. 2019), subjects were administered OCA for three weeks prior to scheduled cholecystectomy. The study showed OCA increased the cholesterol saturation index, increased the gallbladder bile hydrophobicity index, and decreased cholesterol solubility. Taken together, this combination of biophysical changes increases the lithogenicity of bile and promotes gallstone or bile stone/sludge formation.

3.2.3.2.3 Assessment

Phase 3 Trial 747-303

The incidence rate of gallbladder disease and related complications was 2.5 events per 100 patient-years in the OCA 25 mg group as compared to 1.2 events per 100 PY in the placebo group. Approximately 12.3 additional gallbladder disease and related complications are expected for every 1000 patients treated with OCA 25 mg for one year that would not be observed if patients received placebo (IRD of 1.23 per 100 PY).

More subjects underwent cholecystectomy in the OCA 25 mg arm (n=38) as compared with the placebo arm (n=17). Approximately 7.6 additional cholecystectomy are expected for every 1000 patients treated with OCA 25 mg for one year that would not be observed if patients received placebo (IRD of 0.76 per 100 PY) (Table 14).

Table 14. Analysis of Cholelithiasis and Complications, Study 747-303

Adverse Events of Special Interest	OCA 10 mg N=825 n [IR]	OCA 25 mg N=827 n [IR]	Placebo N=825 n [IR]	IR Difference (95% CI) (OCA 25 mg vs. Placebo)
Gallbladder disease and related complications	50 [1.8]	67 [2.5]	35 [1.2]	1.23 (0.52, 1.95)
Severe gallbladder disease and related complications*	10 [0.3]	23 [0.8]	7 [0.2]	0.57 (0.19, 0.94)
Post-baseline cholecystectomy	15 [0.5]	38 [1.3]	17 [0.6]	0.76 (0.25, 1.27)

Source: Statistical reviewer's analysis based on Applicant-submitted data, adtteir4.xpt.
*Preferred terms of biliary abscess, biliary sepsis, biliary tract infection, gal bladder abscess, gallbladder empyema, bile duct necrosis, bile duct obstruction, bile duct stenosis, biliary colic, cholangitis, cholangitis acute, cholangitis chronic, cholecystocholangitis, or perforation bile duct.
*On-Study Analyses up to cutoff date of 12/31/2021.
Abbreviations: CI, confidence interval; IR, incidence rate per 100 PY; IR Difference, incidence rate difference between OCA and placebo per 100 PY; OCA, obeticholic acid; PY, patient-years of follow-up until the earliest date of study discontinuation, loss of follow-up, cut-off date, first event, or death

Some subjects who developed biliary stone disease required additional procedures beyond cholecystectomy, such as endoscopic retrograde cholangiopancreatography (ERCP), or more severe complications such as ascending cholangitis (requiring hospitalization).

For example, Subject 1, 65-year-old female, with a baseline NAS of 4, stage 3 fibrosis, and normal TB (0.61 mg/dL). Subject had a cholecystectomy on Day 444 after starting OCA 25 mg. After surgery the TB did not return to baseline, and she continued to have elevated bilirubin. On Day 461, the TB was 7.2 mg/dL with symptoms (abdominal pain, back pain, nausea) and the first ERCP was performed. Her symptoms improved but TB increased to 11.9 mg/dL; a second ERCP was performed and OCA was discontinued. Four days after discontinuing OCA she had a significantly higher than expected total OCA concentration at 3950 ng/mL. Because total OCA concentration prior to the AE is not available, it is unknown if the high concentration is a result of cholestasis or a cause of cholestasis if the subject had higher concentrations before the AE. This case highlights intersubject variability in PK that may be associated with cholestasis. Since OCA undergoes biliary excretion patients with cholestasis can develop potentially toxic levels of intra-hepatic OCA leading to higher exposure with potential for liver injury.

3.2.3.2.4 Conclusion

OCA is lithogenic and demonstrates an increased risk of biliary stone disease with related complications (cholecystitis, cholangitis, pancreatitis, choledocholithiasis), requiring hospitalization, cholecystectomy, and other biliary interventions (ERCP). Patients are expected to discontinue OCA therapy when they develop cirrhosis or hepatic decompensation. However, gallstones that develop while on therapy may not resolve when they discontinue OCA therapy, and therefore these subjects may continue to be at risk for complications of stone disease as they progress to decompensated cirrhosis.

3.2.3.3 Dyslipidemia

3.2.3.3.1 Issue

Treatment with OCA is associated with increases in low-density lipoprotein cholesterol (LDL-C) and decreases in high-density lipoprotein cholesterol (HDL-C). These directional shifts are conventionally considered adverse in assessments of cardiovascular risk. This OCA-associated dyslipidemia is of particular concern, given that individuals with NASH at baseline are at higher cardiovascular (CV) risk (Duell et al. 2022). The clinical impact of OCA's effect on lipids in this population is uncertain.

3.2.3.3.2 Background

The potential for increased CV risk associated with drug-induced dyslipidemia is likely dependent on multiple factors, including the underlying disease condition, the drug's mechanism, baseline traditional risk factors, duration of therapy, and the resultant lipid abnormalities.

The evidence for LDL-C as a causal mediator of atherosclerosis and resultant cardiovascular disease is robust. A meta-analysis of statin trials estimated that each 1.0 mmol/L (38.7 mg/dL) reduction in LDL-C with statin treatment results in an approximate 22% reduction in major CV events (Cholesterol Treatment Trialists et al. 2010). Although an inverse correlation likely exists for pharmacologically induced increases in LDL-C, there is uncertainty about the magnitude of this risk, largely because the available data regarding the CV effects of pharmacologically induced LDL-C increases are limited compared with the data for decreases in LDL-C. Despite the uncertainty, the potential adverse impact on CV risk associated with increases in LDL-C caused by OCA is an important consideration in the overall benefit-risk assessment.

The Applicant provided additional analyses such as LDL subfractions and functional properties of HDL in the original supplement application; the effect of these subfractions on cardiovascular risk is uncertain.[10] The conclusions of OCA's effect on lipids are, therefore, based primarily on assessments of LDL-C.

The protocol prespecified monitoring for LDL-C in Study 747-303, and included frequent assessment of lipids (at baseline, month one, every three months for first 18 months, and then every six months). Alerts were sent to the investigators when a subject's LDL-C increased ≥15%. Based on the atherosclerotic cardiovascular disease (ASCVD) risk lipid-lowering agents were either added or intensified.

3.2.3.3.3 Assessment

In Study 747-303, baseline lipid parameters of interest were comparable across treatment groups. Approximately half of subjects were on lipid-modifying therapy at baseline, which was primarily moderate intensity statin therapy,[11] a third of subjects had baseline LDL-C ≥130 mg/dL, 56% had low HDL-C values, and the median triglyceride (TG) value was 150 mg/dL. Baseline LDL-C values were similar across treatment groups (overall mean 114 mg/dL). See Table .

A higher proportion of OCA 25 mg-treated subjects (47%) compared with placebo-treated subjects (23%) reported TEAEs within the "Dyslipidemia SMQ", risk difference 24% (95% CI 19, 28). The most frequently reported TEAE (≥15%) was 'low density lipoprotein increased'. There were no dyslipidemia-related serious AEs, but 4 (0.2%) OCA-treated subjects discontinued study drug treatment due to an adverse event related to lipid abnormalities. Relative to baseline, elevations in LDL-C associated with OCA treatment peaked at the Month 1 timepoint (Figure 7).

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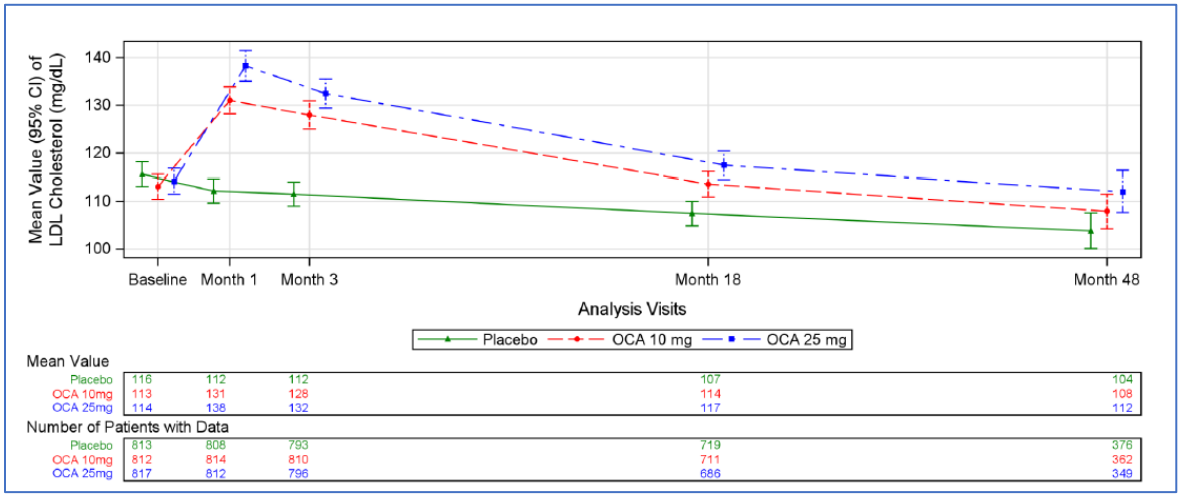
[10] In Trial 747-209, 84 subjects with biopsy proven NASH were randomized to OCA or placebo for 16 weeks. Analyses of LDL particles by nuclear magnetic resonance, suggest the increase in LDL-C observed with OCA treatment reflects a greater increase in large LDL particles versus smaller LDL particles, the latter being purportedly more atherogenic. It is unknown what impact, if any, this observation on cardiovascular risk with OCA treatment would be in this patient population. Analyses of high-density lipoprotein (HDL) function showed no significant changes in reverse cholesterol transport and minimal fluctuations in HDL subfractions; these analyses conducted by the Applicant are of unclear significance.

[11] Moderate-intensity statin defined as expected LDL-C lowering of 30% to 49%.

- LDL-C mean at Month 1 for PBO 112 mg/dL versus OCA 25 mg 138 mg/dL. Least square mean (LSM) absolute and percent difference between PBO and OCA 25 mg was 27 mg/dL and 25%.
- At the Month 18 timepoint, LDL-C in the OCA 25 mg-treated subjects had declined, at least partly due to the introduction of statin therapy, but remained above baseline and greater than placebo (OCA 25 mg group LSM absolute and percent difference of 10 mg/dL and 11%).
- At the Month 48 timepoint, LDL-C values in the OCA 25 mg group continued to decline, were below baseline, but remained numerically greater than placebo (LSM absolute and percent difference of 6 mg/dL and 8%).
- The longitudinal LDL-C versus time plot does not represent true pharmacological effect, since a substantial portion of the participants treated with OCA initiated a statin following randomization refer to Table 17.

Figure 7. Mean LDL-C, Study 747-303



Source: Response to FDA IR, submitted 24 February 2023, SDN 114, Figure 486.7.1.1
Abbreviations: CI, confidence interval; LDL, low-density lipoprotein; OCA, obeticholic acid

The incidence rate (IR) for dyslipidemia-related TEAEs (using dyslipidaemia SMQ), elevations in LDL-C ≥15%, and sustained (defined as two or more consecutive visits) LDL-C ≥15% on-treatment were higher in OCA-treated versus placebo-treated subjects (Table 15). The median time to first post-baseline LDL-C ≥15% was 31 days for OCA 25 mg group versus 175 days for the placebo group.

Table 15. Analysis of Dyslipidemia (On-Treatment Plus 30 Days), Study 747-303

Adverse Events of Special Interest	OCA 10 mg N=825 n [IR] IR Diff. (95% CI)	OCA 25 mg N=827 n [IR] IR Diff. (95% CI)	Placebo N=825 n [IR]
Dyslipidaemia SMQ	354 [21.26] 12.53 (9.99, 15.06)	390 [28.50] 19.77 (16.68, 22.85)	193 [8.74]
LDL-C ≥15%	684 [116.4] 89.8 (80.7, 98.9)	697[152.5] 125.9 (114.3,137.5)	419 [26.6]
Sustained LDL-C ≥15%[1]	468 [34.8] 25.6 (22.2, 29)	488 [42.6] 33.4 (29.4, 37.4)	204 [9.2]

Source: Statistical reviewer's analysis using Applicant-submitted data adtte.xpt.
[1] Sustained LDL-C increase ≥15% was defined as any postbaseline LDL-C result after the first investigational product dose with a 15% increase from the baseline for two or more consecutive visits.
Abbreviations: CI, confidence interval; [IR], incidence rate per 100 PY; IR Diff., incidence rate difference between OCA and placebo per 100 PY; LDL-C, low-density lipoprotein cholesterol; OCA, obeticholic acid; n, number of subjects who experienced at least one event; PY, patient-years until first dyslipidemia; SMQ, standardized Medical Dictionary for Regulatory Activities query

More OCA-treated subjects experienced elevations of LDL-C on study above defined thresholds than placebo-treated subjects (Table 15 and Table 16).

Table 16. Post-Baseline LDL-C Categorical Increases, Study 747-303

Adverse Event	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)	PBO N=825 n (%)
LDL-C >100 mg/dL	736 (89.2)	738 (89.2)	666 (80.7)
LDL-C >130 mg/dL	562 (68.1)	606 (73.3)	454 (55.0)
LDL-C >190 mg/dL	167 (20.2)	210 (25.4)	77 (9.3)

Source: Study 747-303 Clinical Study Report, Table 79.
Abbreviations: LDL-C, low-density lipoprotein cholesterol; OCA, obeticholic acid

Statin Use and Effect on LDL-C

In Study 747-303, 43% of subjects were taking a statin at baseline.The use of statins at baseline was similarly distributed across treatment groups. Approximately 28% were on moderate-intensity statin doses, followed by high-intensity statin therapy (10%). [12]

Overall, a higher proportion of OCA-treated subjects either initiated statin therapy or intensified statin therapy compared to placebo-treated subjects during the study (Table 17). Subjects treated with OCA were initiated on statins or dose was increased or switched to higher intensity statin therapy, more often than placebo arm. The median time to initiation of statin therapy or intensification of statin therapy was 172 days for OCA-treated subjects and 277 days for the placebo-treated subjects.[13]

[12] High intensity statin defined as expected lower LDL-C lowering 50% or greater

[13] Response to FDA IR, submitted 24 February 2023, SDN 114, Table 486.9.1.3.

Table 17. Statin Use, Study 747-303

Statin Use	OCA 10 mg (n=825) n (%)	OCA 25 mg (n=827) n (%)	Placebo (n=825) n (%)
Not taking statins at baseline	466 (56.5)	450 (54.4)	448 (54.3)
Initiated statins during study	257/466 (55.2)	265/450 (58.9)	142/448 (31.7)
Taking statins at baseline	359 (43.5)	377 (45.6)	377 (45.7)
Increased statin dose or switched to higher intensity during study	75/359 (20.9)	75/377 (19.9)	45/377 (11.9)

Source: Response to FDA Information Request, submitted 24 February 2023, SDN 114, Table 486.3.1.
Denominators for the rows Not taking statins at baseline and Taking statins at baseline are based on N, the number of subjects in the population.
Denominators for the row Initiated statin are based on the number of subjects not receiving statins at baseline.
Denominators for Increased statin dose or switched to higher intensity during study are based on the number of subjects receiving statins at baseline.
Abbreviation: OCA, obeticholic acid

The incidence rate difference in proportions between the OCA treated groups and placebo for starting a lipid-modifying agent (including statins) in those not on lipid modifying therapy at baseline is shown in Table 17.

Table 18. Analysis of New Lipid-Modifying Agent (On-Treatment Plus 30 Days), Study 747-303

	OCA 10 mg N=389 n [IR] IR Diff. (95% CI)	OCA 25 mg N=375 n [IR] IR Diff. (95% CI)	Placebo N=375 n [IR]
New lipid-lowering agent among subjects not receiving any lipid-lowering agent at baseline	236 [35.4] 21.21 (16.1, 26.3)	256 [44.2] 30.02 (24.1, 35.9)	134 [14.2]

Source: Statistical reviewer's analysis using Applicant-submitted data adtte.xpt.
Abbreviations: CI, confidence interval; [IR], incidence rate per 100 PY; IR Diff., incidence rate difference between OCA and placebo per 100 PY; LDL-C, low-density lipoprotein cholesterol; OCA, obeticholic acid; n, number of subjects who experienced at least one event; PY, patient-years until first new lipid-lowering agent among subjects not receiving any lipid-lowering agent at baseline

- Reductions were observed in HDL-C in Study 747-303. The clinical significance of small reductions in HDL-C in this patient population is unknown. The mean values of HDL-C are listed below:
  - Baseline OCA 25 mg 44.9 mg/dL (n=817); PBO 45.2 mg/dL (n=813)
  - At Month 18, OCA 25 mg 41.9 mg/dL (n=688); PBO 45.1 mg/dL (n=715)
  - At Month 48, OCA 25 mg 42.9 mg/dL (n=347); PBO 45.6 mg/dL (n=375)
- Reductions were observed in TG in Study 747-303. However, as observed in the trials with fibrates, there is no evidence that pharmacologic reduction of TG in high-risk, statin-treated patients will reduce cardiovascular risk (Keech et al. 2005; Accord Study et al. 2010; Das Pradhan et al. 2022). The median TG values are listed below:
  - Baseline OCA 25 mg 152 mg/dL (n=817); PBO 147 mg/dL, (n=813)
  - At Month 18, OCA 25 mg 128 mg/dL (n=689); PBO 141 mg/dL (n=719)
  - At Month 48, OCA 25 mg 126 mg/dL (n=349); PBO 139 mg/dL (n=376)

Conclusion

An increase in LDL-C and reduction in HDL-C was observed in subjects treated with OCA. The early treatment effect of OCA on LDL-C was attenuated by 48-months, however, this appears to be due to a treatment difference in initiation or intensification of statin therapy, rather than a pharmacologic effect.

OCA-treated subjects required either initiation or intensification of lipid-lowering agents (statins) more rapidly than placebo-treated controls (172 days versus 277 days).

In terms of absolute changes in LDL-C, it is possible that more aggressive hyperlipidemia management (e.g., addition of statins or intensification of lipid-lowering therapy) could ameliorate the difference in LDL-C between OCA-treated and placebo groups. However, beyond LDL-C measurements, the impact of this treatment-related hyperlipidemia on the clinical course of NASH patients is unknown.

3.2.3.4 Dysglycemia

Issue

In the 747-303 study, subjects treated with OCA had worse glycemic control compared to placebo.

Background

Research in animal models suggests OCA mediated agonism of FXR ameliorates (Adorini et al. 2012) various components of metabolic syndrome, including improved insulin sensitivity, glycemic control, and dyslipidemia. Study 747-303 enrolled subjects without T2D or with T2D and a HbA1c below 9.5%. Dosages of diabetes medications were to be stable for 3 months prior to randomization. Antidiabetic medications could be adjusted at the discretion of the Investigator or treating physician, according to standard of care and clinical guidelines. Safety monitoring included collection of AEs related to hyperglycemia, fasting plasma glucose (FPG) and HbA1c (assessed at months 1, 3, and then at 3-month intervals for the first 18 months, and subsequently every 6 months).

Assessment

The majority of trial participants had T2D at baseline[14] (~65%) and were receiving antidiabetic therapy at baseline (~57%). The remainder of the participants had prediabetes[15] (~19%) and normal glycemia (~16%). The mean participant HbA1c at baseline was approximately 6.5%. Baseline characteristics related to glycemic control were balanced among treatment arms. There was comparable intensification of antidiabetic therapy recorded between treatment groups. Overall, the study was adequately designed to assess a causal treatment effect on glycemic control.

In subjects with diabetes at baseline, there was a treatment difference not favoring OCA 25mg in mean HbA1c emerging at 3 months and persisting (i.e., stable) throughout 36 months (data not shown). The mean treatment difference between arms ranged from 0.06% to 0.36%, with a median difference of 0.15% versus placebo. There was a similar pattern in the treatment difference, albeit smaller, observed in subjects with prediabetes and normoglycemia at baseline (median treatment difference between arms was 0.08 and 0.04%, respectively).

Given the apparent time dependence (i.e., early and sustained glycemic shift) of the dysglycemia and differing follow up times of individual participants, we relied on Kaplan-Meier (KM) methods to assess the risk for clinically significant dysglycemia.,[1617] We defined clinically relevant endpoints for glycemic

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[14] Diabetes was defined as having (1) a recorded diagnosis per CRF, or (2) HbA1c ≥ 6.5 at baseline, or (3) having one or more recorded concomitant antidiabetic drugs at baseline

[15] Prediabetes was defined as having an HbA1c at baseline between 5.7 and 6.4% (inclusive)

[16] We report KM estimated cumulative incidence difference at 3, 24, and 36 months since these timepoints coincide with acute onset of dysglycemia observed in mean-level HbA1c data, and long-term landmarks with a majority of subjects providing follow up data. For completeness, full KM curves are provided in the appendix.

[17] This analysis treats deaths, study discontinuations, and administrative censoring the same.

deterioration from routinely collected HbA1c and FPG data for the different baseline glycemic subsets (i.e., normal glycemia, prediabetes, and preexisting diabetes). The definition of biochemical endpoints, their rationale, and accompanying KM plots are located in the appendix.

These time to event analyses revealed the following:

Diabetes at baseline:

- In both placebo and OCA 25mg treatment arms, subjects with diabetes experienced progressive deterioration in glycemic control. At 24 months, 87% and 81% of study subjects experienced clinically significant worsening of glycemic control for OCA 25mg and placebo, respectively. At 36 months, these proportions were 88% and 84% for OCA 25mg and placebo, respectively.
- Treatment with OCA 25mg hastens the median time to onset of clinically significant dysglycemia by approximately 2 months compared to placebo (4 months for placebo vs 2 months for OCA 25mg).

Prediabetes at baseline:

- In both placebo and OCA 25mg treatment arms, subjects with prediabetes progressed to T2D. Prediabetic subjects with NASH progress to T2D at a gradual and fairly consistent pace. Because the rate of progression to T2D occurred through the study duration and the effect of OCA seems to persist through out the study period, therefore, the data are presented as cumulative incidence instead of accelerating the disease in months.
- Relative to placebo, there was a treatment difference not favoring OCA 25mg that emerged within 3 months of randomization and persisted to 36 months. The observed cumulative difference in the proportion of subjects who progressed to T2D at months 3, 24, and 36 was 10.3% (95% CI: 2.1, 18.5), 11.7% (95% CI: 0.6, 22.8) and 8.5% (95% CI: -2.9, 20.0), respectively. This corresponds to an approximate NNH for prediabetic subjects treated with OCA 25mg of 10; for every 100 NASH patients with prediabetes treated with OCA 25mg for a year, 10 will progress to T2D status who would not have progressed if they had been treated with placebo.

Normoglycemia at baseline:

- In both placebo and OCA 25 mg treatment arms, normoglycemic subjects progressed to prediabetes during the study participation. By 36 months, 79% and 86% of subjects progressed to prediabetes status in the placebo and OCA 25 mg treatment arms, respectively.
- Treatment with OCA 25 mg accelerates the median time to incident prediabetes by approximately 9 months compared to placebo (12 months for placebo vs 3 months for OCA 25 mg).

Conclusion

The general trial population experienced a steady deterioration in glycemic control, with the OCA treatment groups showing worse outcomes compared to placebo. Treatment with OCA 25 mg accelerated the rate of conversion to incident diabetes and prediabetes in non-diabetic subjects and accelerated the rate of clinically significant loss of glycemic control in diabetic subjects. However, the difference in median time to deterioration was generally on the order of months, whereas diabetes and its important sequelae occur over years to decades.

In terms of absolute changes in HbA1c in the diabetic population, it is possible that more aggressive diabetes management (e.g., a weak hyperglycemic agent) could ameliorate the difference in glycemic control between OCA-treated and placebo groups. However, beyond HbA1c measurements, the impact of this treatment-related dysglycemia on the clinical course of NASH patients is unknown due to the lack of a causal mechanism underlying the hyperglycemia.

3.2.3.5 Pruritus

Issue

Pruritus was the most common AE in subjects administered OCA 25 mg and the most common cause of treatment discontinuation relative to placebo. Furthermore, pruritus led to dose modification, decrease in dosing frequency, treatment interruption, interventions (pharmacological and over the counter remedies), and permanent treatment discontinuation. The mechanism by which OCA causes pruritus is not known at this time.

Background

Pruritus is a known adverse reaction of OCA.[18] Severity of pruritus was graded as follows:

- Grade 1 or mild pruritus: Mild or localized; topical intervention indicated.
- Grade 2 or moderate pruritus: Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental activities of daily living.
- Grade 3 or severe pruritus: Intense or widespread; constant; limiting self-care activities of daily living or sleep; oral corticosteroid or immunosuppressive therapy indicated.

Protocol prespecified intervention based on severity of pruritus for managing pruritus included:

- Pruritus ≥Grade 1 in severity – topical interventions
- Pruritus ≥Grade 2 in severity – consider one or more:
  a. Drug holiday or less frequent dosing (every other day dosing, interrupting treatment)
  b. Use of bile acid sequestrants (BAS) – if after 4 to 6 weeks of BAS therapy still unable to tolerate the IP, then discontinue the IP
- Pruritus ≥Grade 3 (Severe AE) in severity – Discontinue the investigational product

Assessment

- Four hundred seventy-six (476 (57.6%)) OCA 25 mg-treated subjects and 221 (26.8%) placebo-treated subjects reported at least one pruritus TEAE. The incidence rate difference and its corresponding 95% CI for pruritus between OCA 25 mg and placebo treatment was 26.3 (22.7, 29.8) events per 100 PY. Severe (Grade 3) pruritus was reported in 57 (6.9%) OCA 25 mg-treated subjects relative to 3 (0.4%) placebo-treated subjects.
- More subjects in the OCA 25 mg arm versus placebo arm required medications (Table 19), drug interruptions (133 versus 17), and discontinuations (100 versus 8) to treat or manage pruritus.
- About 220 (26.6%) OCA 25 mg-treated subjects versus 36 (4.4%) placebo-treated were treated with antihistamines.
- About 6.8% OCA 25 mg-treated subjects compared to 1.1% placebo-treated subjects received steroids for treatment of pruritus. Most subjects received topical corticosteroids, however, 9 OCA 25 mg-treated subjects compared to 0 placebo-treated subjects were treated with oral, intramuscular, or subcutaneous steroids.
- Bile acid sequestrants (cholestyramine, colsevalam, etc.) were administered to 101 (12.2%) of OCA 25 mg-treated subjects relative to 10 (1.2%) placebo-treated subjects.

[18] See OCALIVA® at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207999s003lbl.pdf.

Treatment withdrawal occurred in 100 (12.1%) OCA 25 mg-treated subjects and 8 (1%) placebo-treated subjects. Pruritus leading to study discontinuation occurred in 37 (4.5%) OCA 25 mg-treated subjects and 1 (0.1%) placebo-treated subject (Table 19).

Table 19. Management Strategies for Treatment-Emergent Adverse Events of Special Interest: Pruritus, Study 747-303

Management Strategy	OCA 10 mg (N=825) n (%)	OCA 25 mg (N=827) n (%)	Placebo (N=825) n (%)
Medication Initiated for Pruritus (≤ Grade 2 Severity)			
Bile Acid Sequestrants	22 (2.7)	101 (12.2)	10 (1.2)
Antihistamines	87 (10.5)	220 (26.6)	36 (4.4)
Corticosteriods	22 (2.7)	56 (6.8)	9 (1.1)
Other	27 (3.3)	76 (9.2)	16 (1.9)
Action Taken With Study Medication for Pruritus (All Grades of Severity)[a]			
Drug interrupted	34 (4.1)	133 (16.1)	17 (2.1)
Dose adjustment	2 (0.2)	9 (1.1)	0
Dose frequency change	4 (0.5)	38 (4.6)	4 (0.5)
Drug withdrawn	14 (1.7)	100 (12.1)	8 (1.0)

Source: Copied and electronically reproduced from Applicant's Clinical Study Report submission, page 237 of 15877; Table 45.
Abbreviation: OCA, obeticholic acid. [a] Subjects who reported more than 1 action with multiple occurrences for Pruritus were counted only once.

Conclusion

The mechanism of pruritus with OCA use has not been elucidated. TEAE of pruritus was previously observed in randomized, controlled, clinical trials in the PBC population and is a known adverse reaction of OCA.

In Trial 747-303, a greater proportion of OCA 25 mg-treated subjects experienced pruritus, including moderate to severe pruritus that caused skin rash, excoriations, and impacted subject quality of life. Pruritus led to treatment interruption and discontinuation which limits adherence to therapy. In addition, management of pruritus required the use of multiple medications (topical and systemic) which can add to the burden of adverse reactions for a therapy intended for long-term use. Because treatment for pruritus may not be effective, this may explain why more subjects in the 25mg OCA treatment arm discontinued study drug or discontinued from the study.

3.2.3.6 Other Safety Issues

Hepatocellular Cancer (HCC)

HCC is a relevant event in this population given the potential for HCC to develop in patients with NASH, even in the absence of cirrhosis. The protocol prespecified collecting hepatobiliary ultrasounds at baseline and every six months during the clinical trial in all subjects, to screen for HCC and presence of gallstones. If subjects had an ultrasound within 3 months of enrollment, then baseline ultrasound was not performed.

In Trial 747-303, a numerically higher number of subjects treated with OCA 25 mg developed HCC relative to placebo:

- OCA 10 mg (N=825) – six subjects (0.7%)
- OCA 25 mg (N=827) – four subjects (0.5%)
- Placebo (N=825) – one subject (0.1%).

This study was not designed to assess HCC risk between placebo and treatment arms and although an imbalance is noted, the clinical relevance of this imbalance is unclear.

Acute Kidney Injury

An imbalance in the acute kidney injuries was observed between OCA 25 mg-treated subjects relative to placebo-treated subjects (15 versus 7) based on on-study analysis. The acute kidney injury event was adjudicated by renal adjudication committee using the Kidney Disease Improving Global Outcomes (Khwaja 2012) clinical practice guidelines. The number of events adjudicated with evidence of AKI was low overall but remained higher in the OCA 25 mg arm compared to placebo arm (12 versus 7).

Cardiac Events

There were no apparent differences in major adverse cardiac endpoints (MACE) endpoints across the three treatment arms. In Study 747-303, 15 subjects randomized to OCA 25mg experienced a core major adverse cardiac event (MACE) compared to 11 subjects randomized to placebo, IRD = 0.2 with 95% CI (-0.2, 0.5); see Table 25 in Appendix 6.6. Study 747-303 is not powered to determine if the observed negative effects on LDL or glycemic control could have a negative effect on MACE events with long-term use, in a larger population. Therefore, a lack of difference in cardiac events between the OCA 25mg and placebo arms cannot rule out an increased risk of CV events with enough precision.

3.3 Concerns about Operationalizing the Use of OCA for NASH with Stage 2 or 3 Fibrosis

Use of this drug to treat NASH with Stage 2 or 3 fibrosis requires consideration of the following safety concerns related to drug utilization:

- Selection of appropriate patients
- Monitoring for DILI
- Assessment of disease progression (progression to cirrhosis) for discontinuing treatment
- Management of increased LDL-C and worsening glucose intolerance in a patient population known to have baseline metabolic derangements including dysplidemia, obesity, and T2D.

3.3.1 Selection of Appropriate Patients

Issue

Identifying subjects who have definite NASH with stage 2 or 3 fibrosis.

Background

In the U.S., there are approximately 5.7 million patients with NASH with fibrosis stage 2 or 3 who would be eligible for treatment with OCA.

NASH subjects with stage 0 and 1 fibrosis do not need OCA therapy because they have very slow disease progression taking 12 to 14 years to develop cirrhosis and poor clinical outcomes. Cirrhosis patients should not be treated either because a trial of OCA 25 mg in subjects with compensated NASH cirrhosis failed to meet its primary endpoint of “one stage reduction in fibrosis.” Thus, only a subset of NASH population i.e., that has definite NASH[19] with stage 2 or 3 fibrosis can be treated with OCA, because of the modest treatment effect and substantial risks associated with OCA.

[19] Definite NASH is defined as NAFLD activity score ≥4.

Non-invasive tests (NITs) lack the specificity needed to adequately identify this population (Patel and Sebastiani 2020). NITs cannot accurately identify NASH nor differentiate fibrosis stage 1 from 2 or stage 3 from 4. Therefore, liver biopsy is the only way to accurately identify patients qualifying for treatment.

Liver biopsy carries risk. Historical data indicate a 1.1% incidence of serious complications, including severe bleeding (1 in 2,500) and mortality (1 in 10,000) (Seeff et al. 2010). Pain is a common complication, and patients may be unwilling to undergo a liver biopsy.

Assessment

Subjects were screened with laboratory tests (ALT, AST), non-invasive tests (TE, FIB-4 etc.), as well as by clinical assessment (obese subjects, presence of T2D). Once subjects were deemed to potentially have NASH based on results from these tests, then a liver biopsy was performed. In Trial 747-303, at baseline, subjects who met the criteria of "definite NASH with stage 2 or 3 fibrosis" on liver biopsy were enrolled. About 10% subjects with stage 1 fibrosis were also enrolled, however, these subjects were not a part of population in which efficacy was assessed.

Despite careful subject selection and performance of biopsies at clinical trial sites where liver biopsy expertise is likely greater than in the general community, a total of 235 (5.8%) adverse events (AE) related to liver biopsy were observed out of 4047 biopsies conducted. Most AEs were mild and limited to liver biopsy site pain (Table 20); however, 35 (0.86%) were graded severe or life threatening. A total of 25 SAEs (0.62%) were reported which included peritoneal hemorrhage, post-procedural hematoma, and abdominal pain.

Table 20. Adverse Events Related to Liver Biopsy

Adverse Event Grade	OCA 10 mg; OCA 25 mg; Placebo Number of Liver Biopsies =4047
Mild	102
Moderate	98
Severe	33
Life-threatening	2
Fatal	0
Total number of events	235

Source: Statistical reviewer's analysis based on Sponsor-submitted data adae.xpt.
Abbreviations: OCA, obeticholic acid

Conclusion

Because NITs lack sufficient accuracy, identifying patients for OCA therapy will require liver biopsy, which carries measurable morbidity risk. OCA's modest efficacy potential will need to be weighed against this morbidity risk taken by not only those who qualify for therapy histologically but also those who fail to qualify. In other words, many patients will have to undergo biopsy to identify the subset that can receive potential benefit from OCA.

3.3.2 DILI Monitoring and Detection of Progression to Cirrhosis

Issues

Monitoring for DILI; Detection of progression of disease to prevent use of OCA in cirrhotic patients

Background

OCA failed to demonstrate efficacy in subjects with compensated cirrhosis due to NASH (2022). Therefore, once a patient progresses to cirrhosis there is no benefit with OCA treatment. Progression to

cirrhosis and risk of OCA related liver injury are intertwined. Cirrhosis may increase DILI risk due to higher OCA exposure, as well as increase the chance of a fatal DILI event due to the cirrhotic liver's impaired ability to tolerate injury. Because of the increased DILI risks in cirrhotic population, hence a need to identify cirrhosis early is imperative, so that OCA can be discontinued. However, identifying DILI and detecting progression to cirrhosis in the earliest stage is likely not feasible in clinical practice. NITs to assess for early cirrhosis are currently suboptimal; furthermore, progression to cirrhosis is typically asymptomatic, but blood tests and other non-invasive tests would be needed. Specific challenges regarding monitoring are outlined below.

Monitoring for DILI

1. Frequent monitoring would be required. The interval for blood test monitoring, implemented in Study 747-303, was set for baseline, at month one, then every three months until month 18, followed by testing every six months thereafter. Even with the protocol prespecified visits, DILI events occurred between two visitation periods. Typically, in clinical practice, NASH patients are followed every six to twelve months, so more frequent monitoring would be a substantial change and may not be achievable outside of the clinical trial setting.
2. Several cases of DILI occurred after one year or more of OCA treatment. Therefore, frequent monitoring would need to be conducted for years, as it is anticipated treatment for NASH with fibrosis will be for many years and may be lifelong. Therefore, the need for long-term monitoring will be difficult for patients and will likely lead to non-compliance.
3. About two thirds of subjects with NASH and fibrosis have baseline liver test abnormalities. Distinguishing early DILI from typical fluctuations in the liver test values of NASH patients will also be difficult. Even if gastroenterologists, hepatologists and their mid-level providers care for these patients, most do not have the expertise to assess a DILI-risk that is neither a dose-dependent nor predictable.

Monitoring for progression to cirrhosis

1. Patients progress to cirrhosis at variable rates so a standard schedule for screening is infeasible and not likely to capture all patients that undergo disease progression.
2. Even though the Applicant does not plan to treat stage 4 fibrosis (i.e., compensated cirrhosis) patients would need to be identified for portal hypertension (PH) which poses a greater risk of OCA-mediated DILI.
3. Early cirrhosis detection and ascertainment of PH will be difficult in all cases because non-invasive tests lack predictive value. Examinations such as hepatic venous pressure measurement, and esophagogastroduodenoscopy to screen for evidence of portal hypertension will require expertise that will be beyond a primary care provider's scope of practice. And, interpretation of FIB-4 and ELF blood tests, transient elastography will also require subspecialty care often in tertiary or quaternary medical centers.

Assessment

During the clinical trial, subjects were followed with laboratory testing at baseline, month 1, month 3, and then every three months for the first 18 months and then every six months for the long-term outcomes portion of the trial.

Triggers for detecting potential DILI and an algorithm to detect progression to cirrhosis were prespecified in the protocol. Site PIs (hepatologists and gastroenterologists), medical monitors, and the Applicant's safety team were monitoring data (laboratory, clinical, and imaging) for potential DILI and cirrhosis. Despite this multi-faceted safety plan, some subjects had DILI or experienced liver decompensation events between visits. For example, there were cases in which OCA was not stopped

despite meeting the endpoint of progression to cirrhosis. A 60-year-old female (Subject) developed "bridging fibrosis with cirrhotic nodule formation" on biopsy by Day 470 on OCA, but OCA was neither dose reduced to 10 mg per protocol nor discontinued. She developed jaundice and cholangitis due to choledocholithiasis that required two ERCP's on days 533 and 538. However, her TB continued to rise to over 20 mg/dL despite duct clearance, and OCA was still continued to Day 551 when it was stopped. Thereafter, she developed severe hepatic encephalopathy and acute kidney injury. She entered palliative care and died on Day 560. Thus, recognition of cirrhosis and OCA reduction/discontinuation were not always done in a timely manner during the trial. FDA is concerned that given the number of eligible patients for OCA treatment such vigilant monitoring and compliance cannot be assured in standard clinical practice.

Conclusion

There are significant challenges and uncertainties for DILI risk mitigation in clinical practice. Compliance with frequent laboratory monitoring, (liver enzymes, non-invasive markers for cirrhosis) over long periods for the duration of a patient's life will be far more frequent than what was observed in study 747-303. Given the lack of predictability for the timing of DILI emergence, and the potential that cholelithiasis may heighten the DILI risk, FDA is concerned that any DILI risk mitigation plan will fall short, and moderate to severe DILI is likely to occur at the same frequency, or possibly at a higher frequently, in the postmarket setting. These concerns are based on subjects who progressed to cirrhosis, with evidence of portal hypertension; this is a population that the Applicant has acknowledged should not be treated with OCA, and it is unclear how practitioners can consistently identify patients who would need to quick discontinuation of OCA.

It is anticipated that somewhere between six to eight million Americans would be eligible for OCA treatment, should it be approved. While FDA recognizes presently there is an unmet need, the Agency's current benefit-risk assessment includes selecting patients for long-term OCA treatment that will require baseline liver biopsy. Further liver biopsies may be required during treatment given the uncertainty of predicting DILI when one considers transaminase fluctuations in NASH, and along with a higher risk than the general population for cholelithiasis and its complications. Therefore, despite the modest treatment effect over placebo, FDA cannot justify OCA use in NASH subjects with Stage 2 or 3 fibrosis.

A clinical trial is the most optimistic setting for monitoring subjects for AE, at frequent interval (at baseline, at month one, then every three months for the first year and then every six months subsequently). Along with this rigorous monitoring with multiple medical teams reviewing data in real-time (Site PI, Applicant's Medical Monitor, Applicant's Safety Team), events of DILI with a fatal or serious outcome (liver transplant and/or liver decompensation events) were not identified at earlier timepoints when more effective medical interventions may have decreased morbidity and mortality. In clinical practice such rigorous monitoring is unlikely to be performed because such intensive monitoring would be difficult to achieve for lifelong treatment among patients treated with OCA. Most practices would be challenged to accommodate and follow-up frequent liver biochemistry testing. Moreover, this testing regimen would create an unacceptable burden for patients, and patients would not likely be able to comply with the schedule. Therefore, this risk likely cannot be mitigated.

DILI monitoring alone would not suffice and does not include the numerous other tests that need to be carefully monitored, i.e., monitoring for increased LDL, dysglycemia, AKI, the higher prevalence of cholelithiasis and its complications, as well as severe pruritus.

FDA concludes that liver panel testing is not likely to be an effective risk mitigation strategy to reduce the risk of DILI or for identifying progression of disease.

3.3.3 Management of Other Treatment-Emergent Adverse Events

Issue

OCA causes adverse events that must be treated with pharmacotherapy

Background

Treatment with OCA 25 mg accelerated the rate of conversion to incident diabetes from prediabetes to prediabetes from normoglycemia and accelerated the rate of clinically significant loss of glycemic control in diabetic subjects. (See Section 3.2.3.4)

For elevations in LDL-C, more subjects in the OCA 25mg treatment arm experienced elevations in LDL-C compared to placebo (87% versus 57%); they required either initiation or intensification of lipid-lowering agents (statins) sooner than placebo-treated controls (172 days versus 277 days). Despite this pharmacologic treatment, LDL-C remained above baseline levels out to 48 months. Low HDL-C cannot be addressed by pharmacotherapeutic intervention. (See Section 3.2.3.3)

Pruritus required treatment with bile acid binding agents, antihistamines, or corticosteroids. (See Section 3.2.3.5)

Conclusion

To take OCA 25mg, that has modest efficacy on a single surrogate endpoint with unknown clinical benefit for NASH, patients will require careful monitoring of glucose, LDL cholesterol, and gallstone formation along with potential polypharmacy to mitigate the to-be-marketed OCA-related adverse events. These newly added medications will expose subjects to potentially other adverse events as well as drug-drug interactions, even though they may attenuate the severity of the condition, they cannot completely eliminate the risks associated with the known adverse events associated with chronic OCA use. This assumes that patients can be followed as meticulously as they were in the clinical trial, which in real GI and Hepatology practices is not practical. Issues concerning handling glucose, lipids, and polypharmacy will likely require patients to seek expertise from other specialties outside of Digestive Disease specialists. Adequate lifelong monitoring for DILI along with these other adverse events in the clinical practice is unlikely.

3.4 Risk Mitigation

Sections 3.2 and 3.3 describe in detail the substantial risks associated with OCA 25mg treatment. We have serious concerns that we have explicated in sections above that the DILI risk cannot be mitigated. Although some adverse events can be treated with pharmacotherapy (e.g., dysglycemia, dyslipidemia), these comorbidities cannot be completely mitigated, and these patients are already at risk for cardiovascular complications and cannot tolerate additional disease burden.

4 Benefit-Risk Framework

Disclaimer: This pre-decisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

Table 21. Benefits and Risks Assessment

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	• Nonalcoholic steatohepatitis (NASH) is a severe form of nonalcoholic fatty liver disease (NAFLD) in which the liver has inflammation and ballooning along with excess fat (≥5%). NASH is associated with metabolic syndrome (MS). MS includes five main components: obesity, hypertension, high blood triglycerides, low levels of HDL cholesterol, and insulin resistance (T2D). Diabetes is associated with NAFLD/NASH, and the relationship seems to be bidirectional. • NASH is slowly progressive over many years, but time to development of severe liver disease increases per stage of fibrosis (9.3 years to liver decompensation in F2 and 2.3 years in F3). • About 16.8 million people potentially have NASH, and it is estimated that ~5.7 million people in the U.S have NASH with fibrosis stage 2 or 3 (target population). • Liver histopathology reading is the only way to diagnose and accurately grade NASH (disease activity), and stage (fibrosis) but in clinical practice most patients do not have this procedure. • Non-invasive tests (NIT) (circulating and imaging biomarkers) are being developed to diagnose and stage NASH. However, NIT lack accuracy in identifying subjects with NASH with stage 2/3 fibrosis.	• NASH is a serious and life-threatening condition. • Progression of disease is variable and slow in the majority of the NASH population; however, in a subset of subjects NASH progresses rapidly, and disease progression is unpredictable. • If left untreated the disease may progress to liver failure necessitating liver transplant or leading to death. • There is an increasing medical burden on the U.S. health-care system for care of these patients. • Liver biopsy to diagnose, stage, and grade NASH carries risks. It is not feasible to biopsy millions of potential subjects to identify those who have NASH with stage 2 or 3 fibrosis. Currently most non-invasive tests are not accurate in staging and grading the disease.
Current Treatment Options	• There are no FDA-approved drugs to treat NASH, although there are multiple drugs in development for NASH and liver fibrosis. • Off-label treatments include use of vitamin E and pioglitazone for NASH with fibrosis.	• There are no approved drug treatments. Clinical benefit of the off-label treatments is uncertain. Lifestyle changes are effective but frequently not sustainable.

	Evidence and Uncertainties	Comments to the Advisory Committee
	• Bariatric surgery, generally performed in morbidly obese patients has demonstrated weight loss and reduction in NASH and fibrosis.	• Bariatric surgery is a high-risk procedure, is associated with complications, and cannot be performed in all NASH subjects. • There is an unmet medical need, especially for high-risk populations.
Benefits	• Study 747-303 is an ongoing phase 3, double-blind, randomized, long-term, placebo-controlled, multicenter study of OCA 10 mg daily and OCA 25 mg daily versus placebo. • An interim analysis of surrogate endpoints at Month 18 in the ITT_old analysis population was intended to support an accelerated approval. An additional interim analysis of the larger ITT_histology analysis population was not pre-specified prior to the CR letter but was conducted by the Applicant to provide additional precision in the estimation of the treatment effects. The study is ongoing to evaluate clinical benefit outcomes intended to support a traditional approval. • Statistical significance can only be discussed for the pre-specified interim analysis of the ITT_old analysis population (refer to Section 3.1.1). The OCA 25 mg arm demonstrated superiority to placebo on the primary endpoint evaluating improvement of fibrosis and no worsening of NASH and failed to achieve statistical significance on the primary endpoint evaluating resolution of NASH and no worsening in fibrosis. • The estimated risk difference (95% confidence interval) comparing OCA 25 mg to placebo on the endpoint of improvement of fibrosis and no worsening of NASH ranged from 8.6% (4.2%, 13.0%) to 12.8% (7.0%, 18.5%) across the different analysis populations and histopathology read methods.	• While OCA 25 mg demonstrated superiority to the placebo on one of two primary endpoints, there was a modest treatment effect on this surrogate endpoint. There is uncertainty how the magnitude of changes in these surrogate endpoints may translate to meaningful changes in clinical outcomes.
Risks and Risk Management	• Several cases of DILI, including a fatality and a liver transplant, were attributed to obeticholic acid. These cases occurred despite a DILI mitigation algorithm that was prespecified in the protocol, that included liver test monitoring, imaging, and close clinical follow-up.	• Risks of obeticholic acid include hepatoxicity, cholelithiasis and its complications, and hastening of the progression of dyslipidemia and dysglycemia. If approved, the risks of liver biopsy will also be a component of any treatment decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
	• Consistent with the mechanism of action, obeticholic acid increased the risk of formation of gallstones and bile duct stones/sludge and subsequent complications. There is a concern for significant clinical implications, including cholecystitis, cholangitis, bile duct stones, and related complications, especially for patients with comorbidities. There was an increased rate of surgical intervention in the subjects on obeticholic acid arm. • Compared to placebo, OCA 25 mg expedited worsening of dyslipidemia and hastened progression from euglycemia to prediabetes, progression from prediabetes to diabetes, and worsened HbA1c in diabetic subjects. • Pruritis was frequently observed and required frequent treatment interruptions and use of additional medications. The majority of subjects who developed DILI and cholelithiasis also experienced pruritus. • If obeticholic acid is approved, liver biopsy, with its attendant risks, will be required to determine who is a candidate for therapy. • Serious Adverse event rates for liver biopsies performed in the trial were 0.6%. Non-invasive methods lack accuracy in staging and grading NASH and fibrosis compared to liver biopsy. • Many patients may be treated without a liver biopsy (i.e., subjects with NAFLD or NASH without fibrosis), exposing them to significant risks without evidence of benefit.	• While effective treatments are available for lowering LDL-C and HbA1C, there are residual risks and uncertainty, as well as the risks of polypharmacy. • Hepatotoxicity, cholelithiasis, and pruritis risks were prevalent, clinically significant, and potentially mechanistically related. • The ability to mitigate the hepatoxicity risk post-approval is a significant concern. The clinical trial setting, which included both careful subject selection and close safety monitoring for DILI, may represent the most optimistic setting for detection of hepatotoxicity. Even in this setting, DILI, in some cases severe or fatal, occurred. Based on the clinical trial experience, the efficacy of any post-market DILI mitigation is questionable. • Should OCA be approved, and DILI is suspected, providers may need to obtain additional liver biopsy to evaluate for DILI. This will be burdensome on the patients.

Summary of Benefit-Risk

For a drug to be approved for marketing in the United States, the FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. During the course of our review, FDA identified modest benefits and serious risks of OCA for treatment of NASH, as shown in the table below (Table 22). The key issues for consideration in the benefit-risk assessment of OCA for NASH with fibrosis include the theoretical clinical benefit of a one stage improvement in fibrosis, along with the risks of drug-induced liver-injury, gallstone or bile duct stone/sludge and related complications, new-onset or worsening dyslipidemia, accelerating progression to developing prediabetes or diabetes, and worsening of glycemic control in diabetic subjects.

	Evidence and Uncertainties	Comments to the Advisory Committee

In addition to the key benefits and risks noted in Table 21 and Table 22, the risks of liver biopsy would also have to be factored in if obeticholic acid were approved. If a baseline liver biopsy is not performed, the risk of treating a patient who is not an appropriate candidate for obeticholic acid, either because the disease is in early stage (NAFL, NAFLD with no fibrosis) or late stage (compensated cirrhosis due to NASH) would increase.

NASH requires life-long drug therapy. Trial results for obeticholic acid indicate it causes multiple off-target effects that require multiple risk mitigation strategies with low likelihood of effectiveness. The Committee will be asked to discuss whether the available efficacy data for OCA 25 mg on a single histologic endpoint are sufficient to justify/counterbalance the observed risks in the proposed population.

Source: F brosis and steatohepatitis Table 5 and Table 6; hepatotoxicity Table 13; cholelithiasis and related complications Table 14; dyslipidemia Table 18; dysglycemia Appendix 6.4; pruritis; Sections 3.1 and 3.2

Table 22. Benefit Risk Effects (Trial 747-303)

Effect	Measure Definition	OCA 25 mg vs Placebo (95% CI)	Uncertainties
Benefit Assessment Using Data from ITT_histology			
Fibrosis	Primary endpoint 1: Risk difference for percentage of subjects achieving an improvement in one or more stage of fibrosis and no worsening of NASH[20] at Month 18 for ITT_histology analysis population (not pre-specified)	8.6% (4.2%, 13.0%)	- Effect on both outcomes not required for approval - ITT_histology analysis was post hoc - Among pre-specified analyses of ITT_old, only fibrosis endpoint was statistically significant for OCA 25mg compared to placebo - Results are for surrogate endpoints with unproven effects on clinical outcomes
Steatohepatitis	Primary endpoint 2: Risk difference for percentage of subjects achieving resolution of NASH[21] and no worsening of fibrosis at Month 18 for ITT_histology analysis population (not-pre-specified)	3.7% (1.0%, 6.4%)	- ITT_histology analysis was post hoc - Among pre-specified analyses of ITT_old, steatohepatitis endpoint was not statistically significant for OCA 25mg compared to placebo

[20] No worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis.

[21] Resolution of NASH by global interpretation and NAS of 0 for ballooning, 0 to 1 for inflammation.

Effect	Measure Definition	OCA 25 mg vs Placebo (95% CI)	Uncertainties
			- Results are for surrogate endpoints with unproven effects on clinical outcomes
Risk Assessment			
Hepatotoxicity	Incidence rate (IR) difference per 100 patient-years (PY) for adjudicated DILI (possible/probable/highly likely causality):		- Compliance with hepatotoxicity prevention and mitigation may be less complete post-approval compared to the clinical trial setting, thereby, potentially increasing the risk of DILI
	• ≥moderate severity	0.24 (0.04, 0.45)	
	• ≥mild severity	1.11 (0.62, 1.60)	
Cholelithiasis and related complications	IR difference per 100 PY for severe gallbladder disease and related complications	1.23 (0.52, 1.95)	Increase in invasive procedures (cholecystectomy and ERCP), risk is unpredictable
Dyslipidemia	IR difference per 100 PY for initiation of lipid-modifying agent for those not on treatment at baseline	30.0 (24.1, 35.9)	- Clinical implications of drug-induced changes (vs. non-drug-induced), and resulting polypharmacy, are uncertain
Dysglycemia	Cumulative incidence difference (%) for to clinically important deterioration in glycemic control at 36 months		-Deterioration of glycemic control occurred in a high incidence of subjects treated with placebo (86%, 56%, and 79% of diabetic, prediabetic, and normoglycemic subjects at 36 months, respectively)
	Diabetic	4.6 (0.2, 9.1)	
	Pre-Diabetic	11.7 (0.6, 22.8)	
	Normoglycemic	9.9 (-0.5, 20.2)	
Pruritus	IR difference per 100 PY for pruritus	26.3 (22.7, 29.8)	- treatment interruptions and discontinuations secondary to severe or persistent pruritus

Source: Generated by the FDA Clinical team from data generated from Sections 3.1, 3.2, and 3.3

5 References

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6 Appendix

6.1 Death

Table 23 described the listing of all deaths that have occurred in the NASH drug development program. It provides the age of subject, treatment assignment, number of days subject treated with OCA or placebo prior to death and study day on death. Cause of death is noted both in preferred term (MedDRA) and verbatim term (as reported by the investigator).

Table 23. Listing of All Deaths in Subjects With Fibrosis Due to NASH

Study Arm	Patient ID	Age	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death	
							Preferred Term	Verbatim Term
OCA 10 mg	5	61	M	10 mg	677	1190	Pneumonia viral	COVID-19 pneumonia
OCA 10 mg	6	62	F	10 mg	699	699	Overdose	Ambien overdose/death
OCA 10 mg	7	52	F	10 mg	523	523	Congestive cardiomyopathy	Dilated cardiomyopathy
OCA 10 mg	8	58	M	10 mg	1613	1620	Acute kidney injury	Acute kidney failure
OCA 10 mg	9	63	F	10 mg	721	1058	Dyspnoea	Worsening shortness of breath
OCA 10 mg	10	54	M	10 mg	143	143	Myocardial infarction	Myocardial infarction
OCA 10 mg	11	72	M	10 mg	358	826	Hepatocellular carcinoma	Hepatocellular carcinoma
OCA 10 mg	12	61	F	10 mg	381	961	Lung adenocarcinoma	Lung adenocarcinoma
OCA 10 mg	13	52	M	10 mg	957	1002	Lung neoplasm	Lung neoplasm
OCA 10 mg	14	66	M	10 mg	403	419	Corona virus infection	Coronavirus (covid -19) infection
OCA 10 mg	15	49	M	10 mg	755	755	Completed suicide	Suicide
OCA 10 mg	16	66	M	10 mg	153	304	Progression of decompensated liver disease*	End stage liver disease
OCA 25 mg	17	68	M	25 mg	278	1793	Cardiac failure	Heart failure
OCA 25 mg	18	67	F	25 mg	1008	1060	Chronic kidney disease	End stage renal disease
OCA 25 mg	19	68	F	25 mg	646	677	Endometrial cancer metastatic	Metastatic endometrial carcinoma
OCA 25 mg	20	62	M	25 mg	243	411	Glioblastoma	Glioblastoma
OCA 25 mg	21	71	F	25 mg	508	1186	Acute respiratory failure	Acute on chronic respiratory failure
OCA 25 mg	22	69	M	25 mg	1810	1835	Corona virus infection	Covid-19 pulmonary infection
OCA 25 mg	23	74	M	25 mg	1207	1208	Cardio-respiratory arrest	Cardiopulmonary arrest
OCA 25 mg	24	62	F	25 mg	712	712	Death	Death of unknown cause

Study Arm	Patient ID	Age	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death	
							Preferred Term	Verbatim Term
OCA 25 mg	25	59	M	25 mg	1433	1458	Pneumonia viral	Covid-19 pneumonia
OCA 25 mg	26	68	M	25 mg	1323	1360	Pneumonia viral	Covid 19 pneumonia
OCA 25 mg	27	65	F	25 mg	56	720	Pulmonary fibrosis	Pulmonary fibrosis deterioration
OCA 25 mg	28	65	M	25 mg	1467	1468	Corona virus infection	Covid-19
OCA 25 mg	29	60	F	25 mg	552	560	Acute hepatic failure	Acute on chronic liver failure
OCA 25 mg	30	62	M	25 mg	940	953	Cardiac arrest	Cardiac arrest
OCA 25 mg	31	73	F	25 mg	35	66	Cardiac failure congestive	Congestive heart failure
OCA 25 mg	32	57	F	25 mg	449	449	Myocardial ischaemia	Myocardial ischemia
OCA 25 mg	33	62	M	25 mg	180	221	Renal failure and liver failure	Acute renal failure and hepatic failure
Placebo	34	71	F	NA	842	848	Pneumonia viral	Covid-19 bilateral pneumonia
Placebo	35	44	M	NA	1828	1828	Completed suicide	Suicide
Placebo	36	60	F	NA	1525	1547	Small cell lung cancer	Small cell lung cancer
Placebo	37	74	M	NA	569	590	Pneumonia viral	Covid-19 pneumonia
Placebo	38	50	M	NA	415	1510	Shock	Shock
Placebo	39	55	F	NA	246	249	Pancreatitis haemorrhagic	Hemorrhagic pancreatitis
Placebo	40	62	M	NA	465	465	Cardiac arrest	Cardiac arrest
Placebo	41	58	M	NA	64	86	Bone cancer	Bone cancer
Placebo	42	40	M	NA	186	186	Completed suicide	Suicide
Placebo	43	52	F	NA	708	2133	Pancreatitis, acute	Severe acute pancreatitis

Source: Statistical reviewer analysis based on Applicant submitted data adae.xpt and the supporting document number 001 (Applicant submitted on September 26, 2019).
*:Verbatim term could not be found for this preferred term.
Abbreviations: COVID-19, coronavirus disease 2019; F, female; M, male; NA, not applicable; NASH, non-alcoholic steatohepatitis; OCA, obeticholic acid

6.2 DILI

Subject 2

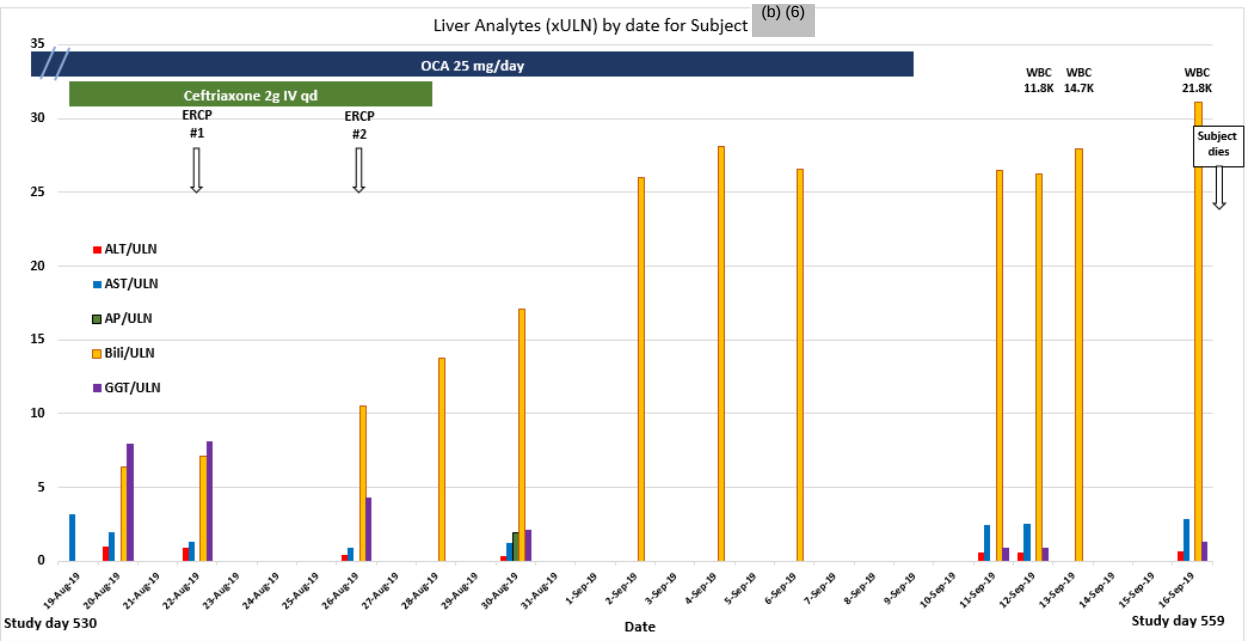
Summary: This is a 60-year-old woman who developed cholangitis followed by acute-on-chronic liver failure occurring 75 weeks after starting OCA 25 mg/d.

At baseline, she had asymptomatic gallstones and diabetes. ALT, AST, AP, GGT and TB were 52 U/L, 44 U/L, 38 U/L, 93 U/L and 1.3 mg/dL, respectively. She was on several medications, but none were pertinent to this liver injury event. No mention of herbal/dietary supplements, over-the-counter agents, or alcohol. Prior to enrollment, ultrasound showed a fatty liver with cholelithiasis. Liver biopsy diagnosed F3 fibrosis.

She started OCA 25 mg/d on Day 1. She had a biopsy on Day 470 showing "bridging fibrosis and cirrhotic nodule formation." On Day 472, liver analytes were at or near baseline. No other liver analyte values are provided between Day 472 and liver injury onset on Day 531. On Day 530, she had right upper quadrant abdominal pain, but no fever, nausea, or vomiting. On Day 531, ALT, AST and TB were 57 U/L, 108 U/L and 7.67 mg/dL respectively. No AP was provided but GGT was 286 U/L. Repeat US now showed a "sclerotic gallbladder described as porcelain." MRCP suggested inflammatory changes in the gallbladder or carcinoma with choledocholithiasis. She received ceftriaxone and metronidazole. Amylase was 611 U/L. On Day 533, ERCP removed an 8 mm stone, and a stent was placed. Nevertheless, TB did not fall, and pruritus developed. She required another ERCP on Day 538 for persistent jaundice, and a residual stone was removed. OCA continued. By Day 540, her cholangitis was considered resolved. She had no fever. Blood cultures were negative. Still, her TB did not fall, and OCA was stopped on Day 551 (Figure 8).

Over the next three days, she developed acute kidney injury while hyperbilirubinemia and pruritus continued. On Day 554, she had “life-threatening” hepatic encephalopathy, which deepened to Glasgow coma scale 4. Her white blood cell count had risen to 21.8K. Her care was changed to palliative, and she died on Day 559. There was no autopsy.

Figure 8. Bar Graph of Liver Analytes Over Time



Source: FDA Clinical Reviewer using adae, adsl,, adcm,and adlb dataset

Assessment: This is possible to probable DILI due to OCA. OCA may have caused injury by gallstone disease progression with concurrent direct cholestatic injury. The subject had baseline gallstone disease and went on to develop a porcelain gallbladder with choledocholithiasis and cholangitis after being on OCA for over 500 days. Despite clearance of the common bile duct by two ERCPs and cholangitis resolution, her TB continued to rise while still on OCA for twelve days after the last ERCP. She died in palliative care with a rising white blood cell count seven days later. Ceftriaxone liver injury is a consideration. Both drugs are cleared substantially by the liver, so bile duct obstruction may have led to higher drug levels for both. However, the antibiotic stopped and yet TB rose further while still on OCA. By the time OCA did stop, cholestasis of infection likely set in and prevented decline in her TB. Thus, we agree that the subject died of acute on chronic liver failure but disagree that OCA had no or an "unlikely" role in the liver injury and failure.

The case highlights the clinical complexities resulting from OCA's ability to cause cholestatic DILI and gallstones in subjects already at risk for gallstone disease. Bile duct obstruction from choledocholithiasis may lead to increased OCA levels and cholestatic DILI perpetuating and prolonging liver injury.

DILI Team score:	3 or 4 (probable or possible DILI due to OCA; split decision by three FDA hepatologists)
HSAC (sponsor's expert panel) score:	5 (Unlikely DILI due to OCA)

6.3 Dyslipidemia

Table 28 shows the baseline characteristics of interest. There were no imbalances in cardiovascular risk factors at baseline in subjects enrolled across the three treatment arms.

Table 24. Baseline Characteristics, Study 747-303

Characteristic	OCA 10 mg N=825	OCA 25 mg N=827	Placebo N=825
LDL-C (mg/dL) mean	113	114	116
LDL-C ≥100 mg/dL (%)	60	63	61
LDL-C ≥130 mg/dL (%)	33	33	36
HDL-C (mg/dL) mean	45	45	45
HDL-C <40 mg/dL (men) or <50 mg/dL (women) (%)	56	58	54
TG (mg/dL) median	150	152	147
Metabolic syndrome[1]	89	88	87
Framingham Risk Score >10% (%)[2]	65	64	62
Ten-year ASCVD risk ≥20% (%)[3]	13	15	11
History of ASCVD (%)[4]	10	11	10

Source: FDA Response to an Information Request, submitted February 17, 2023 SDN 110; February 23, 2023 SDN 112.
[1] Metabolic Syndrome defined as the presence of any of three of the five traits of metabolic syndrome - presence of any three of the five traits: (1) Abdominal obesity: waist circumference ≥102 cm (40 in) in males and ≥88 cm (35 in) in females, (2) serum triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides, (3) serum HDL-C <40 mg/dL in males and <50 mg/dL (1.3 mmol/L) in females, or drug treatment for low HDL-C, (4) blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure, (5) fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.
[2] Baseline Framingham Risk Score: the 10-year cardiovascular disease risk (%) for women = [1 − 0.95012exp(B − 26.1931)] × 100%, where B = 2.32888 × ln (age) + 1.20904 × ln (total cholesterol) − 0.70833 × ln (high-density lipoprotein cholesterol) + 2.76157 × ln (systolic blood pressure if not treated) + 2.82263 × ln (systolic blood pressure if treated) + 0.52873 (if current smoker) + 0.69154 (if diabetic) The 10-year cardiovascular disease risk (%) for men = [1 − 0.88936exp(B - 23.9802)] × 100%, where B = 3.06117 × ln (age) + 1.12370 × ln (total cholesterol) − 0.93263 × ln (high-density lipoprotein cholesterol) + 1.93303 × ln (systolic blood pressure if not treated) + 1.99881 × ln (systolic blood pressure if treated) + 0.65451 (if current smoker) + 0.57367 (if diabetic).
[3] The 10-year risk for incident ASCVD is given by the formula: ASCVDs = 1 − (baseline survival)exp(ASCVDx − group mean) × 100%. Where ASCVDx = c1 × ln(age) + c2 × (ln(age))2 + (c3 + c4 × ln(age)) × ln(total cholesterol) + (c5 + c6 × ln(age)) × ln(HDLc) + (c7 + c8 × ln(age)) × ln(treated systolic BP) + (c9 + c10 × ln(age)) × ln(untreated systolic BP) + (c11+ c12 × ln(age)) × (if current smoker) + c13 × (if diabetic), and the baseline survival, coefficients, and group means were provided in the Applicant's original New Drug Application, ADRG, Appendix 5
[4] ASCVD defined as embolic and thrombotic broad SMQ, ischemic heart disease broad SMQ, and central nervous system vascular disorders narrow SMQ in the medical history.
Abbreviations: ADRG, Analysis Data Reviewer's Guide ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OCA, obeticholic acid.

6.4 Dysglycemia

KM methods were used to analyze the OCA 25 mg and placebo treatment arms for the occurrence of clinically significant dysglycemia for subsets of the study population based upon baseline glycemia (i.e., diabetes, prediabetes, and normal glycemia). For the normoglycemic and prediabetic populations, the incidence of biochemical conversion to prediabetes and diabetes, respectively, was captured using ADA diagnostic criteria. For the diabetic population, clinically significant loss of glycemic control was assessed by the composite of therapeutic intensification (i.e., initiation of new antidiabetic medications or increased dosage of current antidiabetic medication) and unfavorable shifts in FPG and HbA1c to levels falling outside of the glycemic goals established by the ADA standards of clinical care guidelines (i.e., increases in FPG over 130 mg/dL or HbA1c greater than 7.3%) (ElSayed et al. 2023).

The data from the KM plots comparing OCA 25 mg and placebo are summarized descriptively for months 3, 24 and 36. We selected these timepoints because the observed separation between the OCA 25 mg and placebo curves emerged at month 3, and months 24 and 36 provided a sufficient number of subjects remaining in each treatment arm to allow comparison of the risk difference (i.e., difference in cumulative incidence of clinically significant dysglycemia) with continued exposure.

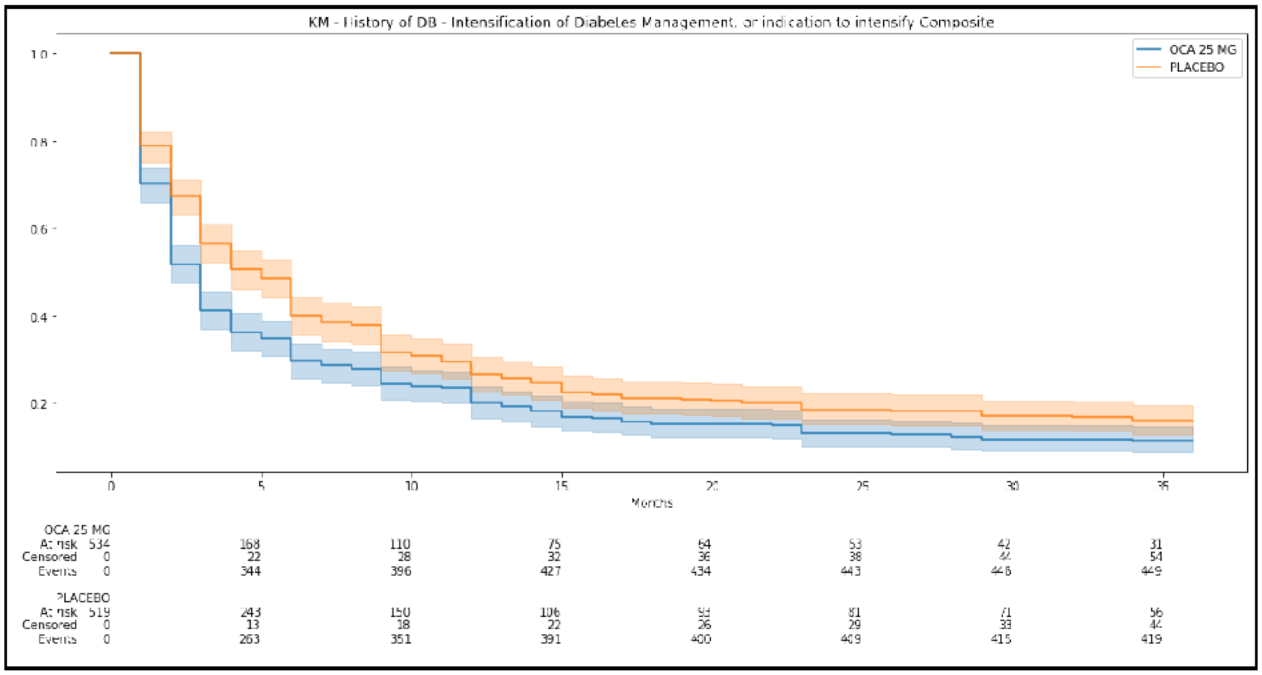
Subjects With T2D at Baseline

Figure 9 plots the time to clinically significant loss of glycemic control, as assessed by the query composite, for study subjects with a diagnosis of T2D at baseline, by OCA 25 mg (blue) and placebo (orange) treatment group.

Both curves have a progressive downward trajectory. The observed separation between these curves began within the first month, reached its maximum between months 3 and 6, and then lessened over the duration of the following 30 months. The observed risk difference between treatments at month 3 is 15.3% (95% CI: 9.3, 21.3). By 24 months, the observed risk difference is 5.4% (95% CI: 0.7, 10.0). At month 36, the observed risk difference is 4.6% (95% CI: 0.2, 9.1), at which time 88% and 84% of subjects experienced clinically significant worsening of glycemic control in OCA 25 mg and placebo arms, respectively.

The median time to loss of glycemic control is approximately 2 months for OCA 25 mg and 4 months for placebo. Thus, OCA 25 mg exposure appears to hasten the inevitable decline of glycemic control in diabetic patients with NASH by approximately 2 months.

Figure 9. Time to Clinically Significant Deterioration of Glycemic Control Composite, OCA 25 mg vs Placebo, Diabetes Subset, Study 747-303



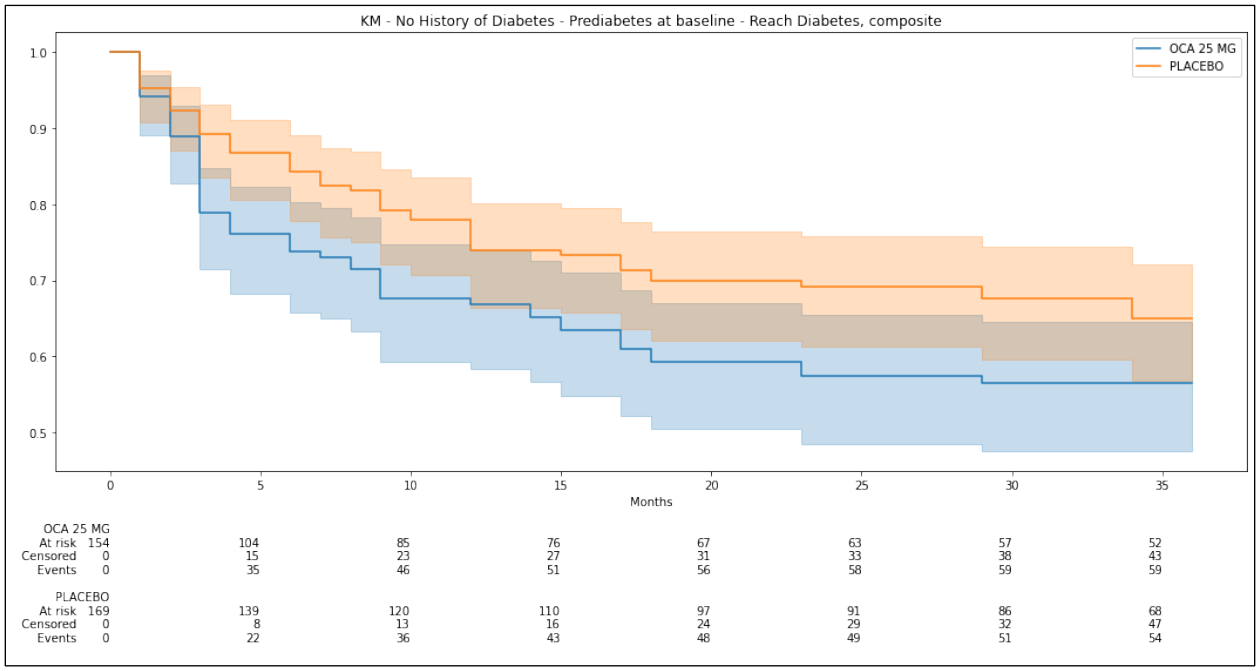
Source: FDA Review staff analysis using Applicant-submitted data adsl.xpt, adlbce.xpt, adlbhb.xpt, adcm.xpt, adexsum.xpt in Python (Ver. 3)
Y-axis represents proportion of trial participants not experiencing at least one event.
Transparent bands represent 95% CI.
Abbreviations: CI, confidence interval; OCA, obeticholic acid

Subjects With Prediabetes at Baseline

Figure 10 plots the observed time to diabetes diagnosis for OCA 25 mg (blue) and placebo (orange) treatment groups for the subset of study subjects with prediabetes at baseline. Separation between the curves began at 3 months with an observed risk difference between treatment arms of 10.3% (95% CI: 2.1, 18.5). The observed risk difference at month 24 is 11.7% (95% CI: 0.6, 22.8) and at month 36 is 8.5% (95% CI: -2.9, 20.0). The risk appears fairly stable over the analysis period, corresponding to a NNH of approximately 10. The time until 30% of the study subjects reach diagnostic criteria of diabetes is 9

months for OCA 25 mg group and 19 months for placebo. Thus, treatment with OCA 25 mg results in a persistently increased risk of incident diabetes.

Figure 10. Time to Diabetes Composite, OCA 25 mg vs Placebo, Pre-Diabetes Subset, Study 747-303

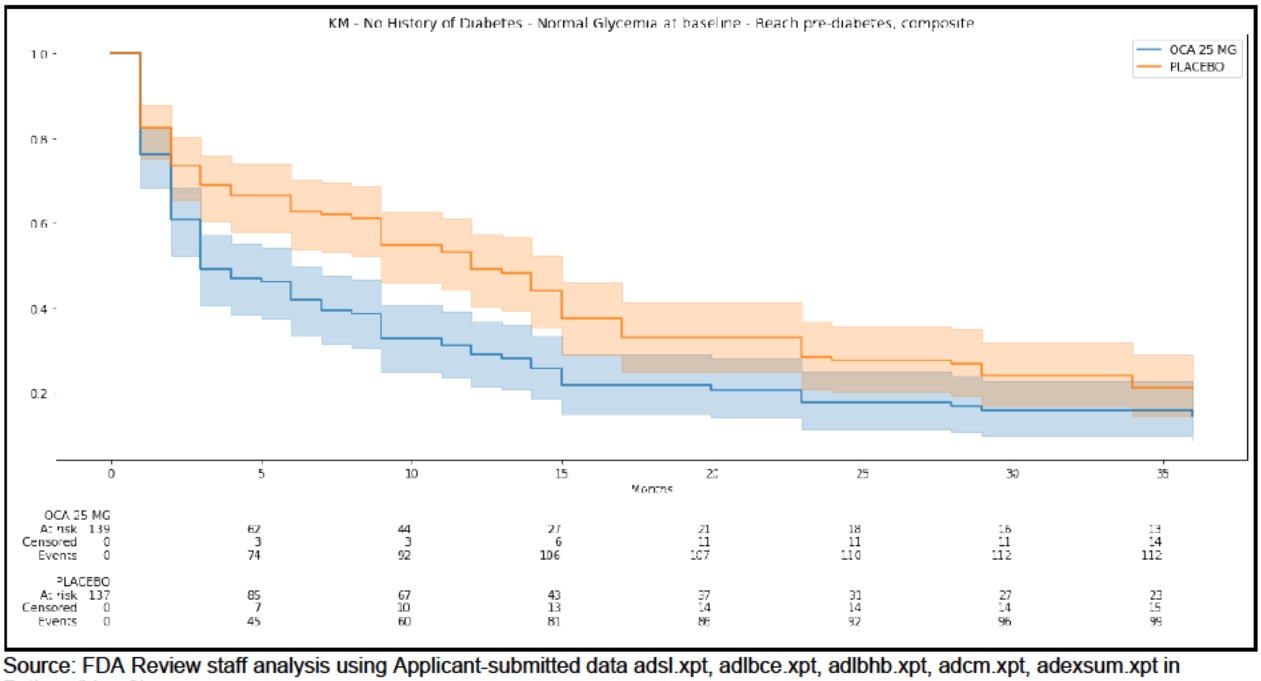


Source: FDA Review staff analysis using Applicant-submitted data adsl.xpt, adlbce.xpt, adlbhb.xpt, adcm.xpt, adexsum.xpt in Python (Ver. 3)
Y-axis represents proportion of trial participants not experiencing at least one event.
Transparent bands represent 95% CI.
Abbreviations: CI, confidence interval; OCA, obeticholic acid

Subjects With Normal Glycemic Control at Baseline

Figure 11 plots the observed time to diagnosis of prediabetes for OCA 25 mg (blue) and placebo (orange) treatment groups for the subset of study subjects with normal glycemia at baseline. Both curves have a progressive downward trajectory. Separation between these curves emerges at month 3, and the observed risk difference is 19.8% (95% CI: 8.4, 31.3). At month 24, the observed risk difference is 9.9% (95% CI: -0.5, 20.2) and at month 36 is 6.8% (95% CI: -2.9, 16.6%). By 36 months, 79% and 86% of subjects have converted to prediabetes in the placebo arm and OCA 25 mg arm, respectively. The median time to diagnosis of prediabetes is 3 months for OCA 25 mg arm and 12 months for placebo. Thus, OCA 25 mg exposure appears to hasten progressive dysglycemia to incident prediabetes in patients with NASH by approximately 9 months.

Figure 11. Time to Prediabetes Diagnosis Composite, OCA 25 MG vs Placebo, Normoglycemia Subset, Study 747-303



Source: FDA Review staff analysis using Applicant-submitted data adsl.xpt, adlbce.xpt, adlbhb.xpt, adcm.xpt, adexsum.xpt in Python (Ver. 3)
Y-axis represents proportion of trial participants not experiencing at least one event.
Transparent bands represent 95% CI.
Abbreviations: CI, confidence interval; OCA, obeticholic acid

6.5 Pruritus

The IR difference for pruritus and severe pruritus was higher for OCA 25 mg treatment arm compared to placebo. A dose dependent effect on TEAE of pruritus is also observed. See Table 25.

Table 25. Analysis of Adverse Events of Special Interest (On-Treatment + 30 Days), Study 747-303

Adverse Events of Special Interest	OCA 10 mg N=825 n[IR] IR Diff. (95% CI)	OCA 25 mg N=827 n[IR] IR Diff. (95% CI)	Placebo N=825 n[IR]
Pruritus	289 [15.14]	476 [36.45]	221 [10.20]
	4.94 (2.73, 7.14)	26.25 (22.71, 29.79)	
Severe pruritus	10 [0.37]	57 [2.28]	3 [0.11]
	0.26 (0.001, 0.52)	2.17 (1.56, 2.77)	

Source: Statistical reviewer's analysis based on Applicant-submitted data, adtte.xpt.
Abbreviations: CI, confidence interval; IR, incidence rate per 100 PY; IR Difference, incidence rate difference between OCA and placebo; OCA, obeticholic acid; PY, patient-years of follow-up until the earliest date of study discontinuation, loss of follow-up, 30 days after last dose of treatment, first event, or death

6.6 Cardiovascular Events

Table 26. Cardiovascular Safety in Study 747-303

Adverse Events of Special Interest	OCA 10 mg N=825 n[IR] IR Diff. (95% CI)	OCA 25 mg N=827 n[IR] IR Diff. (95% CI)	Placebo N=825 n[IR]
MACE (Core)[1]	5 [0.17]	15 [0.52]	11 [0.37]
	-0.20 (-0.47, 0.06)	0.15 (-0.20, 0.49)	
4-Point MACE[2]	9 [0.31]	18 [0.63]	13 [0.44]
	-0.14 (-0.45, 0.18)	0.18 (-0.19, 0.56)	
5-Point MACE[3]	9 [0.31]	18 [0.63]	16 [0.54]
	-0.24 (-0.57, 0.10)	0.08 (-0.31, 0.48)	

Source: Statistical reviewer's analysis based on Applicant-submitted data, adadj.xpt abd adsl.xpt.
* On-Study Analyses up to cutoff date of 12/31/2021
Abbreviations: CI, confidence interval; IR, incidence rate per 100 PY; IR Difference, incidence rate difference between OCA and placebo per 100 PY; OCA, obeticholic acid; PY, patient-years of follow-up until the earliest date of study discontinuation, loss of follow-up, cut-off date, first event, or death
[1] Core MACE: CV death, non-fatal MI, non-fatal.
[2] 4-point MACE: CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina
[3] 5-point MACE: CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization/urgent visit for heart failure.

6.7 Efficacy

6.7.1 Study 747-303 Clinical Benefit Endpoint

Study 747-303 is ongoing to evaluate clinical benefit outcomes. The primary composite clinical endpoint that will be evaluated at the end of the trial is measured as the time to first occurrence of any of the following adjudicated events:

- Death (all cause)
- Model of end-stage liver disease (MELD) score ≥15
- Liver transplant
- Hospitalization (as defined by a stay of ≥24 hours) for onset of:
  - Variceal bleed
  - Hepatic encephalopathy (HE; as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Ascites secondary to cirrhosis and requiring medical intervention (e.g., diuretics or paracentesis)
- Histological progression to cirrhosis

6.7.2 Details of Histopathology Reading

Central Method of Histological Assessment (Original NDA Submission)

Two central pathologists split the workload of scoring the liver biopsies. Scoring of the liver biopsies for endpoints were read in a paired fashion, i.e., baseline and 18-month biopsies for a given subject were read side by side. Pathologists were blinded to subject ID, site ID and location, subject's treatment assignment, and chronological sequence (screening/ baseline versus post-treatment) of the biopsies.

Consensus Method of Histological Assessment (NDA Resubmission)

The Applicant's Central Histology Manual (Version 4.0, August 19, 2021) states that biopsies collected at Baseline, Month 18, Month 48, EOT/EOS, and unscheduled visits were read using whole slide images employing the independent consensus read approach. The pathologists were blinded to the subject, site ID and location, and subject's treatment assignment.

According to the Central Histology Manual, each panel included three pathologists. Panel A pathologists read images of slides stained with H&E to characterize NAS scores and Panel B pathologists read images of slides stained with Trichrome to characterize NASH CRN fibrosis scores.

Stage 1: Independent Read

All 3 pathologists (e.g., from Panel A) independently read each subject's slide image and entered the results into the database.

The following rules were applied to the scores for fibrosis stage, inflammation, ballooning, and steatosis from the 3 pathologists.

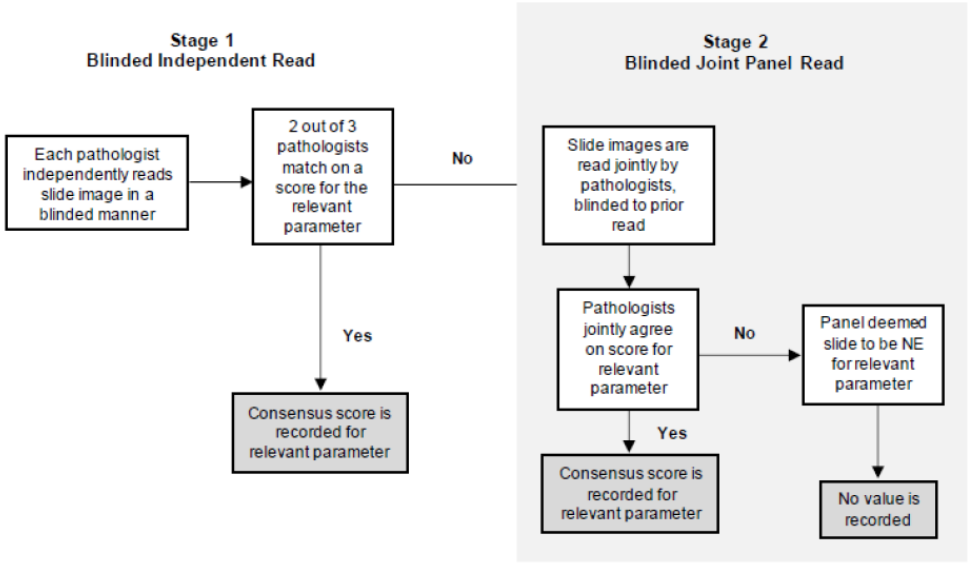
- If 2 pathologists matched on the score for a specific component, it is chosen as the consensus score for that component.
- If the scores from all 3 pathologists for a specific parameter are discordant, the slide image will be flagged for a joint panel read (Stage 2) for the discordant component.

Stage 2: Joint Panel Read

All 3 pathologists met (physically or virtually) to review the slide images identified from Stage 1. The panel members were blinded to their original scores. For each slide:

- The result of this read provides a single consensus score for component(s) for which the Stage 1 score(s) were discordant.
- If the panel determines that the slide is not evaluable (NE), then no consensus score is entered for the discordant component(s).

Figure 12. Independent Consensus Read Method



NE = non-evaluable.
Note: Harmonization calls and re-training will be convened at regular intervals.
Source: Figure 6 in the Sponsor's Central Histology Manual Version 4.0, August 19, 2021.

6.7.3 Additional Histopathology Baseline and Efficacy Results

Table 27 presents the baseline histopathology characteristics for the ITT_old population. There are subjects included in the main analyses of the Month 18 interim analysis primary endpoint (Table 5 and Table 6) who do not have fibrosis stage 2 or fibrosis stage 3 according to the consensus method. The results of a sensitivity analysis evaluating subjects with fibrosis stage 2 or fibrosis stage 3 according to the consensus method is presented in Table 28.

Table 27. Baseline Histopathology Characteristics (ITT_old)

ITT_old	OCA 10 mg N=312 n (%)	OCA 25 mg N=308 n (%)	Placebo N=311 n (%)
Baseline fibrosis stage (central method)			
Stage 2	130 (42)	139 (45)	142 (46)
Stage 3	182 (58)	169 (55)	169 (54)
Baseline fibrosis stage (consensus method)			
Stage 0	0	0	1 (<1)
Stage 1	3 (1)	5 (2)	10 (3)
Stage 2	99 (32)	104 (34)	99 (32)
Stage 3	159 (51)	150 (49)	152 (49)
Stage 4	40 (13)	41 (13)	43 (14)
Not evaluable	4 (1)	0	0
Missing	7 (2)	8 (3)	6 (2)
Hepatocellular ballooning (central method)			
1	93 (30)	83 (27)	84 (27)
2	219 (70)	225 (73)	225 (72)
Missing	0	0	2 (1)
Lobular inflammation (central method)			
1	49 (16)	46 (15)	55 (18)
2	124 (40)	120 (39)	110 (35)
3	139 (45)	142 (46)	144 (46)
Missing	0	0	2 (1)
Steatosis (central method)			
1	126 (40)	128 (42)	120 (39)
2	82 (26)	69 (22)	88 (28)
3	104 (33)	111 (36)	101 (32)
Missing	0	0	2 (1)

Source: Statistical reviewer's analysis of adsl.xpt.
Abbreviations: ITT, intention-to-treat; OCA, obeticholic acid

Table 28. Study 747-303 Month-18 Interim Analysis Primary Endpoint Results (All Randomized Subjects Expected to Complete Month-18 Visit Under Protocol Version 8 or Earlier and Baseline Fibrosis Stage 2 or 3 Based on the Consensus Method)

Endpoint	OCA 10 mg N=409 n (%)	OCA 25 mg N=413 n (%)	Placebo N=427 n (%)	Risk Difference 10 mg-Placebo (95% CI)	Risk Difference 25 mg-Placebo (95% CI)
Improvement of fibrosis and no worsening of NASH	62 (15.2)	101 (24.5)	50 (11.7)	3.4 (-1.2, 8.1)	12.7 (7.5, 17.8)
Resolution of NASH and no worsening of fibrosis	29 (7.1)	40 (9.7)	19 (4.4)	2.6 (-0.6, 5.7)	5.2 (1.7, 8.6)

Source: Applicant's response to Information Request on April 5, 2023.
Note: 95% confidence intervals cannot be used to determine statistical significance.

Table 29 and Table 30 present the results of the Month 18 primary analyses using a population summary measure of an odds ratio.

Table 29. Study 747-303 Month-18 Interim Analysis Primary Endpoint Odds Ratio Results—Improvement of Fibrosis and No Worsening of NASH (ITT_old and ITT_histology)

	OCA 10 mg	OCA 25 mg	Placebo	Odd Ratio 10 mg vs. Placebo (95% CI)	Odds Ratio 25 mg vs. Placebo (95% CI)	P-Value 10 mg	P-Value 25 mg
ITT_old							
Central method (original results)	N=312	N=308	N=311				
N (%)	55 (17.6)	71 (23.1)	37 (11.9)	1.5 (1.0, 2.2)	1.9 (1.3, 2.8)	0.0446	0.0002*
Consensus method	N=312	N=308	N=311				
N (%)	44 (14.1)	69 (22.4)	30 (9.6)	1.5 (0.9, 2.3)	2.3 (1.6, 3.5)	0.0863	<0.0001*
ITT_histology							
Consensus method	N=532	N=539	N=536				
N (%)	86 (16.2)	113 (21.0)	66 (12.3)	1.3 (1.0, 1.8)	1.7 (1.3, 2.2)	N/A	N/A

Source: Statistical analyst's analysis of adsl.xpt, admi.xpt, and adbx.xpt datasets; same as Applicant's results. P-values calculated using CMH test stratified by randomization strata (diabetes at enrollment [yes/no] and use of TZDs or vitamin E at baseline [yes/no]). The Mantel-Haenszel method was used to construct the CIs.
* denotes statistical significance.
Note: 95% confidence intervals cannot be used to determine statistical significance.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; N/A, not applicable; OCA, obeticholic acid

Table 30. Study 747-303 Month-18 Interim Analysis Primary Endpoint Odds Ratio Results—Resolution of Nash and no Worsening of Fibrosis (ITT_old and ITT_histology

	OCA 10 mg	OCA 25 mg	Placebo	Odd Ratio 10 mg vs. Placebo (95% CI)	Odds Ratio 25 mg vs. Placebo (95% CI)	P-Value 10 mg	P-Value 25 mg
ITT_old							
Central method (original results)	N=312	N=308	N=311				
N (%)	35 (11.2)	36 (11.7)	25 (8.0)	1.4 (0.9, 2.3)	1.5 (0.9, 2.3)	0.1814	0.1268
Consensus method	N=312	N=308	N=311				
N (%)	19 (6.1)	20 (6.5)	11 (3.5)	1.7 (0.8, 3.6)	1.8 (0.9, 3.8)	0.1377	0.0926
ITT_histology							
Consensus method	N=532	N=539	N=536				
N (%)	34 (6.4)	39 (7.2)	19 (3.5)	1.8 (1.0, 3.1)	2.0 (1.2, 3.5)	N/A	N/A

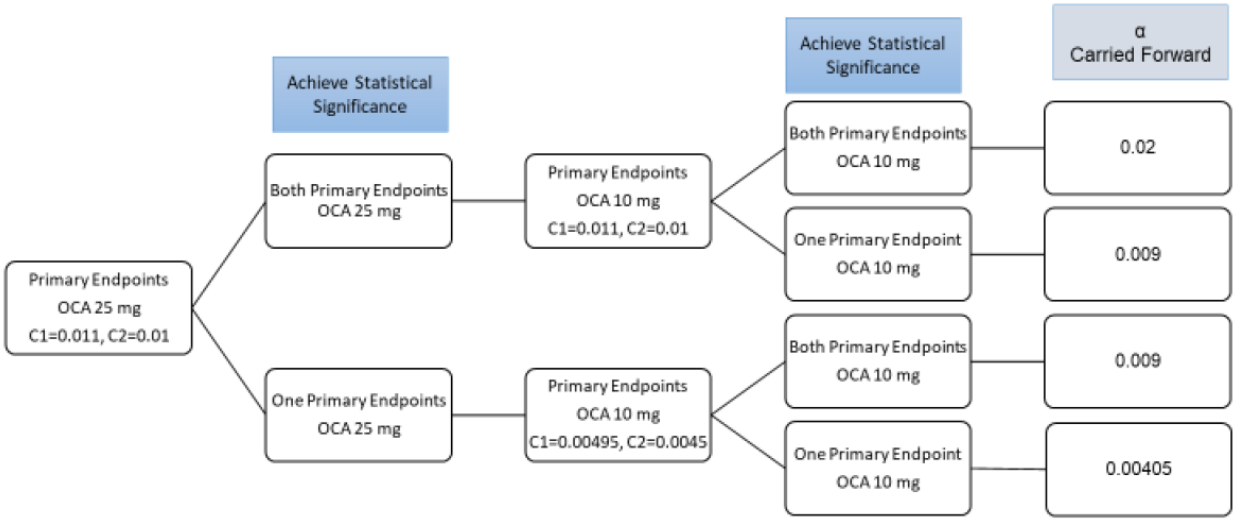
Source: Statistical analyst's analysis of adsl.xpt, admi.xpt, and adbx.xpt datasets; same as Applicant's results. P-values calculated using CMH test stratified by randomization strata (diabetes at enrollment [yes/no] and use of TZDs or vitamin E at baseline [yes/no]). The Mantel-Haenszel method was used to construct the CIs.
Note: 95% confidence intervals cannot be used to determine statistical significance.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; N/A, not applicable; OCA, obeticholic acid

6.7.4 Type I Error Control

Figure 13 depicts the statistical testing for the Month 18 interim analysis and the potential alpha that may be carried over for the final analysis of the clinical benefit outcome (Section 6.7.1).

As described in Section 3.1.1, the overall type I error rate was controlled at the two-sided alpha =0.05 significance level with alpha of 0.02 allocated to evaluate histological endpoints for the 18-month interim analysis and alpha of 0.03 allocated to the clinical outcome endpoint at the end of study. At the 18-month interim analysis, the testing hierarchy started with the comparison of OCA 25 mg to placebo. The truncated Hochberg procedure with truncation parameter of 0.1 was used to test the two Month 18 primary endpoints. If at least one of the two Month 18 primary endpoints demonstrated statistical significance in the OCA 25 mg arm, the two Month 18 primary endpoints were to be subsequently tested (also based on the truncated Hochberg procedure with truncation parameter equal to 0.1) for the comparison of OCA 10 mg to placebo.

Figure 13. Statistical Testing for the Month 18 Interim Analysis



Source: Statistical Analysis Plan for Protocol 747-303 dated January 24, 2019.

Based on the results of the ITT_old population in Table 5 and Table 6, the procedure went as follows using the pre-specified method to control the overall type I error rate:

- The two primary endpoints for the OCA 25 mg arm were tested by first comparing the larger p-value to 0.011.
- As the larger of the two p-values for the OCA 25 mg arm (resolution of NASH and no worsening in fibrosis endpoint) was greater than 0.011, the smaller of the two p-values was compared to 0.01 (improvement of fibrosis and no worsening of NASH).
- This p-value was less than 0.01, so OCA 25 mg demonstrated superiority to placebo on the improvement of fibrosis and no worsening of NASH endpoint.
- Given the statistical significance of OCA 25 mg arm on one of the primary endpoints, 0.02-0.011= 0.009 was passed on to testing the primary endpoints for the OCA 10 mg arm compared to placebo.

- The primary endpoints for the OCA 10 mg arm were tested by first comparing the higher p-value for the OCA 10 mg arm (resolution of NASH and no worsening in fibrosis endpoint) to 0.00495 and then comparing the smaller p-value for the OCA 10 mg arm (improvement of fibrosis and no worsening of NASH) to 0.0045 when the first test failed.
- The second test also failed to achieve statistical significance, so OCA 10 mg did not demonstrate superiority to placebo on either primary endpoint.

6.7.5 Missing Data

Methods for Handling Missing Data

For the original NDA submission, the SAP specified that any subject who discontinued from the study prior to the Month 18 biopsy visit and did not have a post-baseline biopsy assessment would be considered a non-responder. Biopsies collected for subjects who discontinued treatment before the Month 18 visit would be included in the Month 18 Interim Analysis of histological endpoints, regardless of the timing of the biopsy. The target study week (window) for Month 18 histological endpoints was Week 72 (60, 96), as specified in the original SAP (January 24, 2019).

For the NDA resubmission, additional details were specified in Addendum 2 to the SAP (April 25, 2022; specified after the original NDA submission). The addendum stated that for subjects in the original Month 18 interim analysis cohort who had a biopsy sample collection date but did not have scores based on the consensus read method, the missing data would be imputed using the original central reader's scores, if available.

Missing Data Results

Non-responder imputation due to missing data was used for 15-25% of subjects for the Month 18 primary endpoints for the ITT_old population across the different biopsy read methods (i.e., central and consensus). There were higher levels of missing data (~30%) for the ITT_histology population. The amount of missing data was comparable across treatment arms. For 10 subjects, results from the central method were used to impute missing data for the consensus method.

A tipping point analysis was conducted during the original NDA review for the primary endpoint evaluating improvement of fibrosis and no worsening of NASH (ITT_old population, central method). There was a tipping point (i.e., a scenario leading to non-significant results [p-value>0.01]) in a scenario where there were approximately 10 more responders for the placebo-treated subjects with missing data than for the OCA 25 mg-treated subjects with missing data. This translates to needing a response rate at least 20 percentage points higher in the placebo-treated subjects with missing data than in the OCA 25 mg-treated subjects with missing data to tip the results to be not significant. This scenario is unlikely to be clinically plausible.

The biopsy results used for the primary endpoint evaluation was outside the Month 18 visit window (study day 420-672) for approximately 2% of subjects. While a few of these subjects achieved response on the primary endpoint(s), all these responses were based on biopsies that occurred prior to the specified Month 18 visit window (range: study days 208-398).

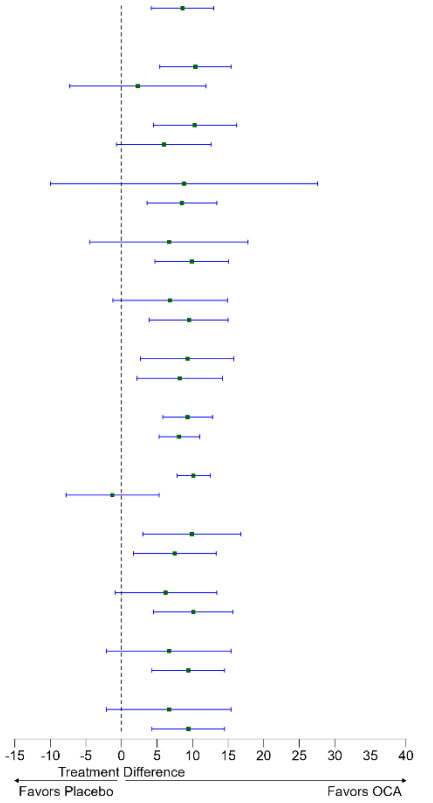
6.7.6 Key Subgroup Results

There were no clear differential results by subgroup comparing OCA 25 mg to placebo, except for the use of TZD or vitamin E use at baseline. Subjects on TZD or vitamin E use at baseline had a slight trend in the direction of favorable results for placebo, but the confidence interval overlaps 0, this subgroup is relatively small, and the finding may be due to chance by examining many subgroups. Figure 14 presents key subgroup results comparing OCA 25 mg to placebo for the Month 18 interim analysis primary

endpoint of improvement of fibrosis and no worsening of NASH in the ITT_histology analysis population. Results for the ITT_old analysis population are not presented, but were similar.

Figure 14. Subgroup Results for OCA 25 mg and Placebo in Study 747-303—Improvement of Fibrosis and No Worsening of NASH (ITT_histology)

Variable	OCA 25mg responders/N (%)	Placebo responders/N (%)	Treatment Difference (95% CI) (%)
Overall	113/539 (21)	66/536 (12.3)	8.6 (4.2,13.0)
Age			
< 65 years	92/419 (22)	49/427 (11.5)	10.4 (5.4,15.4)
>= 65 years	21/120 (17.5)	17/109 (15.6)	2.3 (-7.3,11.9)
Sex			
F	75/324 (23.1)	41/320 (12.8)	10.3 (4.5,16.2)
M	38/215 (17.7)	25/216 (11.6)	6.0 (-0.7,12.6)
Race			
Other races	12/53 (22.6)	3/22 (13.6)	8.8 (-10.0,27.6)
White	93/437 (21.3)	57/448 (12.7)	8.5 (3.6,13.4)
Ethnicity			
Hispanic or Latino	18/86 (20.9)	14/95 (14.7)	6.7 (-4.5,17.8)
Not Hispanic or Latino	87/400 (21.8)	45/379 (11.9)	9.9 (4.7,15.1)
Region			
Europe	25/142 (17.6)	15/144 (10.4)	6.8 (-1.2,14.9)
North America	87/376 (23.1)	49/361 (13.6)	9.5 (3.9,15.0)
Baseline Fibrosis Stage			
Stage 2	48/238 (20.2)	24/223 (10.8)	9.3 (2.7,15.8)
Stage 3	65/301 (21.6)	42/313 (13.4)	8.2 (2.2,14.2)
Diabetes			
N	54/235 (23)	31/226 (13.7)	9.3 (5.8,12.8)
Y	59/304 (19.4)	35/310 (11.3)	8.1 (5.3,11.0)
TZD/Vitamin E Medication			
N	101/473 (21.4)	52/464 (11.2)	10.1 (7.8,12.5)
Y	12/66 (18.2)	14/72 (19.4)	-1.3 (-7.8, 5.3)
Anti-diabetic Medication Use at Baseline			
N	57/249 (22.9)	30/229 (13.1)	9.9 (3.0,16.8)
Y	56/290 (19.3)	36/307 (11.7)	7.5 (1.7,13.3)
Anti-hypertensive Medication Use at Baseline			
N	35/196 (17.9)	20/173 (11.6)	6.2 (-0.9,13.4)
Y	78/343 (22.7)	46/363 (12.7)	10.1 (4.5,15.7)
BMI 30			
< 30	28/140 (20)	19/140 (13.6)	6.7 (-2.1,15.4)
>= 30	85/399 (21.3)	47/396 (11.9)	9.4 (4.3,14.5)
BMI 35			
< 35	81/346 (23.4)	44/335 (13.1)	6.7 (-2.1,15.4)
>= 35	32/193 (16.6)	22/201 (10.9)	9.4 (4.3,14.5)



Source: Statistical analyst's analysis.
Note: 95% confidence intervals cannot be used to determine statistical significance.
Abbreviations: BMI, body mass index; CI, confidence interval; F, female; ITT, intention-to-treat; M, male; N, no; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; Y, yes

7 Attachments

7.1 HSAC Review Case - Subject 3

Voting Form

Intercept Pharmaceuticals

Member name: [redacted]
Project name: intOCADILI
Site #: [redacted]
Case ID: [redacted]
Panel: HSAC

Voted On: 06-Apr-2020
Study Name: 747-303
Country N/A
Subject ID: [redacted]

Trigger	Onset Date	Description	Unique ID	Event Type	Lab Test	Lab Result	Lab Uni		
ACUTE CHOLESTATIC LIVER NJURY	18-Aug-2017	Cholestatic liver injury	7	S1: Cholestasis and jaundice of hepatic origin (SMQ)					
4N: ALP >=2x BL and > ULN	18-Aug-2017		LOCAL						
HYPERB LARU B NEMIA	18-Aug-2017	Hyperbilirubinae mia	5	S1: Cholestasis and jaundice of hepatic origin (SMQ)					

Does the subject have potential evidence of liver injury? (choose one)

[ ] No evidence of liver injury - lab error likely or other explanation (specify):

[X] Potential evidence for liver injury

[ ] Review Grouping/Send for panel review

Assess drug relatedness (choose one):

[ ] Insufficient Information. What is missing (specify):

[ ] Unlikely drug related; Please specify other potential etiology (specify):

[X] **Possible drug related; Please specify other potential etiology (specify):** :

[ ] Probable drug related

[ ] Highly likely drug related

Assess severity (choose one):

[ ] Not Assessable. What is missing (specify):

[ ] Mild Hepatic Injury

[ ] Moderate Hepatic Injury

[ ] Moderate-Severe Hepatic Injury

[X] Severe Hepatic Injury

[ ] Fatal Case

Provide Date of Liver Injury:

[X] **Provide Date of Liver Injury (dd-MMM-yyyy)** :

18-AUG-2017

[ ] Not Applicable

[redacted]

Clinical Review Findings (required):

Clinical Review Findings (required): :

This is a case of acute liver failure very similar to the recently described cases in patients with PBC/PSC (Eeaton et al, Hepatology, epub) and concerning. The patient was on multiple drugs including diclofenac but the timing of these medications is unclear. This case should be discussed at a conference call with the other hepatologists for a true consensus assessment.

Member Comments (optional):

Member Comments (optional): :

This is an acute liver failure leading to liver transplantation about 4 months on study drug treatment. This case should be presented and discussed with all the expert hepatologists.

Member Name: [redacted]

[X] *By checking this box, I certify that I have adjudicated this case.*

Date: 0 6 (day) A P R (month) 2 0 2 0 (year)

[redacted]

Voting Form

Intercept Pharmaceuticals

Member name: [redacted] **Voted On:** **09-Apr-2020**
Project name: intOCADILI Study Name: 747-303
Site #: [redacted] Country N/A
Case ID: [redacted] **Subject ID:** [redacted]
Panel: HSAC

Trigger	Onset Date	Description	Unique ID	Event Type	Lab Test	Lab Result	Lab Unit		
ACUTE CHOLESTATIC LIVER NJURY	18-Aug-2017	Cholestatic liver injury	7	S1: Cholestasis and jaundice of hepatic origin (SMQ)					
4N: ALP >=2x BL and > ULN	18-Aug-2017		LOCAL						
HYPERB LARU B NEMIA	18-Aug-2017	Hyperbilirubinae mia	5	S1: Cholestasis and jaundice of hepatic origin (SMQ)					

Does the subject have potential evidence of liver injury? (choose one)

[ ] No evidence of liver injury - lab error likely or other explanation (specify):

[X] Potential evidence for liver injury

[ ] Review Grouping/Send for panel review

Assess drug relatedness (choose one):

[ ] Insufficient Information. What is missing (specify):

[ ] Unlikely drug related; Please specify other potential etiology (specify):

[ ] Possible drug related; Please specify other potential etiology (specify):

[X] Probable drug related

[ ] Highly likely drug related

Assess severity (choose one):

[ ] Not Assessable. What is missing (specify):

[ ] Mild Hepatic Injury

[ ] Moderate Hepatic Injury

[ ] Moderate-Severe Hepatic Injury

[X] Severe Hepatic Injury

[ ] Fatal Case

Provide Date of Liver Injury:

[X] **Provide Date of Liver Injury (dd-MMM-yyyy)** :
UU-aug-2017

[ ] Not Applicable

[redacted]

Clinical Review Findings (required):

Clinical Review Findings (required): :

patient got both OCA and diclofenac and so I have classified it as probable rather than definite. The patient clearly had DILI.

Member Comments (optional):

Member Comments (optional): :

Member Name: [redacted]

X *By checking this box, I certify that I have adjudicated this case.*

Date: 0 9 (day) A P R (month) 2 0 2 0 (year)

[redacted]

Voting Form

Intercept Pharmaceuticals

Member name: [redacted]
Project name: intOCADILI
Site #: [redacted]
[redacted]
Panel: HSAC

Voted On: 18-Apr-2020
Study Name: 747-303
[redacted]
Subject ID: [redacted]

Trigger	Onset Date	Description	Unique ID	Event Type	Lab Test	Lab Result	Lab Unit		
ACUTE CHOLESTATIC LIVER NJURY	18-Aug-2017	Cholestatic liver injury	7	S1: Cholestasis and jaundice of hepatic origin (SMQ)					
4N: ALP >=2x BL and > ULN	18-Aug-2017		LOCAL						
HYPERB LARU B NEMIA	18-Aug-2017	Hyperbilirubinae mia	5	S1: Cholestasis and jaundice of hepatic origin (SMQ)					

Does the subject have potential evidence of liver injury? (choose one)

[ ] No evidence of liver injury - lab error likely or other explanation (specify):

[X] Potential evidence for liver injury

[ ] Review Grouping/Send for panel review

Assess drug relatedness (choose one):

[ ] Insufficient Information. What is missing (specify):

[ ] Unlikely drug related; Please specify other potential etiology (specify):

[X] **Possible drug related; Please specify other potential etiology (specify):** :

[ ] Probable drug related

[ ] Highly likely drug related

Assess severity (choose one):

[ ] Not Assessable. What is missing (specify):

[ ] Mild Hepatic Injury

[ ] Moderate Hepatic Injury

[X] Moderate-Severe Hepatic Injury

[ ] Severe Hepatic Injury

[ ] Fatal Case

Provide Date of Liver Injury:

[X] **Provide Date of Liver Injury (dd-MMM-yyyy)** :

18-AUG-2017

[ ] Not Applicable

[redacted]

Clinical Review Findings (required):

Clinical Review Findings (required): :

Developed acute kidney injury during August, 2017. Very severe and progressive. Liver tests deteriorated with peak level 23 mg/dl and patient underwent liver transplantation on 09-24-2017. Peak direct bilirubin had been 16.6 at a time the MELD score was 37. Must consider some contribution of study drug to these events.

Member Comments (optional):

Member Comments (optional): :

Member Name: [redacted]

[X] *By checking this box, I certify that I have adjudicated this case.*

Date: 1 8 (day) A P R (month) 2 0 2 0 (year)

[redacted]

Decision Form

Intercept Pharmaceuticals

User:	[redacted]	**Voted On:**	**04-May-2020**
Project name:	intOCADILI	Study Name:	747-303
Site #:	[redacted]	Country	N/A
Case ID:	[redacted]	**Subject ID:**	[redacted]
Panel:	HSAC		

Trigger	Onset Date	Description	Unique ID	Event Type	Lab Test	Lab Result	Lab Unit		
ACUTE CHOLESTATIC LIVER NJURY	18-Aug-2017	Cholestatic liver injury	7	S1: Cholestasis and jaundice of hepatic origin (SMQ)					
4N: ALP >=2x BL and > ULN	18-Aug-2017		LOCAL						
HYPERB LARU B NEMIA	18-Aug-2017	Hyperbilirubinae mia	5	S1: Cholestasis and jaundice of hepatic origin (SMQ)					

Does the subject have potential evidence of liver injury? (choose one)

[ ] No evidence of liver injury

[X] Potential evidence for liver injury

Assess drug relatedness (choose one):

[ ] Insufficient Information

[ ] Unlikely drug related

[X] Possible drug related

[ ] Probable drug related

[ ] Highly likely drug related

Assess severity (choose one):

[ ] Not Assessable

[ ] Mild Hepatic Injury

[ ] Moderate Hepatic Injury

[ ] Moderate-Severe Hepatic Injury

[X] Severe Hepatic Injury

[ ] Fatal Case

Provide Date of Liver Injury:

[X] **Provide Date of Liver Injury (dd-MMM-yyyy)** :

18-AUG-2017

[ ] Not Applicable

[redacted]

Clinical Review Findings:

Clinical Review Findings: :

Baseline elevation in ALT (116/87) and AST (94/76) with normal AP and bili. Started IP on 3/21/17 and on 7/28/17 developed vesicles, N/V, dizziness, darker urine, wt loss. On 8/10/17 patient self-d/c'ed IP. Took Acyclovir beginning 8/11/17. Hospitalized on Day 150 for AKI and acute liver injury: ALT to 139, AST to 233, AP to 399 and bili to 25.70 (direct 20.20). Skin lesions were biopsied and showed abdominal folliculitis. 1 bottle of 4 blood cultures was positive for S. aureus bacteremia and started on Vancomycin followed by Cephazolin. Blood cultures were negative on 8/20/17 and pt remained afebrile for remainder of hospitalization. CT showed mild peri-pancreatic inflammation, CXR showed no acute process, and ultrasound showed only mild perinephric fluid. MRI/MRCP showed only mild GB wall thickening (but patient had marked hypoalbuminemia) and small gall stone in gallbladder with no biliary tree dilation. Transjugular liver biopsy showed steatohepatitis with stage 3 fibrosis, canalicular cholestasis, bile duct proliferation, and pericholangitis, consistent with biliary obstruction or possible drug injury. INR not provided but said to improve with IV vitamin K. On 8/28/17 placed on transplant list with liver failure, ascites, encephalopathy. Working dx was DILI. Over the month after hospitalization, bili stayed elevated to similar levels while ALT, AST, and AP declined. Albumin had dropped to 1.8 on 8/19/17 but increased to 4.0 on 9/5/17 - although received albumin infusion(s). Transplant on 9/24/17. Other drugs include diclofenac, first prescribed 9/13/16 for prn use. This was revealed only with subsequent interrogation of the subject's wife, and she was unable to find the bottle at home. Additional medications included amlodipine and allopurinol, first prescribed July, 2014. This case was discussed on three separate occasions, as additional information was obtained, as included above. The HSAC was aware of some similarities between this case and those liver failure cases recently attributed to OCA, as referenced in Hepatology 2020, vol 71, #4, pp 1511-1514. However, the presence of likely concurrent bacteremia, possible biliary obstruction not captured on imaging, but consistent with biopsy findings, and possible recent use of diclofenac are confounders. After considerable deliberations whether this case should be considered possibly or probably related to study drug, all members of the HSAC came to agreement that this case should be considered possibly related to study drug.

Panel Review Required:

[X] Yes

[ ] No

[redacted]

Panel Comments (optional):

Panel Comments (optional): :

Decision Date:

Decision Date: :

01May2020

Member Name: [redacted]

[X] *By checking this box, I certify that I have adjudicated this case.*

Date: 0 4 (day) M A Y (month) 2 0 2 0 (year)

[redacted]