ADVISORY COMMITTEE BRIEFING DOCUMENT
GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

Meeting Date: 19 May 2023

New Drug Application for Obeticholic Acid (OCA) for the Treatment of Adult Patients with Pre-Cirrhotic Liver Fibrosis Due to Nonalcoholic Steatohepatitis (NASH)
(New Drug Application [NDA] 212833)

Sponsor:

Intercept Pharmaceuticals, Inc.
305 Madison Avenue
Morristown, NJ 07960
USA

ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APP	advanced practice provider
APRI	aminotransferase to platelet ratio index
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BMI	body mass index
C_{max}	peak (maximum) plasma concentration
C_{trough}	predose plasma concentration at steady state
CAC	Cardiovascular Adjudication Committee
CI	confidence interval
CKD	chronic kidney disease
CRL	Complete Response Letter
CRN	Clinical Research Network
CV	cardiovascular
CYP	cytochrome P
DB	double-blind
DCO	data cutoff
DDI	drug-drug interaction
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eDISH	evaluation of drug-induced serious hepatotoxicity
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis

Abbreviation	Definition
EOS	End of Study
EOT	End of Treatment
F0, 1, 2, 3, or 4	fibrosis stage 0, 1, 2, 3, or 4
FDA	Food and Drug Administration
FIB-4	fibrosis-4
FLINT	Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment
FXR	farnesoid X receptor
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1c
HCC	hepatocellular carcinoma
HDL	high-density lipoprotein
HSAC	Hepatic Safety Adjudication Committee
IA	interim analysis
ICH	International Conference on Harmonisation
ID	identification
INR	international normalized ratio
ITT	Intent-to-Treat
KDIGO	Kidney Disease Improving Global Outcomes
LDL	low-density lipoprotein
LTSE	long-term safety extension
MACE	Major Adverse Cardiac Events
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified Intent-to-Treat
MOA	mechanism of action
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
NDA	New Drug Application
NE	not evaluable
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIT	noninvasive test
OCA	obeticholic acid
PBC	primary biliary cholangitis

Abbreviation	Definition
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
PY	patient year
QD	once daily
RAC	Renal Adjudication Committee
SAE	serious adverse event
SOC	system organ class
SMQ	standardized MedDRA Query
TE	transient elastography
TEAE	treatment-emergent adverse event
TZD	thiazolidinedione
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
US	United States

1. OVERVIEW

Intercept Pharmaceuticals, Inc. (hereafter referred to as Intercept) is seeking accelerated approval for obeticholic acid (OCA), a farnesoid X receptor (FXR) agonist, for the treatment of pre-cirrhotic fibrosis (stages 2 and 3 [F2 and F3]) due to nonalcoholic steatohepatitis (NASH), excluding patients with evidence of cirrhosis, portal hypertension, hepatic decompensation, or a history of prior hepatic decompensation. The proposed oral dose of OCA is 25 mg once daily (QD) and labeling will state that patients should be supervised and managed by a hepatologist or gastroenterologist.

According to US Food and Drug Administration (FDA) guidance, a product may qualify for accelerated approval if it treats a serious condition, provides a meaningful advantage over available therapy, and demonstrates an effect on an endpoint that is reasonably likely to predict clinical benefit. This pathway has been primarily used in settings in which the disease course is long, and an extended period of time would be required to measure the intended clinical benefit. Postmarketing confirmatory trials are required to verify and describe the anticipated benefit (FDA 2014).

Per FDA's non-cirrhotic NASH with liver fibrosis draft guidance for industry, the ultimate goal of NASH treatment is to slow the progress of, halt, or reverse disease progression and to improve clinical outcomes. Because of the slow progression of NASH and the time required to conduct a trial that would evaluate clinical endpoints such as progression to cirrhosis or survival, FDA recommends sponsors consider liver histological improvements as endpoints that are reasonably likely to predict clinical benefit to support accelerated approval (FDA 2018).

A Month 18 interim analysis (IA) of a randomized, double-blind (DB), placebo-controlled Phase 3 study (747-303 [REGENERATE], hereafter referred to as Study 303), which achieved positive results on an accepted histological endpoint, is the basis of this New Drug Application (NDA) for accelerated approval. Confirmation of clinical benefit will be established through the ongoing phase of Study 303 in which outcomes (all-cause mortality and liver-related clinical outcomes) are being collected in a blinded manner to provide the final endpoint for the study.

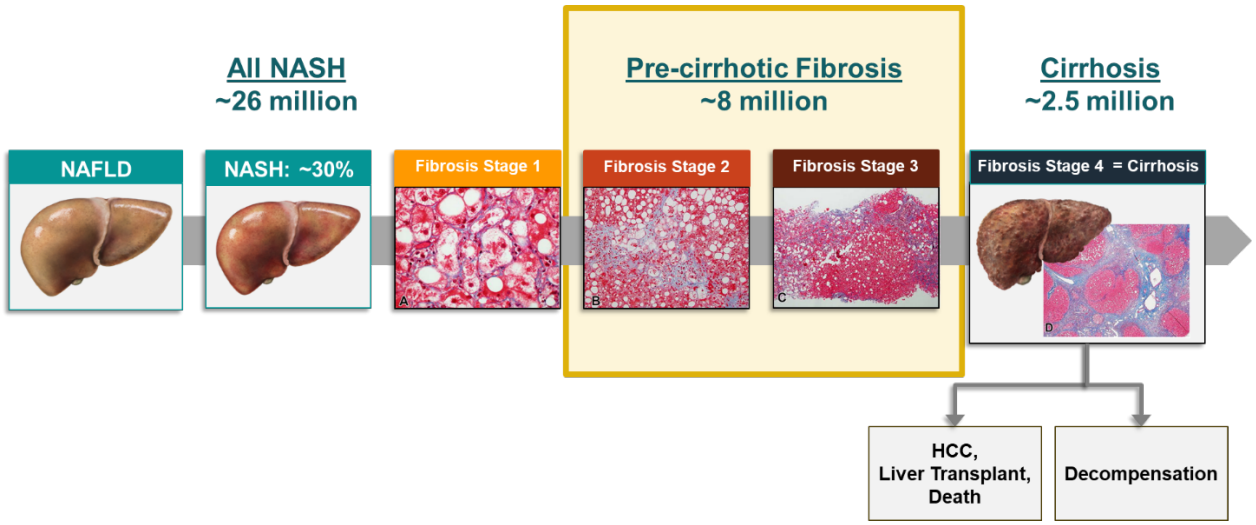
NASH (Section 2)

Nonalcoholic fatty liver disease (NAFLD) is a metabolic disease characterized by fat deposition in the liver and is correlated with increasing rates of obesity and type 2 diabetes in the United States (US). The prevalence of NAFLD in US adults is rising and projected to increase by ~30% by 2040. Of those, 39 million US adults are estimated to be diagnosed with NASH (Razavi 2022). NASH is a serious, progressive liver disease characterized not only by the presence of hepatic fat (steatosis), but also inflammation and hepatocyte injury (ballooning), which can lead to fibrosis and ultimately to cirrhosis, liver failure, liver cancer, and death (Rinella 2023). NASH is now the second most common indication for adults on the liver transplant waitlist and is the leading indication for liver transplantation for women in the US (Noureddin 2018).

The NASH Clinical Research Network (NASH CRN) defines the stages of fibrosis from F0 to F4. Patients progress from steatohepatitis through multiple stages of fibrosis (F1 to F3) before reaching cirrhosis (F4) (Figure 1). The evolution to NASH occurs in about 30% of the population with NAFLD. Liver fibrosis in NASH progresses to F2 and F3 in about 2.5% of the

US adult population, and up to 20% of patients with F3 will progress to cirrhosis within 2.5 years (Sanyal 2019).

Figure 1: NASH is a Progressive Disease Associated with the Development of Fibrosis and Cirrhosis



HCC=hepatocellular carcinoma; NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis

There is now a clear correlation between increased fibrosis stage and the risk of both liver-specific outcomes and all-cause mortality. Data published in 2017 showed that fibrosis stage, rather than steatohepatitis, predicts liver-specific and all-cause mortality (Hagström 2017) and in 2021, the seminal paper was published in the New England Journal of Medicine by the NASH CRN that conclusively showed fibrosis is the single strongest predictor of outcomes in NASH (Sanyal 2021a).

The estimated annual number of deaths to be expected among US persons who currently have F3 disease is 17,800 and among persons with F4 disease is 22,880 (Sanyal 2021a). Further, an additional 15,000 deaths annually occur among persons with NASH whose disease transitions into F3 or F4. There is considerable overlap in liver function and physiology between patients identified with F2 and F3 fibrosis histologically. Therefore, patients with pre-cirrhotic fibrosis (F2 or F3) represent the greatest opportunity for intervention.

Sustained >10% weight loss has been shown to improve hepatic steatosis, underlying steatohepatitis, and hepatic fibrosis, although very few patients are able to achieve or maintain this degree of weight loss (Rinella 2023, Vilar-Gomez 2015). In patients with NASH, bariatric surgery has been shown to lead to fibrosis improvement, decreased risk of progression to cirrhosis, and the need for liver transplant (Lassailly 2020, Aminian 2021).

The agreed goal of pharmacologic therapy for NASH is to reverse or prevent fibrosis progression while patients are still pre-cirrhotic. However, there is currently no approved pharmacologic therapy.

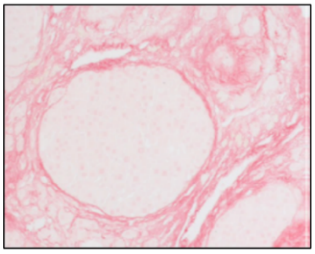
Because of the slow progression through the early stages of fibrosis due to NASH and the time required to conduct a trial that would evaluate clinical endpoints such as progression to cirrhosis or survival, FDA guidance recommends improvements in liver histology as surrogate endpoints reasonably likely to predict clinical benefit to support accelerated approval (FDA 2018). This

guidance has been supported by recent literature demonstrating histologic improvement (regression) of ≥1 stage of fibrosis was associated with reduced liver-related outcomes (Sanyal 2021b).

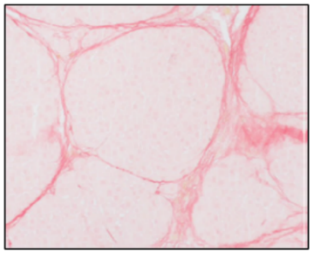
OCA

OCA is a selective and potent agonist for FXR, a nuclear receptor expressed in the liver, gut, and kidney. OCA is 100-fold more potent than any natural bile acid and has 2 conjugates that are equipotent. In cell cultures, OCA has been shown to decrease the expression of key pro-fibrotic proteins and genes. This indication of decreased hepatic stellate cell activation has a direct impact on the production of extracellular matrix or fibrosis. In addition, OCA was able to reverse cirrhosis in multiple animal models of NASH (Verbeke 2016) (Figure 2). Consistent with these nonclinical findings, clinical studies have shown that OCA reverses liver fibrosis in patients with liver fibrosis due to NASH.

Figure 2: OCA is a Potent FXR Agonist with Anti-Fibrotic Effects



Cirrhosis



After Treatment with OCA

- In cell cultures, OCA:
  - Inhibits fibrosis progression
  - Promotes fibrosis resolution
  - Inhibits stellate cell activity
- In multiple animal models of NASH, OCA reversed cirrhosis

FXR= Farnesoid X Receptor; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid
Adapted from Verbeke 2016

OCA Regulatory History

The regulatory timeline for OCA is presented in Figure 3.

OCA was granted accelerated approval for the treatment of primary biliary cholangitis (PBC) under the tradename Ocaliva® by the FDA in 2016, and has received conditional marketing authorization in Europe, Canada, and several other countries for the treatment of PBC. The dose of Ocaliva is 5 mg to 10 mg QD; these are lower doses than the 25 mg QD proposed for NASH due to the higher liver concentrations expected in cholestatic liver diseases like PBC. OCA has been studied in over 4500 patients enrolled in PBC and NASH clinical trials.

OCA was evaluated in NASH patients in a Phase 2 study (Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment [FLINT]), which was designed and conducted by the NASH CRN and sponsored by Intercept and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). FLINT was stopped early after a planned Month 18 IA in which approximately 50% of patients had completed both baseline and 72-week biopsies showed efficacy of treatment with OCA 25 mg. Based on the results, OCA was awarded Breakthrough Therapy designation by the FDA. Intercept worked with FDA to define a path forward for accelerated approval in NASH, using a single Phase 3 registrational trial.

Study 303 is the pivotal Phase 3, DB, randomized, long-term, placebo-controlled, multicenter study evaluating the safety and efficacy of OCA in patients with NASH.

According to FDA guidance (FDA 2018), either of the following is considered acceptable as endpoints reasonably likely to predict clinical benefit to support accelerated approval:

1) resolution of steatohepatitis on overall histopathological reading and no worsening of liver fibrosis on NASH CRN fibrosis score; resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAFLD Activity Score (NAS) score of 0 to 1 for inflammation, 0 for ballooning, and any value for steatosis, or
2) improvement in liver fibrosis greater than or equal to 1 stage, and no worsening of steatohepatitis (defined as no increase in NAS for 302 ballooning, inflammation, or steatosis).

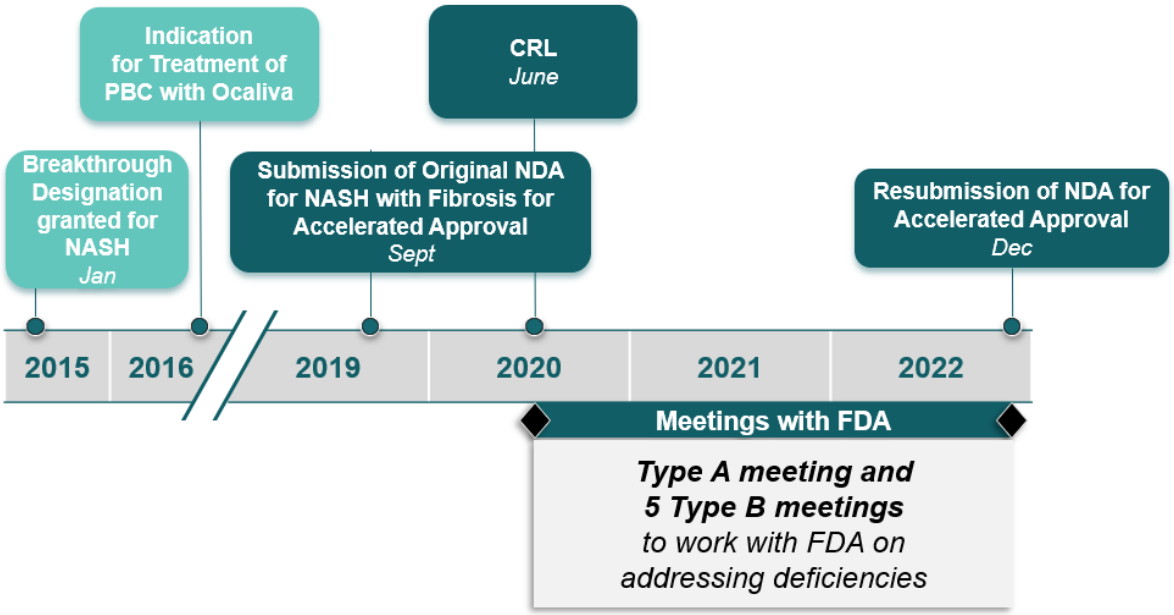
In line with FDA guidance, the Month 18 IA of liver histology results from Study 303 pre-specified that only 1 of the 2 primary endpoints was required to achieve statistical significance for a successful study.

For the Original Analysis, Study 303 achieved the primary endpoint of improvement in liver fibrosis greater than or equal to 1 stage, and no worsening of steatohepatitis. Twice the proportion of patients on OCA 25 mg achieved the fibrosis primary endpoint compared to placebo (p=0.0002). These results were based on an independent central read (herein referred to as the Central Method).

In 2019, Intercept submitted a NDA for NASH fibrosis in support of accelerated approval. This submission included primary efficacy data from Study 303, supported by FLINT, as well as pooled safety data from Study 303 and Phase 2 Studies FLINT and 2001. Because of differences in the dose regimen (doses of 10, 20, or 40 mg/day), data from Study 2001 were not integrated in the efficacy analyses. Data on the placebo and OCA 10 mg groups were included in the pooled safety analyses.

In 2020, the Agency issued a Complete Response Letter (CRL). Since then, Intercept has collaborated with FDA to address the deficiencies outlined in the CRL, including conducting six Type A and Type B meetings.

Figure 3: Obeticholic Acid Regulatory Timeline



CRL=Complete Response Letter; FDA=Food and Drug Administration; NASH=nonalcoholic steatohepatitis; PBC=primary biliary cholangitis; NDA=New Drug Application

The CRL outlined the Agency's concerns regarding the overall benefit-risk of OCA. On the efficacy side, the statistically significant difference between OCA 25 mg and placebo on the antifibrotic endpoint was acknowledged. However, the discordance between expert pathologists led to uncertainty regarding the benefit assessment. In addition, potential safety signals were identified by the Agency that could not be addressed with the data in the original submission: the median follow-up for patients in Study 303 at that time was 15 months, and no patient had reached 36 months.

NDA Resubmission

Since the original submission, Study 303 has completed enrollment with 2477 patients with pre-cirrhotic fibrosis due to NASH who received at least 1 dose of investigational product. The Sponsor addressed the efficacy and safety concerns from the CRL and is resubmitting for accelerated approval as follows:

- In 2021, FDA requested that all Sponsors in the NASH field utilize a consensus approach for interpretation of the NASH CRN staging of liver biopsies (Anania 2021). This is reflected in our updated NDA, wherein, as agreed with FDA, at least 2 out of 3 pathologists must agree on fibrosis stage and each of the NAS parameters.
    - As agreed with FDA, the current submission includes additional analysis of the same Month 18 liver biopsies for the 931 patients in Study 303 from the original submission, re-read by consensus panels of 3 pathologists (herein referred to as the Consensus Method).

- In addition, 3 adjudication committees of independent experts reviewed blinded case narratives of events triggered by a prospectively defined set of relevant adverse event (AE) terms and laboratory values for hepatic, cardiovascular (CV), and renal AEs. These events were selected based on laboratory values or AEs that had been agreed with the FDA.
- Pooled safety data were reanalysed based on a new data cutoff (DCO) of 31 Dec 2021. This represents an increase in exposure by more than 3-fold since the original submission. Intercept resubmitted an NDA for accelerated approval in December 2022. This included data from over 2800 patients from the following 3 long-term, double-blind, placebo-controlled studies: Study 2001, FLINT, and Study 303. Data from subjects with more than four years of exposure to blinded study drug has now been included, providing increasing confidence in the long-term safety of OCA in a patient population with pre-cirrhotic fibrosis due to NASH.

Study 303 remains ongoing, with collection of clinical outcomes toward an agreed composite endpoint (all-cause mortality and liver-related clinical outcomes) to confirm clinical benefit and achieve full approval, as defined by FDA guidance. Hepatic outcomes are evaluated by the Hepatic Outcomes Committee (HOC) and remain blinded until the End of Study (EOS) analysis. Therefore, clinical outcomes data have not been analyzed and are not included in this document. Intercept is currently updating the model to predict the timing when a sufficient number of outcomes will be reached based on adjudicated blinded outcome data.

A separate Phase 3 Study, (Study 747-304 [REVERSE], also referred to as Study 304), was conducted in over 900 patients with compensated cirrhosis due to NASH under a separate IND. This study was not included in the NDA because it was not completed by the DCO for the NDA resubmission.

Resubmission Efficacy Results in Study 303 (Section 5.1)

Efficacy analysis populations for Study 303 Resubmission are presented in Table 1. All patients included in the efficacy analyses had F2 or F3 (defined using the NASH CRN criteria) at study entry based on the centrally read biopsy slide.

The original (intent-to-treat) ITT (N=931) population included all randomized patients with F2 or F3 at inclusion who received at least 1 dose of investigational product and had/were expected to have completed a Month 18 visit (including biopsy) by the time the pre-specified IA sample size was reached (DCO of 26 Oct 2018). As the original ITT (N=931) population was the pre-specified population for the Month 18 IA, the histology analyses for the resubmission were conducted on liver biopsies from the same 931 patients (herein referred to as ITT_old).

Supportive analyses on histology were also conducted in a broader ITT_histology population (N=1607), which includes patients with F2 or F3 at inclusion who received at least 1 dose of investigational product and were expected to have completed Month 18 visit (including biopsy) under Protocol Version 8 or earlier. The study protocol was amended after the completion of the original Month 18 IA to remove the mandatory Month 18 biopsy under Protocol Version 9.

In the resubmission, histology data (baseline and Month 18) for the ITT_old (N=931) and ITT_histology (N=1607) populations were analyzed with scores from the Consensus Method.

Additional supportive efficacy analyses based on long-term liver biochemistries and noninvasive markers of fibrosis were conducted in an even broader ITT_all population (N=2187), which

includes all patients with F2 or F3 at inclusion who received at least 1 dose of investigational product and have a postbaseline measurement, e.g., even those without a Month 18 biopsy.

Table 1: Efficacy Analysis Populations: Study 303

<table>
<tr><th colspan="4">Patients with Original Eligibility Baseline of Fibrosis Stage 2 or 3</th></tr>
<tr><th colspan="4">Key Efficacy Analysis Population: Original NDA and NDA Resubmission</th></tr>
<tr><td colspan="3">ITT_old
(N=931)</td><td rowspan="2">Population Definition
All patients randomized by 15 Jul 2017 who received at least 1 dose of investigational product and who had or were expected to have completed Month 18 Visit (including biopsy) by the DCO of 26 Oct 2018.
Original submission biopsies were read by Central Method.
NDA resubmission biopsies were read by Consensus Method.
Direct comparison of results between Central and Consensus Methods</td></tr>
<tr><td>Placebo
(n=311)</td><td>OCA 10 mg
(n=312)</td><td>OCA 25 mg
(n=308)</td></tr>
<tr><th colspan="4">Supportive Efficacy Analysis Populations: NDA Resubmission Only</th></tr>
<tr><td colspan="3">ITT_histology
(N=1607)</td><td rowspan="2">Population Definition
All patients randomized, received at least 1 dose of investigational product by the DCO of 31 Dec 2021, and who had or were expected to have completed Month 18 Visit (including the Month 18 biopsy) per Protocol Version 8 (08 Jan 2019) or earlier[a]
NDA resubmission biopsies were read by Consensus Method.</td></tr>
<tr><td>Placebo
(n=536)</td><td>OCA 10 mg
(n=532)</td><td>OCA 25 mg
(n=539)</td></tr>
<tr><td colspan="3">ITT_all
(N=2187)</td><td rowspan="2">Population Definition
All patients who were randomized, received at least 1 dose of investigational product by the DCO of 31 Dec 2021, and have a post-baseline measurement.
Non-histologic efficacy analyses (liver biochemistry and imaging NITs)</td></tr>
<tr><td>Placebo
(n=728)</td><td>OCA 10 mg
(n=729)</td><td>OCA 25 mg
(n=730)</td></tr>
</table>

DCO=data cutoff; ITT=Intent-to-Treat; NDA=New Drug Application; NIT=non-invasive test; OCA=obeticholic acid

[a] Study protocols Version 8 (dated 08 Jan 2019) or earlier required a Month 18 biopsy. The study protocol was amended on 29 Jul 2019 (Version 9) to remove the Month 18 biopsy assessment.

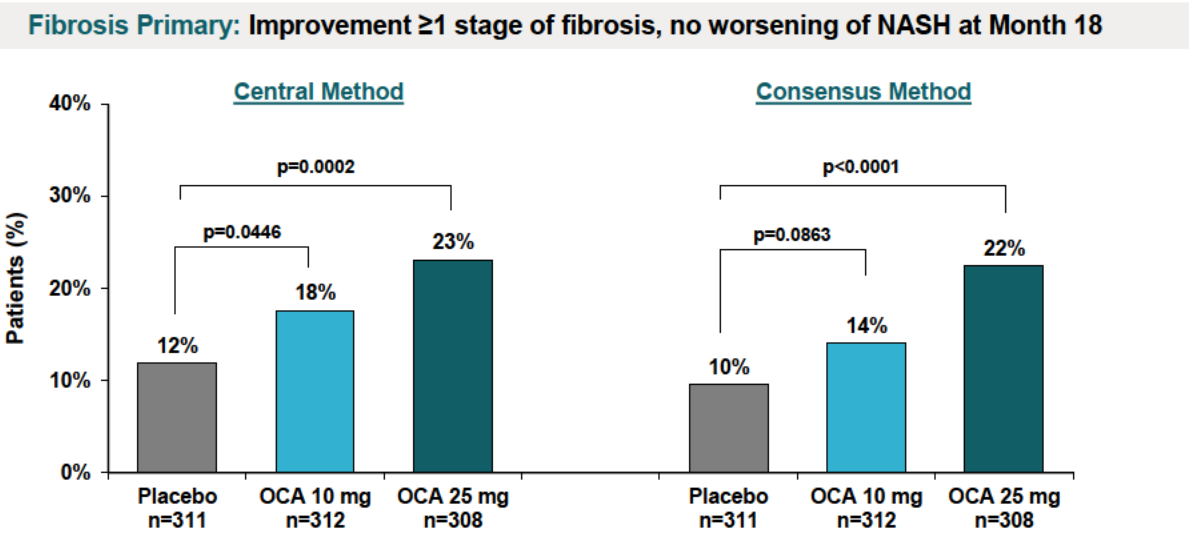
The totality of data from the Original Analysis and Resubmission Analysis of Study 303, including improvements in non-invasive tests (NITs) (e.g., liver stiffness and serum alanine aminotransferase [ALT]), provides robust evidence of efficacy for OCA 25 mg in adult patients with pre-cirrhotic liver fibrosis due to NASH, demonstrating a consistent antifibrotic effect that is likely to predict clinically meaningful benefit.

Primary Endpoints

The primary endpoint of improvement in fibrosis by ≥1 stage with no worsening of NASH was achieved in both methodologies, with a notable dose-dependent response. For the ITT_old population (N=931), the statistically significant treatment effect of OCA 25 mg observed at Month 18 with the Central Method (Original Analysis as submitted in prior NDA) was

confirmed, with a doubling (2.3-fold increase) of the responder rate for OCA 25 mg compared to placebo in the Consensus Method (Resubmission Analysis).

Figure 4: Fibrosis Primary Endpoint by Central and Consensus Methods: Study 303 ITT_old Population (N=931)



IA=interim analysis; ITT=Intent-to-Treat; NASH=nonalcoholic steatohepatitis; NS=not significant; OCA=obeticholic acid; TZD=thiazolidinedione

Notes: The Original Analysis used the Central Method to read liver biopsies. The Resubmission Analysis (ITT_old population [N=931]) used the Consensus Method to re-read the same liver biopsies.
Any patient with a missing Month 18 biopsy was considered as a nonresponder.

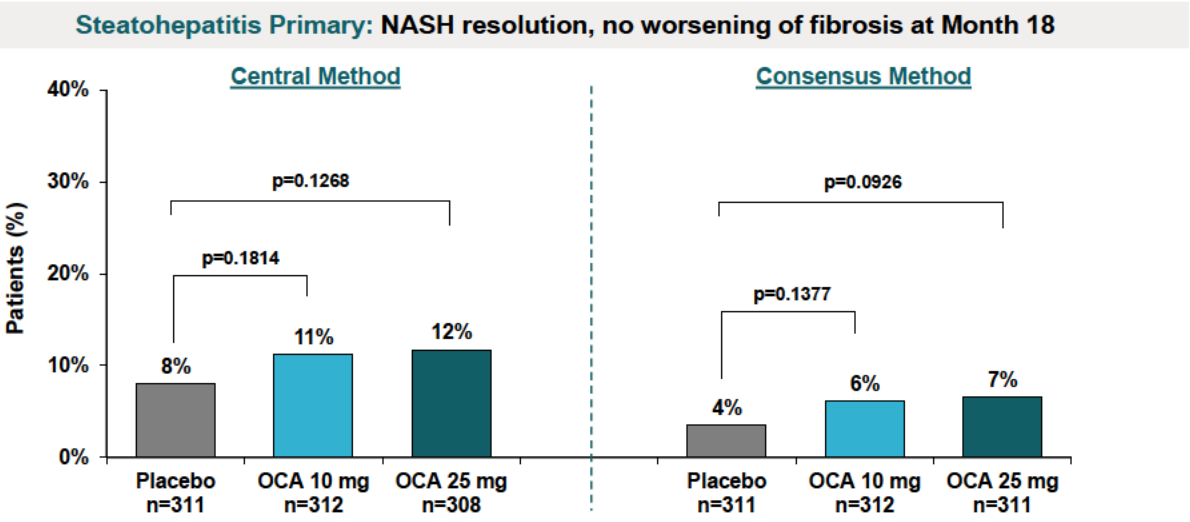
OCA / Placebo Odds Ratio = Percentage of Responders in Active Treatment Arm / Percentage of Responders in Placebo, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no); the Mantel-Haenszel estimate of the common odds ratio and the associated asymptotic CIs are reported.

p-value versus Placebo: Using the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).

Subgroup analyses for the fibrosis primary endpoint based on the Consensus Method were performed and the results were generally consistent with those for the overall population (Section 5.1.5.2).

For the ITT_old population (N=931), the primary endpoint of steatohepatitis at Month 18 based on the Consensus Method (Resubmission Analysis), which required hepatocellular ballooning of 0 and lobular inflammation of 0 or 1, was consistent with the Central Method (Original Analysis) in which proportions of responders were higher in both OCA groups; however, the treatment effect was not statistically significant (Figure 5).

Figure 5: Steatohepatitis Primary Endpoint by Central and Consensus Methods: Study 303 ITT_old Population (N=931)



IA=interim analysis; ITT=Intent-to-Treat; NASH=nonalcoholic steatohepatitis; NS=not significant; OCA=obeticholic acid; TZD=thiazolidinedione

Notes: The Original Analysis used the Central Method to read liver biopsies. The Resubmission Analysis (ITT_old population [N=931]) used the Consensus Method to re-read the same liver biopsies.

Any patient with a missing Month 18 biopsy was considered as a nonresponder.

OCA / Placebo Odds Ratio = Percentage of Responders in Active Treatment Arm / Percentage of Responders in Placebo, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no); the Mantel-Haenszel estimate of the common odds ratio and the associated asymptotic CIs are reported.

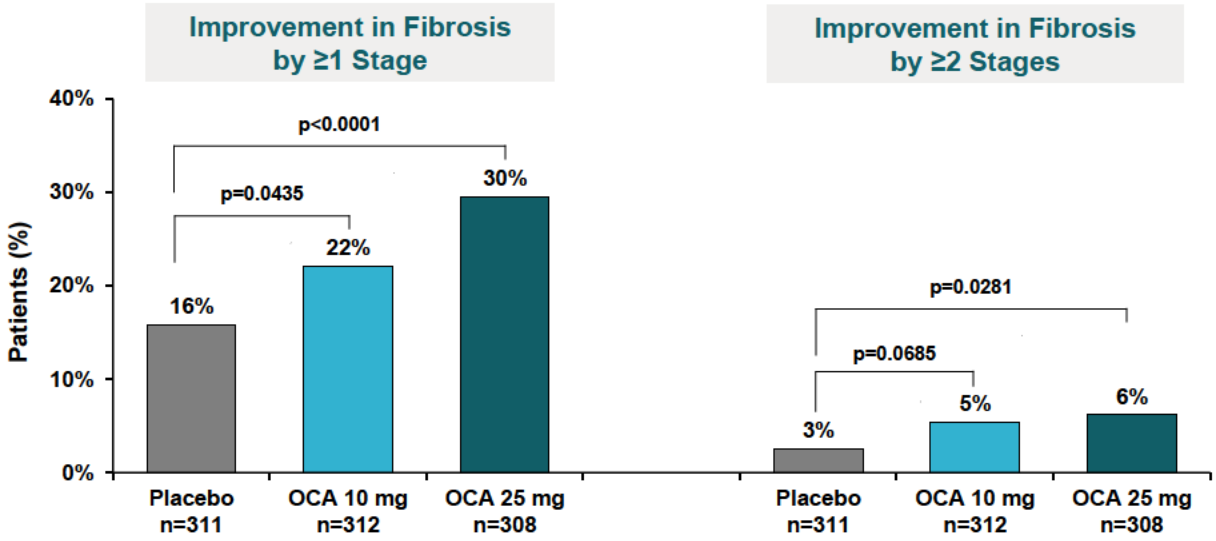
p-value versus Placebo: Using the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).

The results for primary efficacy endpoints based on the Consensus Method observed for the ITT_histology population (N=1607) were consistent with the ITT_old population (N=931) (Section 5.1.4.1.1).

Key Supportive Histologic Fibrosis Endpoints

For the ITT_old population (N=931), a consistent dose-related antifibrotic effect was observed across other histologic endpoints of both reversal and lack of fibrosis progression based on the Consensus Method (Resubmission Analysis) (Figure 6). These results were consistent with the Central Method (Original Analysis) and also consistent with the ITT_histology population (N=1607) (Section 5.1.4.1.2).

Figure 6: Key Secondary Histology Endpoints at Month 18 by Consensus Method: Study 303 ITT_old Population (N=931)



IA=interim analysis; ITT=Intent-to-Treat; NASH=nonalcoholic steatohepatitis; NS=not significant; OCA=obeticholic acid; TZD=thiazolidinedione

Notes: The Original Analysis used the Central Method to read liver biopsies. The Resubmission Analysis (ITT_old population [N=931]) used the Consensus Method to re-read the same liver biopsies.

Any patient with a missing Month 18 biopsy was considered as a nonresponder.

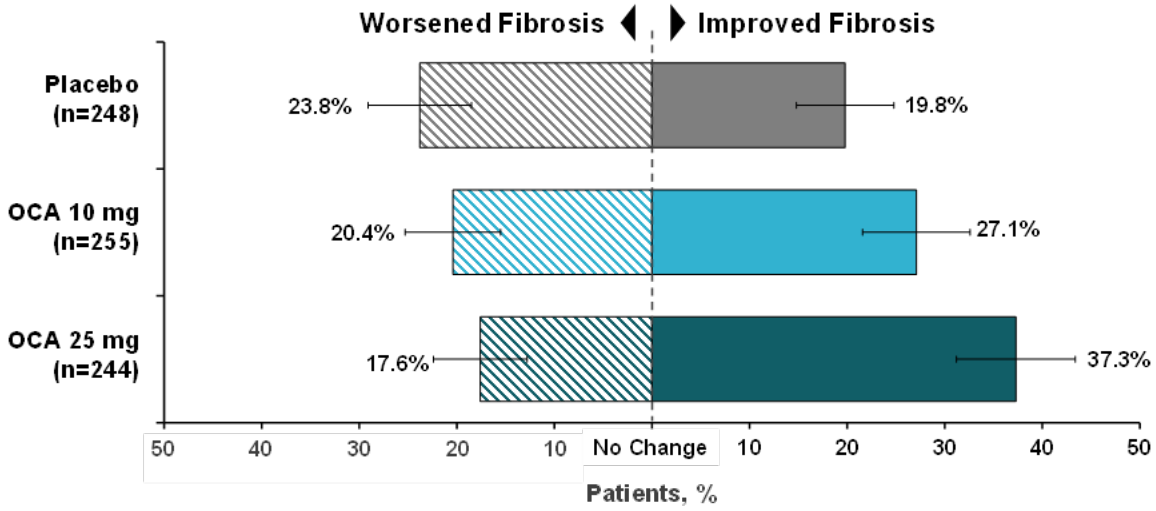
OCA / Placebo Odds Ratio = Percentage of Responders in Active Treatment Arm / Percentage of Responders in Placebo, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no); the Mantel-Haenszel estimate of the common odds ratio and the associated asymptotic CIs are reported.

p-value versus Placebo: Using the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).

The analysis of shift in fibrosis stage is an additional supportive efficacy measure as it takes into account proportions of patients with improvement and proportions with worsening in fibrosis. In patients with available baseline and Month 18 biopsies (e.g., excluding missing Month 18 biopsies), a greater proportion of patients in the OCA 25 mg group improved fibrosis by ≥1 stage, while more patients in the placebo group had worsening of fibrosis (Figure 7). Improvement in fibrosis by ≥1 stage was achieved by 19.8% of patients receiving placebo, 27.1% of those receiving OCA 10 mg, and 37.3% of those receiving OCA 25 mg. These results likely translate to clinical benefit, as fibrosis stage is the strongest predictor of outcomes in NASH.

These results were consistent with the Central Method (Original Analysis) and also consistent with the ITT_histology population (N=1607) (Section 5.1.4.1.2).

Figure 7: Fibrosis Shift Analysis by Consensus Method: Study 303 ITT_old Population, Baseline and Postbaseline (n=747)



IA=interim analysis; ITT=Intent-to-Treat; OCA=obeticholic acid
Notes: Of the 931 patients in the ITT_old population, 747 had both a baseline and post-baseline biopsy.
Any patient with a missing Month 18 biopsy was considered as a nonresponder.

Non-invasive Tests

Historically, liver biopsy has been the reference standard for diagnosis of NASH and fibrosis staging. However, NITs are now recommended by several practice guidelines due to the well-known limitations of liver biopsies, including invasiveness and variability due to sampling or pathologist assessment (Rinella 2023).

NITs in Study 303 reflect sustained and cumulative hepatic benefits of OCA through Month 48, supporting potential long-term clinical benefit in patients beyond those identified as histologic responders at Month 18 (Section 5.1.4.2):

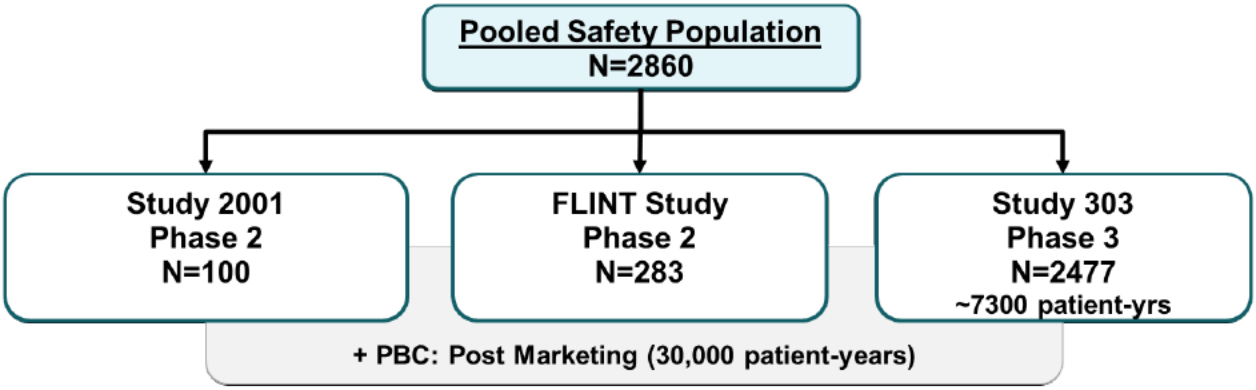
- Dose-dependent improvements in markers of hepatocellular injury (ALT, aspartate aminotransferase [AST]) and oxidative stress (gamma-glutamyl transferase [GGT]) suggest a potentially clinically meaningful impact on underlying liver injury.
- Consistent trends for improvements in multiple markers of fibrosis, including liver stiffness (TE) and serum-based composite markers (fibrosis-4 [FIB-4], enhanced liver fibrosis [ELF], and aminotransferase to platelet ratio index [APRI]) reflect persistent antifibrotic effect.

Collectively, the observed improvements in the histology and non-invasive endpoints are reasonably likely to predict positive clinical benefit to support accelerated approval of OCA 25 mg for the treatment of patients with pre-cirrhotic fibrosis due to NASH.

Resubmission Safety Results in Pooled Safety Population (Section 6)

The safety data for the resubmission represents an increase in OCA exposure by more than 3-fold since the original submission and a significantly longer duration, relevant for a compound likely to require chronic dosing. OCA's safety database is now comprised of 40,000 patient years (PYs) of data, including studies in patients with NASH (Study 2001, FLINT, Study 303, Study 304) and the post-marketing safety database from the PBC indication, which includes over 30,000 PYs of exposure. In the resubmission, a total of 2860 patients were included in the Pooled Safety Population, of which the majority of patients (approximately 87%, N=2477) were from Study 303 (Figure 8). For Study 2001, only data from the placebo and OCA 10 mg groups were included in the Pooled Safety Population.

Figure 8: Pooled Safety Population (N=2860)



FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; PBC=primary biliary cholangitis

Since the original submission, Study 303 has completed enrollment. The original NDA included a median 15 months of study drug exposure, and no patient had reached Month 36. The Safety_all (N=2477) population in Study 303 includes all randomized patients who received at least 1 dose of investigational product and were included in the Pooled Safety Population (Table 2).

Table 2: Safety Analysis Populations: Study 303

Patients with Original Eligibility Baseline of Fibrosis Stage 1, 2, or 3			
Safety Analysis Population: Original NDA			
Safety (N=1968)			Population Definition
Placebo (n=657)	OCA 10 mg (n=653)	OCA 25 mg (n=658)	All randomized patients who received at least 1 dose of investigational product by the DCO of 26 Oct 2018.
Safety Analysis Population: Resubmission			
Safety_all (N=2477)			Population Definition
Placebo (n=825)	OCA 10 mg (n=825)	OCA 25 mg (n=827)	All patients randomized, received at least 1 dose of investigational product by the DCO of 31 Dec 2021.

DCO=data cutoff; NDA=New Drug Application; OCA=obeticholic acid

OCA was generally safe and well-tolerated based on a comprehensive assessment from the Pooled Safety Population.

There is now a significantly longer duration of follow-up since the original submission.

- For the resubmission, the median duration of OCA exposure in the Pooled Safety Population was approximately 37 months (3.09 and 3.08 years in OCA 10 mg and OCA 25 mg groups, respectively), with approximately 700 patients across OCA treatment groups (including 335 patients in the OCA 25 mg group) having ≥4 years of exposure.
- The larger safety database with longer follow-up allows for a comprehensive characterization of risks, which informs appropriate monitoring and management according to existing patient care standards and clinical practice guidelines.

Integrated safety data from the Pooled Safety Population are provided when available; specific safety analyses were conducted based on Study 303 data only (e.g., adjudicated CV and renal data); hence, these analyses have been presented for Study 303. Study 303 contributes approximately 87% of the integrated safety data. No differences in the safety profile were observed between Study 303 and the Pooled Safety Population.

The safety analyses in the Pooled Safety Population included a robust evaluation of the following:

- Adverse events of special interest (AESIs) including pruritus, hepatic safety events, CV events, dyslipidemia, gallstones, pancreatitis, renal disorders, urolithiases, and hyperglycemia
- Additionally, 3 independent and blinded committees of experts were utilized to adjudicate CV events (Cardiovascular Adjudication Committee [CAC]), hepatic safety/potential drug-induced liver injury (DILI) events (Hepatic Safety Adjudication Committee [HSAC]), and renal safety/acute kidney injury (AKI) events (Renal Adjudication Committee [RAC])

In line with standard pharmacovigilance practices, data summaries for safety data are treatment-emergent (i.e., onset date after initiation of investigational product through up to 30 days after last dose). Safety data for CV events are on-study, (i.e., onset after initiation of investigational product up to the earliest date of EOS, death, or DCO [31 Dec 2021]) and are defined as AEs that occurred from the first dose date in FLINT and Study 2001.

General Safety Profile in the Pooled Safety Population

An overview of safety in the Pooled Safety Population is summarized in Figure 9.

The incidence rate of common treatment-emergent adverse events (TEAEs) (affecting ≥10% of any treatment group) was generally similar across the 3 treatment groups with the exception of a dose-dependent increase in events of pruritus. Low-density lipoprotein (LDL) increases were also generally more frequent with OCA as compared to placebo, but with no correlation with dose.

The incidence rate of TEAEs leading to investigational product withdrawal was 10.7% in the placebo group, 12.0% in the OCA 10 mg group, and 21.6% in the OCA 25 mg group, with the

difference primarily due to pruritus (exposure-adjusted incidence rate [EAIR] of 3.34, 3.81, and 7.22 per 100 PYs in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively).

The incidence rate of serious adverse events (SAEs) was 19.7% in the placebo group, 24.0% in the OCA 10 mg group, and 24.8% in the OCA 25 mg group (EAIR of 7.31, 8.67, and 10.14 per 100 PYs in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively). The higher incidence rate of SAEs with OCA was primarily driven by pruritus (which was reported only in the OCA 25 mg group), cholecystitis, cholecystitis acute, cholelithiasis, AKI, and diabetes mellitus.

Twenty-nine patients experienced a TEAE leading to death (8 patients in the placebo group, 9 patients in the OCA 10 mg group, and 12 patients in the OCA 25 mg group). The EAIR of TEAEs leading to death was 0.26, 0.32, and 0.43 per 100 PYs in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively. No clear patterns were observed between the OCA and placebo groups for underlying etiology of the events that led to death. Deaths are further described in Section 6.3.

Figure 9: Overview of Safety: Pooled Safety Population (N=2860)

	Placebo N=1017 n (%)	OCA 10 mg N=875 n (%)	OCA 25 mg N=968 n (%)
TEAEs	**900 (88.5)**	**839 (95.9)**	**912 (94.2)**
TEAEs Leading to Investigational Product Discontinuation[a]	94 (10.7)	105 (12.0)	179 (21.6)
Severe TEAEs	189 (18.6)	184 (21.0)	263 (27.2)
SAEs	200 (19.7)	210 (24.0)	240 (24.8)
Deaths	8 (0.8)	9 (1.0)	12 (1.2)

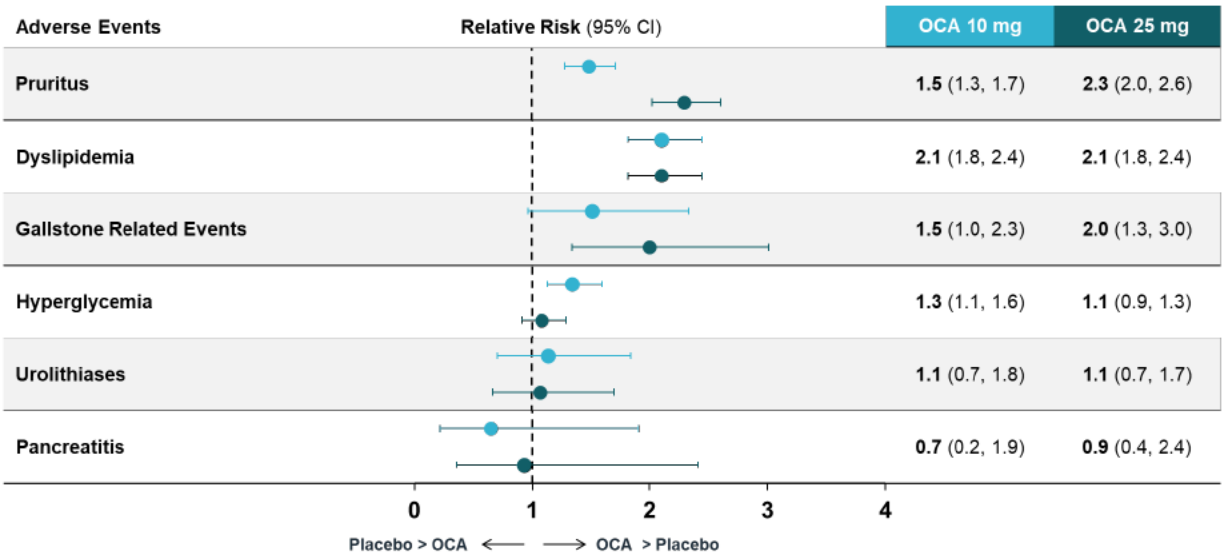
FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; IP=investigational product; OCA=obeticholic Acid; SAE=serious adverse event; TEAE=treatment-emergent adverse event
[a] TEAEs leading to investigational product discontinuation were not collected in FLINT.

Investigator-Reported AESIs in the Pooled Safety Population

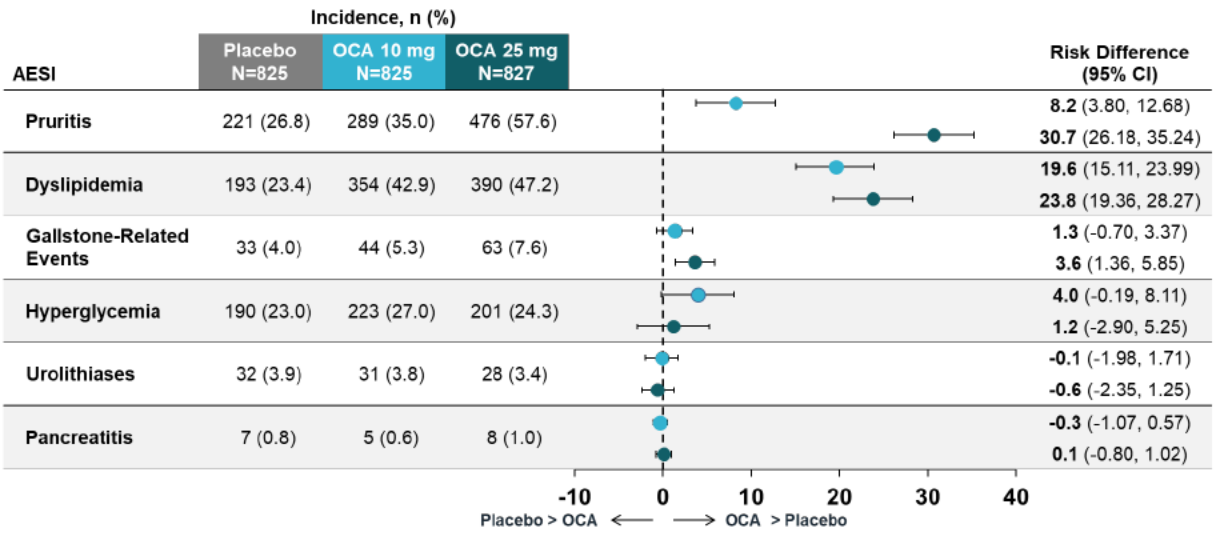
Pruritus and dyslipidemia were the most common AEs. Pruritus, dyslipidemia, and gallstone-related events were more likely to occur in the OCA treatment groups compared to placebo and are described as adverse drug reactions (ADRs) in the proposed label. A dose association was most notably observed for pruritus and gallstone-related events, as expected based on OCA's FXR agonism. No increased risk was observed for hyperglycemia, urolithiasis, or pancreatitis (including biliary pancreatitis) based on the large integrated safety population (Figure 10a). Incidence rates and risk differences of AESIs are displayed in Figure 10b.

Figure 10: Overview of Investigator-Reported AESIs: Pooled Safety Population (N=2860)

a. Relative Risk of Investigator-Reported AESIs



b. Incidence and Risk Difference of Investigator-Reported AESIs



AESI=adverse event of special interest; OCA=obeticholic acid

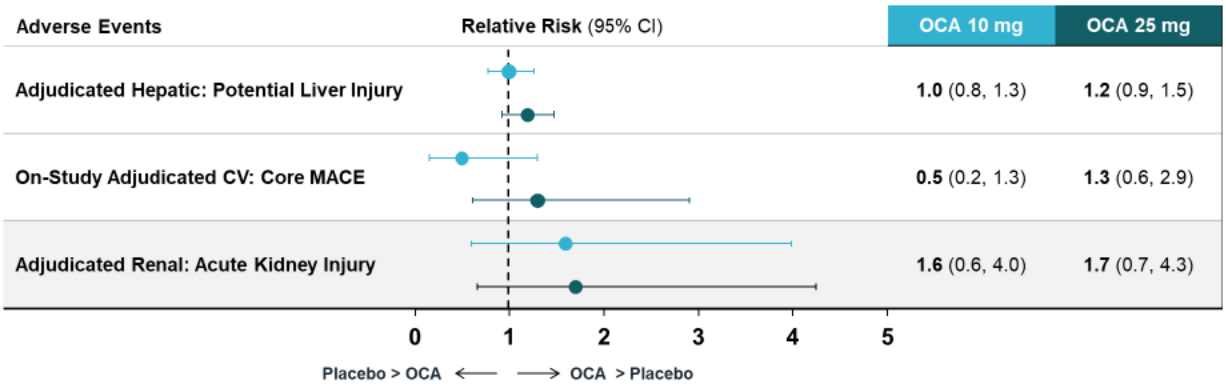
Adjudicated Events in Study 303

Relative risks of adjudicated events are displayed in Figure 11a and incidence rates and risk differences of adjudicated events are displayed in Figure 11b. Incidence rates of adjudicated CV, hepatic, and AKI events were low overall, but higher in the OCA 25 mg group compared to placebo.

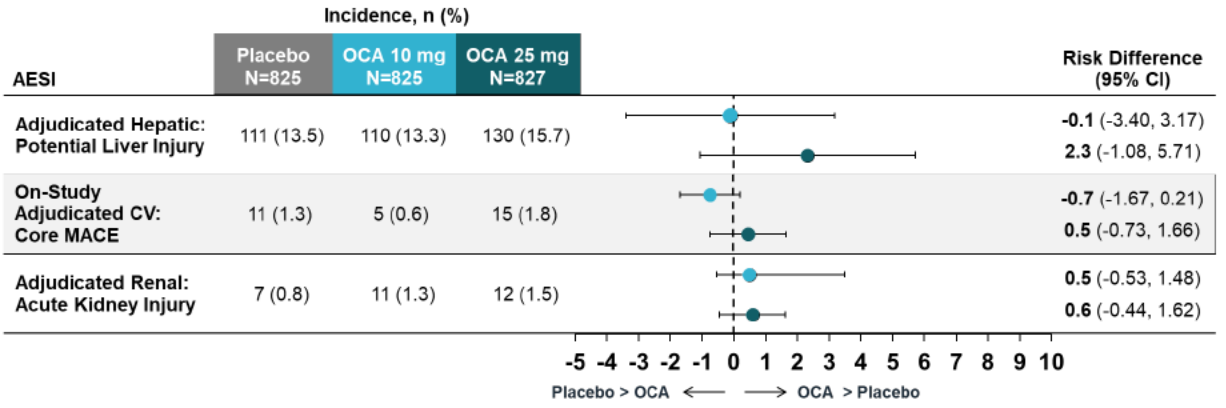
Adjudicated events in each category are discussed further in their respective sections below.

Figure 11: Overview of Adjudicated Events: Study 303 Safety_all Population (N=2477)

a. Relative Risk of Adjudicated Events



b. Incidence and Risk Difference of Adjudicated Events



CV=cardiovascular; IP=investigational product; OCA=obeticholic acid

Notes: For adjudicated CV events, data are presented for on-study, defined as date of adjudicated event that occurred between start date of receipt of IP and earliest date of end of study date, death date, or data cutoff date (31DEC2021).

Hepatic Safety (Section 6.4.1)

Investigator-Reported AESIs in the Pooled Safety Population

Hepatic safety was assessed comprehensively by 3 types of analyses. It is important to acknowledge that evaluation of hepatic safety, especially potential DILI, is challenging in patients with progressive chronic liver disease. These analyses were performed and interpreted based on FDA feedback and in keeping with FDA clinical guidance and published consensus guidelines (FDA 2009, Regev 2019). The first type of analysis included an assessment of hepatic AEs by preferred terms (PTs), defined by system organ class (SOC) and then by a broad set of PTs per Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ).

The incidence rate of hepatic TEAE reports was similar across treatment groups; the incidence rate of serious hepatic TEAE reports was higher in OCA treatment groups compared to placebo (0.2%, 1.0%, and 1.7% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively).

The second analysis identified hepatic events using an assessment of liver-related biochemistries, including evaluation of drug-induced serious hepatotoxicity (eDISH) screening plots for ALT, AST, and alkaline phosphatase (ALP) in addition to a series of 18 different biochemical triggers, and evaluated risk differences between the placebo and OCA treatment groups.

Assessments by eDISH screening plots and liver-related biochemical triggers did not reveal any imbalance across treatment arms suggestive of DILI related to OCA.

Adjudicated Hepatic Events in the Pooled Safety Population

The third analysis involved a comprehensive, patient-level review of cases identified by a broad set of lab-based triggers and SMQ defined AEs agreed to with FDA. This review was performed by a blinded independent adjudication committee (HSAC) comprised of experts with experience in DILI. The adjudication committee assessed the potential for liver injury, assigned likelihood of causality and degree of severity, and provided potential etiology for all cases.

In the Pooled Safety Population, there was 1 case adjudicated as highly likely related (mild in severity); this patient was taking OCA 25 mg and developed elevated total bilirubin (peak 1.61 mg/dL by Month 1) and elevated ALP (peak 393 U/L by Month 3), with complete resolution after discontinuation of OCA.

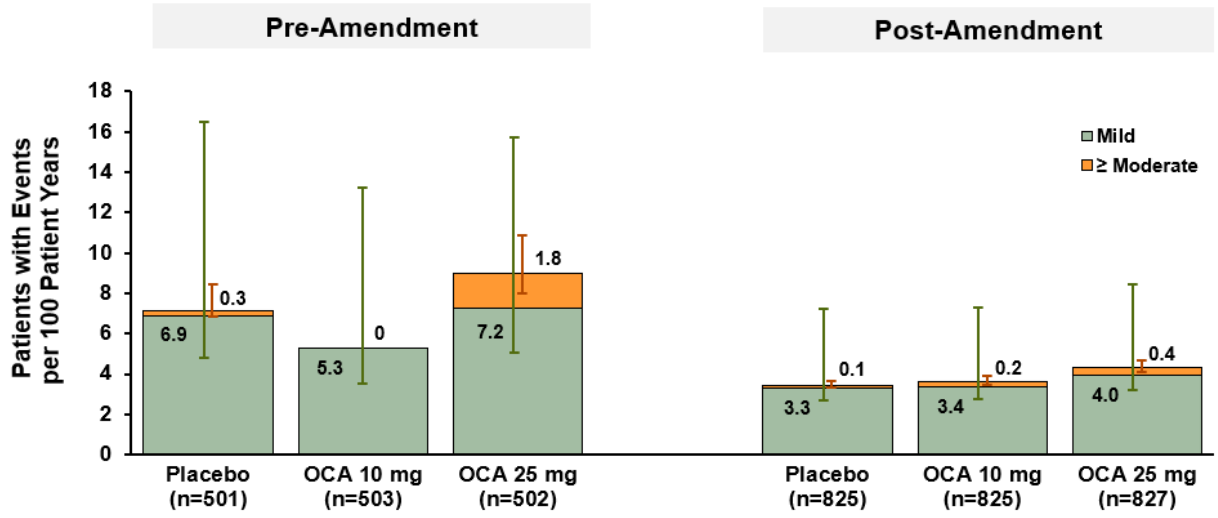
Five patients experienced events adjudicated as severe, 2 (0.2%) in the OCA 10 mg group and 3 (0.3%) in the OCA 25 mg group; 1 case was assessed as probably related (OCA 10 mg), 1 case as possibly related (OCA 25 mg), and 3 cases as unlikely related (detailed in Section 6.4.1.2).

Adjudicated Hepatic Events in Study 303

Following the recognition of the potential for liver safety events early in the conduct of Study 303, a major safety amendment was implemented for Study 303 (Protocol V6) on 02 Oct 2017 for monitoring and management of hepatic events (detailed in Section 6.4.1.3). This amendment provided specific safety monitoring instructions, patient and provider education for prompt recognition of signs and symptoms of liver injury, and appropriate dosing adjustments, interruptions, and discontinuations in scenarios when liver injury or progression of disease was suspected. The amendment mandated drug discontinuation and investigation of underlying cause based on ALT, bilirubin, and ALP excursions.

- An analysis comparing adjudicated hepatic events pre- and post-implementation of the safety amendment revealed a clinically meaningful decrease in the EAIR of overall adjudicated hepatic safety events, including a 4-fold reduction in moderate-to-severe adjudicated events for OCA 25 mg (Figure 12).
- No case resulting in a liver transplant or death due to DILI was reported in the post-amendment period.
- The post-amendment safety experience provides evidence to support that similar guidance in labelling would be effective for the risk management plan.

Figure 12: Exposure-adjusted Incidence Rates of Positively Adjudicated Potential Livery Injury Events Pre and Post Safety Amendment: Study 303 Safety_all Population (N=2477)



EAIR=exposure-adjusted incidence rate; IP=investigational product; OCA=obeticholic acid; PY=patient years
Notes: Patients with ≥1 adjudicated hepatic event considered related to IP.

CV Safety (Section 6.4.2)

Investigator-Reported AESIs in the Pooled Safety Population

Patients with NASH and hepatic fibrosis have an increased rate of cardiometabolic risk factors compared to the general population (Sanyal 2021a).

Considering the background risk for CV disease in this population, as well as the known effect of FXR agonism on lipids, a comprehensive assessment for CV safety, including analyses of lipids and glycemic parameters, Investigator-reported CV events, and adjudication of CV events by an independent committee (CAC), was performed.

Consistent with the real-world population, the majority of patients in the Pooled Safety Population had CV risk factors at baseline, including elevated LDL, clinical features of metabolic syndrome, and type 2 diabetes (Section 6.4.2.1). Approximately half of patients were on a lipid-lowering agent at baseline.

A mean 15 mg/dL to 20 mg/dL increase in serum LDL cholesterol occurred within the first 30 days of OCA treatment, decreased with continued treatment, and returned to near baseline

levels by Month 12. The duration of increased LDL was shorter in patients treated with statins. New use of lipid-lowering agents (including statins), defined as use that started after the initial dose of investigational product, occurred with a higher incidence rate in OCA treatment groups compared to placebo (17.4%, 29.8%, and 28.5% of patients in placebo, OCA 10 mg, and OCA 25 mg groups, respectively). Study 747-209, a Phase 2 study conducted to characterize OCA-mediated lipid changes, reported similar changes in lipid parameters and demonstrated that increases in LDL and total cholesterol can be managed by the addition of a statin.

An increase in fasting plasma glucose and hemoglobin A1c (HbA1c) also occurred within 30 days of initiation of OCA treatment, with no difference observed between the placebo and OCA groups after Month 6 (glucose) and Month 9 (HbA1c) with continued treatment.

Adjudicated CV Events in Study 303

For the resubmission, treatment-emergent positively adjudicated Core Major Adverse Cardiac Events (MACE), defined as CV death, non-fatal MI, and non-fatal stroke, were analyzed. The incidence rate of treatment-emergent Core MACE was 10 (1.2%), 5 (0.6%), and 11 (1.3%) patients in placebo, OCA 10 mg, and OCA 25 mg groups, respectively.

Since the NDA resubmission, analyses for on-study CV AESIs and adjudicated events have been performed. On-study analyses are considered more clinically relevant for CV events, since there is a potential for a lag in the development of CV events. The incidence rate for on-study positively adjudicated Core MACE was 11 (1.3%), 5 (0.6%), and 15 (1.8%) in placebo, OCA 10 mg, and OCA 25 mg groups, respectively. 4-point MACE (defined as Core MACE + hospitalization for unstable angina) incidence rates were 13 (1.6%), 9 (1.1%), and 18 (2.2%) and 5-point MACE (defined as Core MACE + hospitalization for unstable angina + hospitalization/urgent visit for heart failure) incidence rates were 16 (1.9%), 9 (1.1%), and 18 (2.2%) in placebo, OCA 10 mg, and OCA 25 mg groups, respectively.

Given the increased CV risk in this patient population, an additional analysis controlling for baseline 10-year atherosclerotic cardiovascular disease (ASCVD) risk was conducted. On-study adjudicated CV events occurred at similar rates in the 3 treatment groups in both the low risk (10-year ASCVD risk <20%) and high risk (10-year ASCVD risk ≥20%) categories (Figure 13).

Figure 13: On-Study Adjudicated Cardiovascular Events by ASCVD Risk: Study 303 Safety_all Population (N=2477)

10-Year ASCVD Risk < 20%	Placebo N=572 n (%)	OCA 10 mg N=541 n (%)	OCA 25 mg N=522 n (%)
Core MACE	4 (0.7)	1 (0.2)	5 (1.0)
4-Point MACE	6 (1.0)	1 (0.2)	8 (1.5)
5-Point MACE	8 (1.4)	1 (0.2)	8 (1.5)

10-Year ASCVD Risk ≥ 20%	Placebo N=90 n (%)	OCA 10 mg N=105 n (%)	OCA 25 mg N=121 n (%)
Core MACE	6 (6.7)	2 (1.9)	8 (6.6)
4-Point MACE	6 (6.7)	4 (3.8)	8 (6.6)
5-Point MACE	6 (6.7)	4 (3.8)	8 (6.6)

ASCVD=atherosclerotic cardiovascular disease; CV=cardiovascular; IP=investigational product; MACE=major adverse cardiovascular events; MI=myocardial infarction; OCA=obeticholic acid

Notes: On-study defined as date of adjudicated event that occurred between start date of receipt of IP and earliest date of end of study date, death date, or data cutoff date (31DEC2021).

[a] Core MACE: CV death, non-fatal MI, non-fatal stroke

[b] 4-point MACE: CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina

[c] 5-point MACE: CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization/urgent visit for heart failure

Renal Safety (Section 6.4.3)

Investigator-Reported AESIs in the Pooled Safety Population

Though a higher incidence rate of serious renal disorder TEAEs was reported in the OCA 25 mg group (mainly attributed to events of AKI), a patient level review of the serious cases showed that a majority had multiple confounding factors, including severe intercurrent illness such as sepsis, volume depletion, or exposure to potentially nephrotoxic medications. In the majority of cases, renal function improved after resolution of the acute event, allowing resumption of investigational product.

No difference was observed between placebo and OCA 25 mg treatment groups for serum creatinine, estimated glomerular filtration rate (eGFR), or albumin-to-creatinine ratio over time. The incidence rate of urolithiasis TEAEs, including serious urolithiasis TEAEs, was similar across treatment groups.

Adjudicated Renal Events in Study 303

The RAC evaluated cases submitted for adjudication of AKI for severity and causal relationship to study drug. Incidence rate of adjudicated AKI was low overall, but higher in the OCA 25 mg group. Most events were adjudicated by the committee as mild (Stage 1) AKI. All seven patients with Stage 3 AKI across the treatment groups were using a concomitant angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) and a statin.

OCA was resumed in 3 of the 6 patients with AKI in the OCA groups after resolution of the acute underlying illness.

Gallstone-Related Investigator-Reported AESIs in the Pooled Safety Population (Section 6.4.4)

The incidence rate of serious gallstone TEAEs was higher in the OCA 10 mg and OCA 25 mg groups (5.0% and 6.7%, respectively) compared with placebo (3.3%). The higher incidence rate of serious gallstone TEAEs in OCA 10 mg and OCA 25 mg groups compared with placebo (risk difference [95% CI] of 0.21 [-0.60, 1.02] and 1.68 [0.59, 2.76], respectively) was mainly driven by cholecystitis and cholelithiasis.

In the Pooled Safety Population, the incidence rate of patients undergoing cholecystectomy during the study was low overall (1.7%, 1.7%, and 3.9% in the placebo, OCA 10 mg, and OCA 25 mg groups), with a risk difference [95% CI] of 0.03% [-1.14, 1.19] and 2.26% [0.81, 3.72] in OCA 10 mg and OCA 25 mg groups, respectively, compared to placebo.

In patients who resumed investigational product after a post-baseline cholecystectomy in Study 303, only 2 patients experienced gallstone-related TEAEs: 1 (0.1%) in the placebo group and 1 (0.1%) in the OCA 10 mg group. No patient who resumed or maintained investigational product after a post-baseline cholecystectomy experienced a pancreatitis-related TEAE. A proportionate risk of gallstone-related TEAEs for OCA 25 mg relative to placebo was observed regardless of gallstone status (gallstones present at baseline versus no gallstones or not documented at baseline).

In the Pooled Safety Population, the incidence rate of pancreatitis TEAEs, including severe and serious pancreatitis, and biliary pancreatitis TEAEs, was balanced across treatment groups.

Pruritus Investigator-Reported AESIs in the Pooled Safety Population (Section 6.4.5)

Pruritus is a well characterized ADR of OCA. The overall incidence rate of pruritus TEAEs was dose-dependent and highest in the OCA 25 mg group. The majority of pruritus events were mild to moderate, occurred within the first 3 months of treatment, and were managed with temporary interruption of OCA treatment or the use of medications such as antihistamines.

Safety in Special Populations and Groups (Section 7)

TEAEs were evaluated for differences based on age group, sex, race, baseline fibrosis stage, and baseline diabetes status. Overall, a review of TEAEs by subgroups did not indicate any obvious differences, and trends across subgroups appeared to be generally similar.

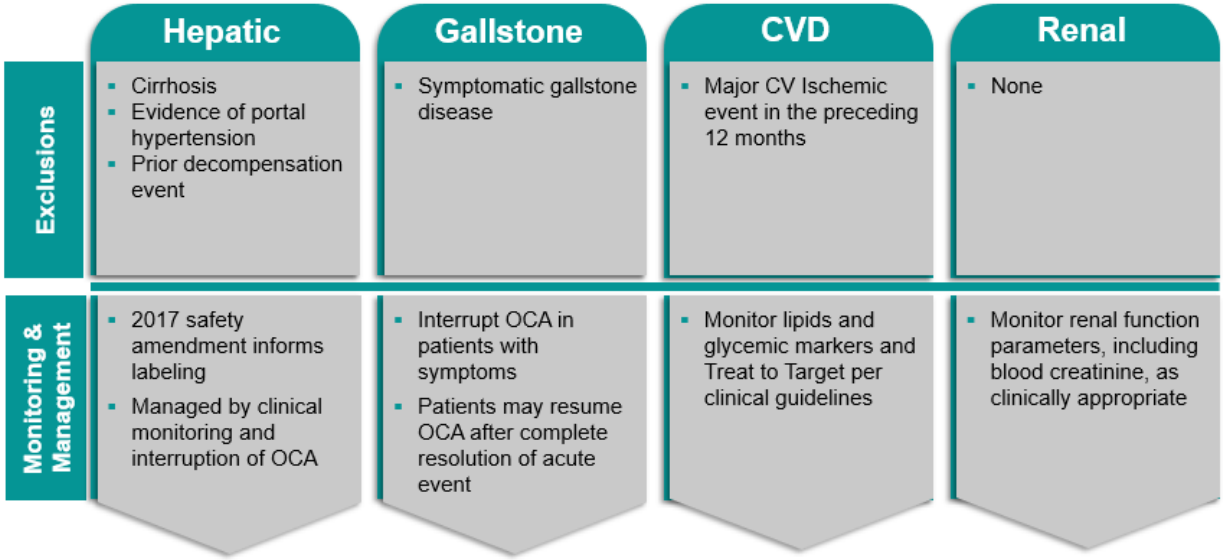
Risks and Risk Management (Section 8)

The larger safety database allows for robust characterization of OCA's safety profile, which informs appropriate monitoring and management according to existing patient care standards and clinical practice guidelines.

No increased risk was observed for hyperglycemia, urolithiasis, or pancreatitis. Pruritus and dyslipidemia were the most common AEs. Pruritus, dyslipidemia, and gallstone-related events were more likely to occur in the OCA treatment groups compared to placebo. Rates of adjudicated CV, hepatic, and AKI events were low overall, but higher in the OCA 25 mg group compared to placebo. Pruritus, the most common TEAE, remains a well characterized ADR of OCA.

Education and management strategies are in place for monitoring hepatic, gallstone, CV and renal events based on our clinical experience from the OCA for NASH development program and real-world OCA experience in PBC (Figure 14).

Figure 14: Key Safety Events: Monitoring and Management



CV=cardiovascular; CVD=cardiovascular disease; OCA= obeticholic acid

Gastroenterologists and hepatologists, and healthcare professionals working with them, are well-qualified to identify and manage appropriate candidates for treatment with OCA using the standard of clinical care and a combination of NITs, as recommended by the AASLD practice guidance for the clinical assessment and management of NAFLD (Rinella 2023). Management of potential safety issues is also within the scope of daily practice, given these specialists' advanced training and expertise managing patients with chronic liver disease. Many of these hepatologists, gastroenterologists, and their advanced practice providers (APPs) have experience treating patients with OCA (i.e., Ocaliva) for PBC.

Serious Liver-Related Adverse Events and Hepatic Impairment

The observed effects of implementation of the 2017 safety amendment provides reassurance that the risk for clinically significant hepatic safety events can be managed with standard of clinical care monitoring and drug interruption in cases when liver injury is suspected. The contents of the safety amendment, along with published guidance, forms the basis of the management recommendations in the proposed label.

The proposed labeling states that efficacy in patients with cirrhosis has not been established, and further excludes patients with decompensated cirrhosis (i.e., Child-Pugh Class B or C), any history of a prior decompensation event, compensated cirrhosis with evidence of portal hypertension (i.e., ascites, gastroesophageal varices, persistent thrombocytopenia), or evidence of complete biliary obstruction.

To further manage hepatic safety risk with OCA, routine liver-related biochemistries (including ALT, AST, ALP, and total and direct bilirubin) should be obtained before initiating treatment with OCA, again early after initiation of treatment, and as clinically indicated thereafter, which is

consistent with recent published guidance (Fontana 2022). In Study 303, patients had safety labs (including liver biochemistries) collected at each study visit including baseline, Month 1, Month 3, Month 6, and every 6 months thereafter.

Patients with suspected liver injury or hepatic impairment should continue to be monitored after OCA treatment interruption as clinically indicated and treatment with OCA resumed only if an alternative cause has been identified and resolution of the event has occurred. Treatment with OCA should be permanently discontinued in patients with established hepatic impairment and/or progression to cirrhosis.

Gallstone-Related Events

Proposed labeling excludes patients with complete biliary obstruction, as OCA undergoes biliary elimination, and is consistent with existing labelling for Ocaliva in PBC. A proportionate risk for OCA 25 mg relative to placebo was observed, regardless of baseline gallstone status; hence, proposed labeling does not require baseline imaging to document gallstone status but recommends interruption of OCA for symptomatic gallstone-related events. Clinical management should be consistent with the existing standard of clinical practice. If symptomatic cholelithiasis is suspected, gallbladder imaging and appropriate clinical management and follow-up are indicated. After complete evaluation, treatment, and resolution of the event, patients may resume OCA treatment, provided there are no signs or symptoms suggestive of an ongoing biliary obstruction (e.g., retained bile duct stones).

These recommendations for expectant management of asymptomatic cholelithiasis and intervention for symptomatic gallstone disease are consistent with bariatric surgery practice (Leyva-Alvizo 2020) and labeling for GLP-1 receptor agonists.

Cardiovascular

Proposed labeling excludes patients with a major CV ischemic event in the preceding 12 months, as these patients were excluded from Study 303.

Given the background risk for CV disease in the NASH population, lipids and glycemic markers should be managed per existing clinical guidelines.

Renal Safety

Proposed labelling recommends monitoring renal function parameters, including blood creatinine, as clinically appropriate.

Pruritus

Pruritus, the most common TEAE, remains a well characterized ADR of OCA. Proposed labeling recommends that for patients with intolerable or severe pruritus, temporary interruption should be considered, along with other treatments for pruritus as clinically appropriate (e.g., bile acid binding resin, antihistamine, or other antipruritic treatment). Discontinuation should be considered in patients who continue to experience persistent intolerable or severe pruritus despite management strategies.

Benefit-Risk Conclusions (Section 9)

NASH is a serious, progressive, and life-threatening disease with no approved therapies.

Fibrosis stage is the single strongest predictor for clinical outcomes. It is estimated that 26 million persons in the US are living with NASH, of which ~15 million have F0 or F1, ~8.3 million have pre-cirrhotic fibrosis (4.9 million F2, 3.4 million F3), and ~2.5 million have F4 (cirrhosis) (Razavi 2022). Based on the NASH CRN mortality estimates (0.89 and 1.76 deaths per 100 PYs for F3 and F4, respectively). The estimated annual number of deaths to be expected among US persons who currently have F3 disease is 17,800 and among persons with F4 disease is 22,880 (Sanyal 2021a). A recent meta-analysis demonstrates that the risk of all-cause mortality, liver-related mortality, and liver events increases by fibrosis stage (Taylor 2020).

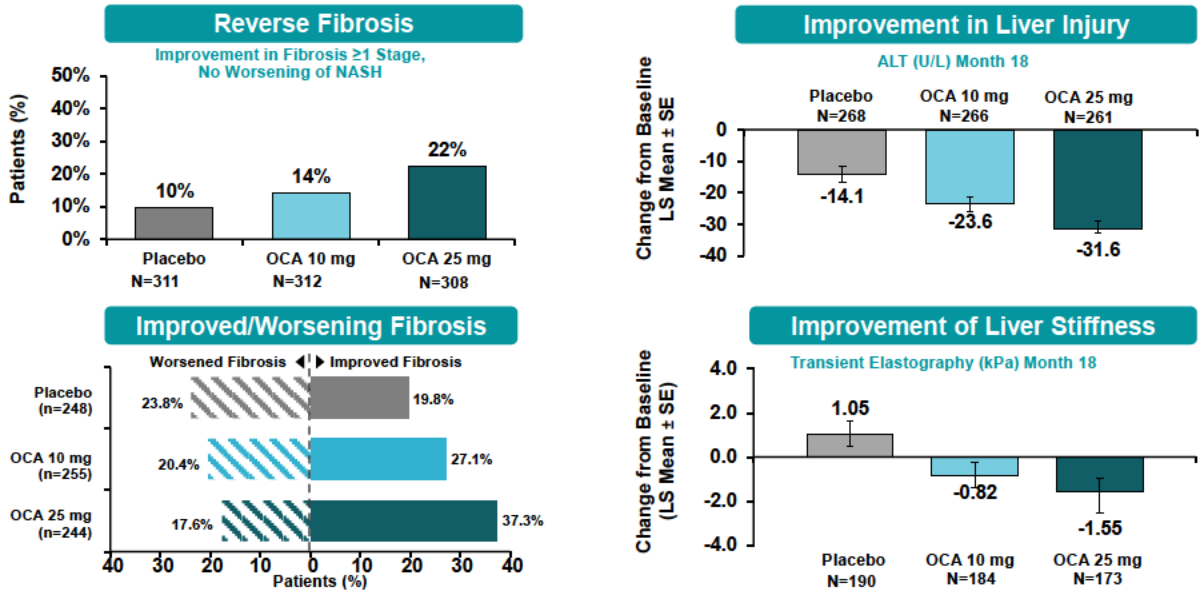
With confirmation of the clinically meaningful, statistically significant histologic fibrosis benefit observed in the original submission, the favorable benefit-risk profile has strengthened with the resubmission. This fibrosis histologic endpoint is the accepted surrogate deemed most likely to predict clinical benefit by the FDA. In addition, with a larger safety database (40,000 PYs of data, including studies in patients with NASH and 30,000 post-marketing safety data from the PBC indication) and longer-term exposure in NASH (~700 patients with ≥4 years of exposure across treatment groups), the safety and tolerability of OCA 25 mg are well-characterized, and support anticipated chronic dosing, with monitoring that is consistent with the current standard of care.

The totality of efficacy data across multiple fibrosis endpoints supports OCA 25 mg as an important antifibrotic advancement for the treatment of NASH. The statistically significant effect of OCA 25 mg observed at Month 18 with the Central Method (Original Analysis) on the fibrosis primary endpoint (improvement of fibrosis by ≥1 stage with no worsening of NASH) was confirmed using the Consensus Method (Resubmission Analysis), with a doubling (2.3-fold increase) of the responder rate compared to placebo. A consistent, dose-related response was also observed across other fibrosis histologic endpoints, including reversal of fibrosis and fewer patients with worsening fibrosis. Improvements in liver biochemistry and noninvasive markers, with persistence observed through Month 48, further support the antifibrotic effect of OCA 25 mg, potentially including patients in whom the fibrosis stage did not reflect improvement at Month 18.

Overall, key safety events include hepatic, gallstone-related, CV, and renal safety events. Management strategies are in place for monitoring hepatic, gallstone-related, CV, and renal events based on our clinical experience from the NASH development program and post-marketing experience in PBC (Figure 14).

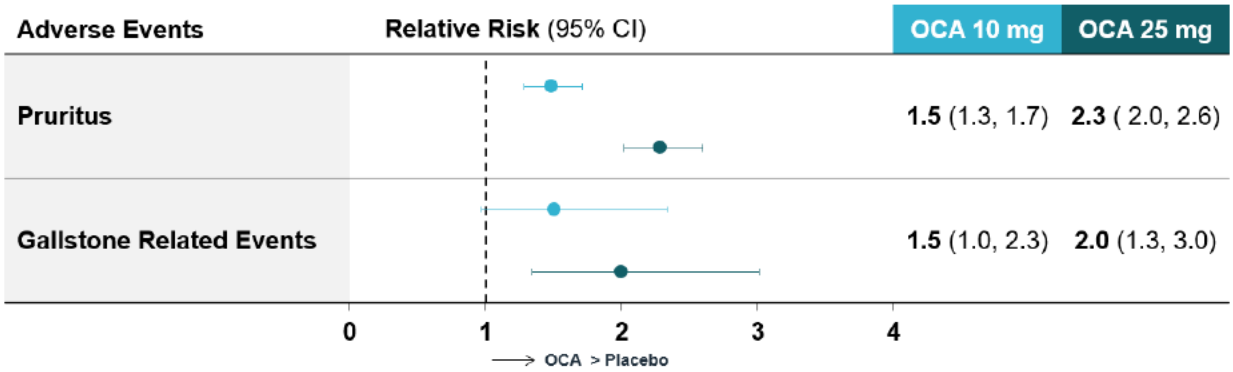
OCA 25 mg has a more favorable benefit-risk profile compared to OCA 10 mg. While most efficacy endpoints were dose-dependent (Figure 15), treatment differences from placebo for OCA 10 mg for both primary endpoints were not statistically significant (Section 5.1.4). A dose-dependent response was observed only for pruritus and gallstone-related events, safety events which are described as ADRs in the proposed label (Figure 16).

Figure 15: Dose-Dependent, Anti-fibrotic Effects Across Multiple Fibrosis Endpoints: Study 303 ITT_old Population (N=931)



ITT=Intent-to-Treat; OCA=obeticholic acid
Note: Results for fibrosis primary endpoint and fibrosis shift analysis are based on Consensus Method.

Figure 16: Dose-Dependent Safety Events: Pooled Safety Population (N=2860)



OCA=obeticholic acid

The totality of evidence supports a favorable benefit-risk profile for OCA 25 mg that meets the criteria for accelerated approval (FDA 2014):

1) Fulfills an urgent unmet medical need for a safe and effective antifibrotic NASH therapy with the ability to slow the progress of, halt, or reverse disease progression and improve clinical outcomes.
2) Demonstrated a clear antifibrotic effect across preclinical and clinical studies.
3) Demonstrated effect on the fibrosis primary endpoint, which is accepted as reasonably likely to predict clinical benefit (FDA 2018) and has now been established as the single strongest predictor of outcomes in NASH.

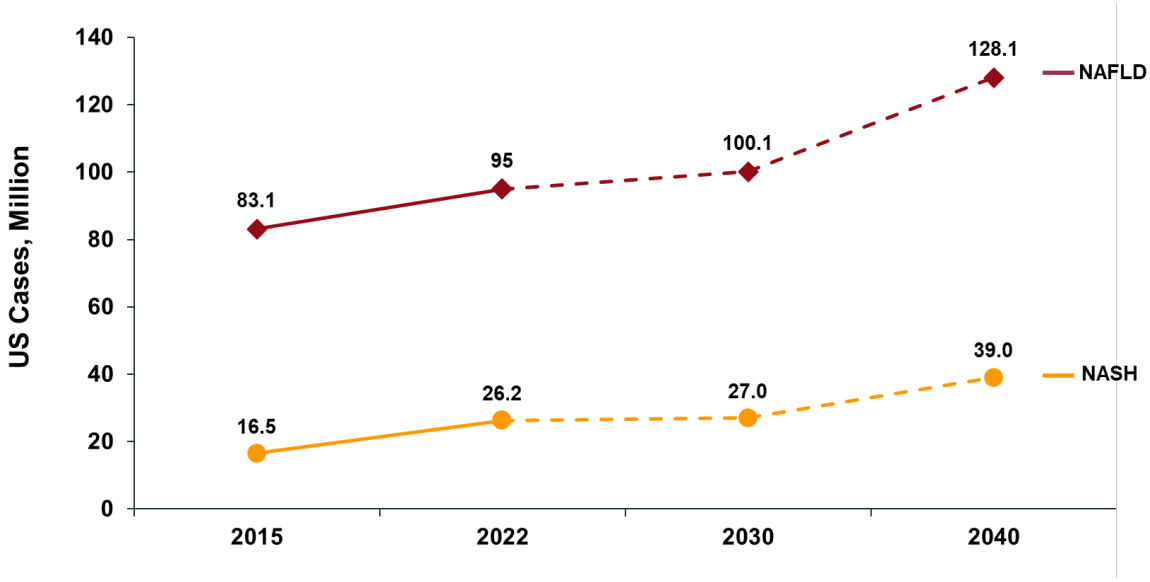
2. NASH IS A SERIOUS, PROGRESSIVE DISEASE

2.1. Prevalence is Increasing Due to Underlying Comorbidities

The prevalence of NASH is high and growing. As the prevalence of obesity and metabolic syndrome has steadily risen over the past several decades, so has the prevalence of several obesity-related conditions, including type 2 diabetes, dyslipidemia, hypertension, and NAFLD. NAFLD has become the most common chronic liver disease in the western hemisphere.

The estimated number of cases of NAFLD over a 25-year period are expected to increase from 83.1 million to 128 million. Similarly, the number of NASH cases is expected to increase from 16.5 to 39 million by 2040 (Razavi 2022).

Figure 17: Prevalence of NAFLD/NASH is Increasing



NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis; US=United States
Adapted from Estes 2018, Razavi 2022.

NASH is associated with significant overall and liver-related mortality. If left untreated, NASH can lead to cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and liver-related death (EASL 2016).

2.2. NASH is a Progressive Disease Associated with Four Stages of Fibrosis

NASH is a progressive disease that advances through 3 stages (F1, F2, F3) of fibrosis before reaching the final stage of cirrhosis (F4) (Figure 1). It is estimated that number of patients with F2 and F3 NASH will increase 54% and 69%, respectively, from 2022 to 2040 (F2: from ~4.9 million to ~7.5 million and F3: from ~3.4 million to ~5.8 million) (Razavi 2022).

The annual transition probabilities of patients progressing from stage 3 to stage 4 (cirrhosis), as well as from stage 2 to stage 3, are estimated to be higher than earlier fibrosis stage transitions such as from stage 0 to stage 1 (Younossi 2019). The incidence rate of progression to pre-cirrhotic fibrosis in the NASH population is estimated to be 67.95 per 1000 person-years (Younossi 2016).

Recent data from randomized, controlled trials suggest that up to 20% of patients with stage 3 bridging fibrosis may progress to cirrhosis in as few as 2 years (Sanyal 2019, Loomba 2019).

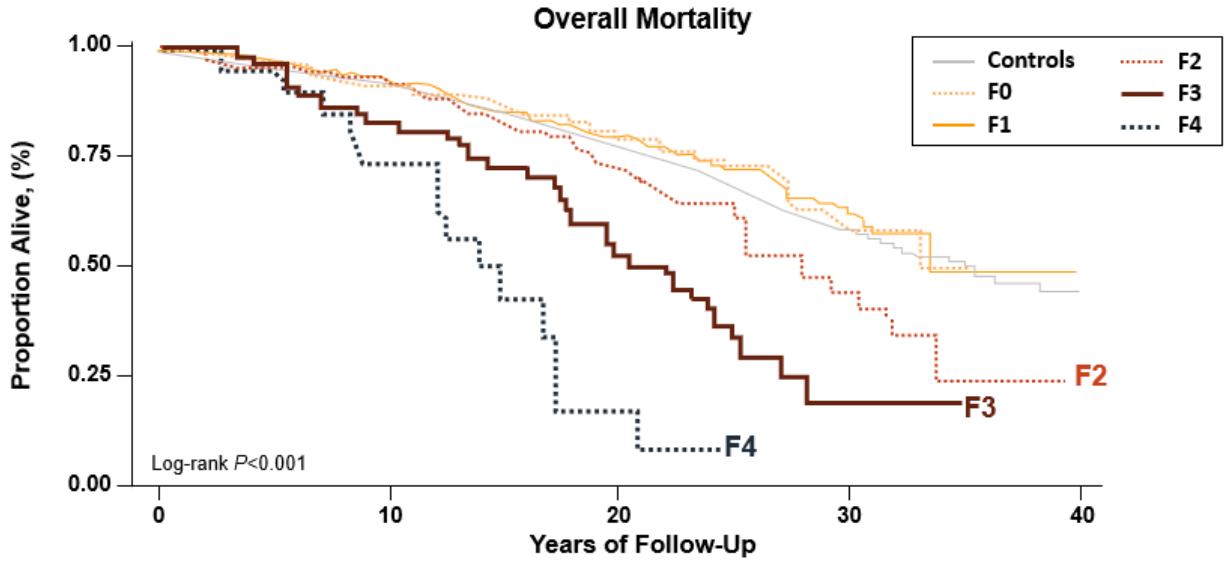
The rate of NASH disease progression is affected by a variety of risk factors, including presence of comorbidities (e.g., type 2 diabetes, hypertension), age, body mass index (BMI), and fibrosis stage (Dufour 2021). New-onset hypertension (7.8 events per 100 person-years) is the most common new non-hepatic outcome in the NASH population, followed by type 2 diabetes (4.8 events per 100 person-years), chronic kidney disease (CKD) (2.5 events per 100 person-years), cardiac events (0.8 events per 100 person-years) (Sanyal 2021a).

2.3. Fibrosis is the Single Strongest Predictor of Progression and Outcomes

Of the histologic features of NASH, fibrosis is the strongest predictor of liver-related adverse outcomes, including liver-related death (Hagström 2017, Taylor 2020, Sanyal 2021a).

There is a step-wise increase in mortality risk as fibrosis stage progresses from F0 to F1, F2, and F3, with a remarkably increased mortality risk in patients with F4 fibrosis or cirrhosis (Figure 18).

Figure 18: Fibrosis is the Strongest Predictor of Overall Mortality

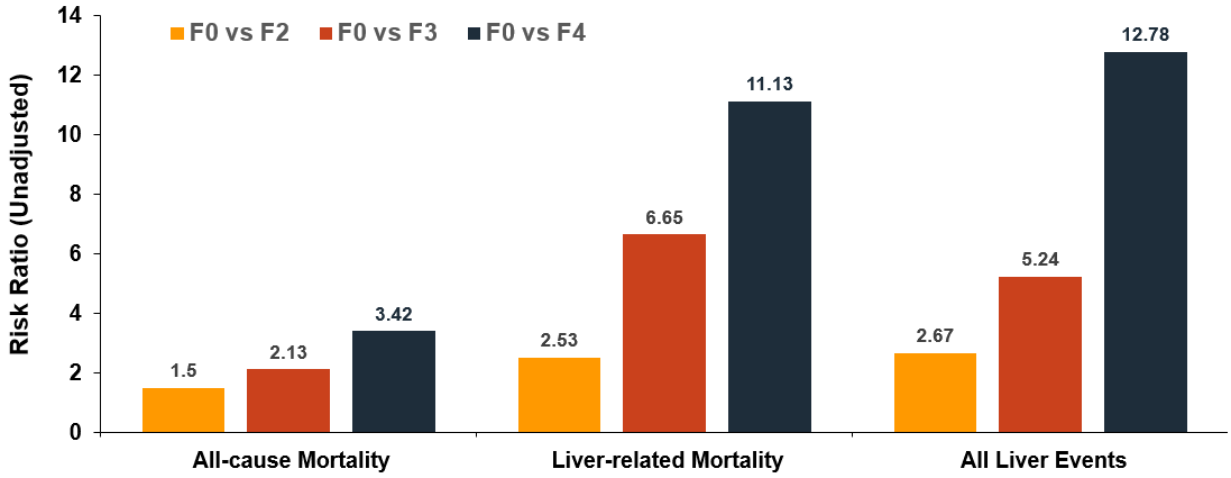


F0=no fibrosis; F1=fibrosis stage 1; F2=fibrosis stage 2; F3=fibrosis stage 3; F4=fibrosis stage 4
Adapted from Hagström 2017.

A recent meta-analysis depicts the risk ratio for all-cause mortality, liver-related mortality, and liver events comparing patients with F0 versus F3 and with F0 versus F4 (Taylor 2020) (Figure 19). All 3 risk categories increase by fibrosis stage; however, the increase is even more dramatic as patients move through each stage for liver related mortality and events.

CV events drive mortality risk among patients with NASH and fibrosis <F2. In patients who have progressed to F3 and F4 fibrosis, the liver pathology drives morbidity and mortality.

Figure 19: Increasing Fibrosis Predicts Mortality and Morbidity



F0=fibrosis stage 0; F2=fibrosis stage 2; F3=fibrosis stage 3; F4=fibrosis stage 4
Adapted from Taylor 2020.

Fibrosis identified histologically or by NITs, such as FIB-4, ELF, and TE is similarly prognostic of overall survival over time (Hagström 2017, Angulo 2015, Day 2019, Boursier 2016).

In patients with compensated cirrhosis at baseline, the data from 2 studies demonstrate that regression in fibrosis is associated with a reduction in liver-related complications. (Sanyal 2021b). Bariatric surgery has been shown to lead to fibrosis improvement in patients with NASH and is associated with a lower risk of major adverse liver outcome (Lassailly 2020, Aminian 2021), further highlighting the link between fibrosis improvement and improved clinical benefit.

3. CLINICAL DEVELOPMENT PROGRAM

As of 26 May 2022, approximately 4518 patients have received ≥1 dose of OCA across all clinical trials sponsored by Intercept and Sumitomo Dainippon Pharma Co., Ltd. (Intercept's former development partner in China, Korea, and Japan). In this resubmission, exposure data were updated for Study 303 based on a DCO of 31 Dec 2021 and include 1652 OCA-treated patients with liver fibrosis due to NASH. Doses evaluated in patients with liver fibrosis due to NASH in the clinical pharmacology and long-term DB studies ranged from OCA 5 mg to 40 mg, but primarily included OCA 10 mg (916 patients) and 25 mg (1010 patients). Given that OCA is intended to be used on a chronic basis, it is noteworthy that 335 patients have been exposed to the proposed marketed dose of OCA 25 mg for at least 4 years.

3.1. Overview of Clinical Trials

To support the indication of treatment of NASH, Intercept submitted data from the pivotal single Phase 3 trial, Study 303, and supportive Phase 2 studies (FLINT, conducted by the NIDDK, and Japanese Study 2001).

3.2. Phase 3 Study 303

Study 303 is an ongoing Phase 3, DB, randomized, long-term, placebo-controlled, multicenter, international study with a Month 18 IA of the histologic endpoints to support accelerated approval, which was confirmed by a Month 18 IA Resubmission Analysis (Figure 20).

Eligible patients were randomized to receive OCA 10 mg, 25 mg, or placebo QD. The 25 mg dose was selected because it had shown to be effective in FLINT; the 10 mg dose was included to assess if a lower dose would be effective.

At EOS, all-cause mortality, and liver related clinical outcomes will be evaluated for full approval. The study population was planned to comprise approximately 2085 patients with biopsy confirmed, pre-cirrhotic NASH with approximately 40% stage 2 (perisinusoidal and portal/periportal) and 60% stage 3 (bridging fibrosis) liver fibrosis. An exploratory cohort of approximately 285 patients with F1 and ≥1 comorbidity was enrolled.

To determine eligibility and primary efficacy endpoints assessments, key features of NASH (i.e., steatosis, lobular inflammation, and hepatocellular ballooning) and fibrosis staging were graded in accordance with the NASH CRN criteria for scoring as summarized in Table 3 (Kleiner 2005).

In addition to fibrosis, patients were to have histologic evidence of NASH (i.e., presence of all 3 key histological features of NASH (steatosis, lobular inflammation, hepatocellular ballooning) with a score of ≥1 for each and a combined NAS of ≥4 out of a possible 8 points according to the NASH CRN criteria) upon central read of a liver biopsy obtained no more than 6 months before Day 1.

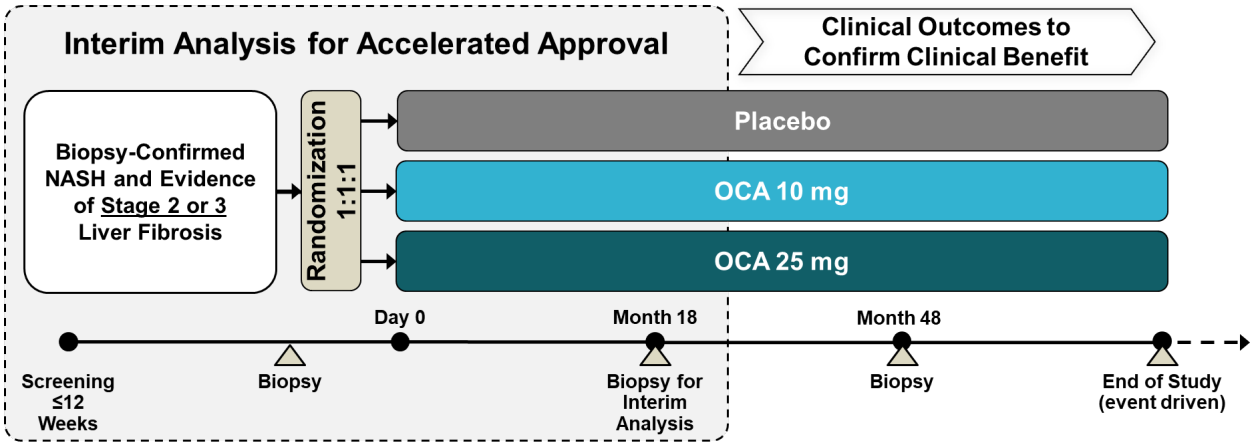
Table 3: NASH CRN Scoring System for Determining Eligibility and Primary Histologic Endpoint Assessment

NAFLD Activity Score (NAS)		Fibrosis Staging	
Parameter	**Scoring Criteria**	**Parameter**	**Staging Criteria**
Steatosis	0: <5% 1: 5% to 33% 2: >33% to 66% 3: >66%	Stage 0	No fibrosis
Lobular Inflammation	0: No foci 1: <2 foci per 200× field 2: 2 to 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, perisinusoidal 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

CRN=Clinical Research Network; NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis
Adapted from Kleiner 2005.

Patients were not to be enrolled if they had current or a history of significant alcohol consumption (>2 units/day for females and >4 units/day for males, on average) for a period of >3 consecutive months within 1 year before Screening or if they had evidence of other forms of known chronic liver disease. Patients with histological presence of cirrhosis, recent history of significant ASCVD, HbA1c >9.5% within 60 days before Day 1, or BMI >45 kg/m2 with ≥1 comorbidity (i.e., hypertension, hyperlipidemia, or type 2 diabetes) were also not to be enrolled in the study.

Figure 20: Study 303 Design



OCA=obeticholic acid

3.2.1. Analysis Populations

The analysis populations in Study 303 Month 18 IA Resubmission are summarized in Table 4 and shown in Figure 21.

As of the DCO of 31 Dec 2021, 2480 patients had been randomized to Study 303. To note, 3 patients who were randomized were not treated. A majority of the patients (90%), including the original 931 patients from the Month 18 IA, were assessed as F2 or F3 by their enrollment biopsy; an exploratory cohort included patients with F1 (Figure 21).

As the ITT_old (N=931) population was the pre-specified population for the Month 18 IA, the histology analyses for the resubmission were performed in the same 931 patients.

Supportive analyses on histology were also conducted in a broader ITT_histology (N=1607) population, which includes patients who were expected to have completed Month 18 visit (including biopsy) under Protocol Version 8 or earlier. The study protocol was amended after the completion of the Month 18 IA to remove the mandatory Month 18 biopsy under Protocol Version 9.

In the resubmission, histology data (baseline and Month 18) for the ITT_old (N=931) and ITT_histology (N=1607) populations were analyzed with scores from the Consensus Method.

Additional supportive efficacy analyses based on long-term liver biochemistries and noninvasive markers of fibrosis were conducted in an even broader ITT_all (N=2187) population, which includes all patients with F2 or F3 at baseline who have a postbaseline measurement, e.g., even those without a Month 18 biopsy.

For the safety analyses, the Safety_all (N=2477) population in Study 303 includes all randomized patients who received at least 1 dose of investigational product.

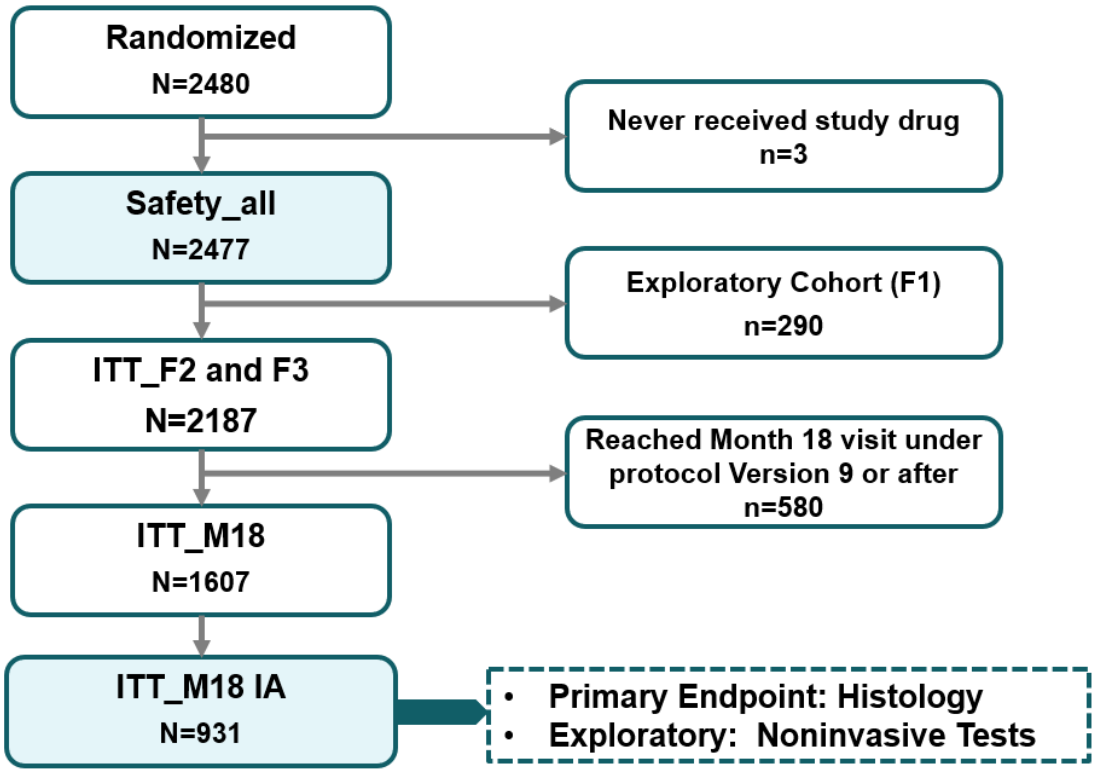
Table 4: Summary of Study 303 Resubmission Analysis Populations

<table>
<tr><th colspan="4">Patients with Original Eligibility Baseline of Fibrosis Stage 2 or 3</th></tr>
<tr><th colspan="4">Key Efficacy Analysis Population: Original NDA and NDA Resubmission</th></tr>
<tr><td colspan="3">ITT_old
(N=931)</td><td rowspan="2">Population Definition
All patients randomized by 15 Jul 2017 who received at least 1 dose of investigational product and who had or were expected to have completed Month 18 Visit (including biopsy) by the DCO of 26 Oct 2018.
Original submission biopsies were read by Central Method.
NDA resubmission biopsies were read by Consensus Method.
Direct comparison of results between Central and Consensus Methods</td></tr>
<tr><td>Placebo
(n=311)</td><td>OCA 10 mg
(n=312)</td><td>OCA 25 mg
(n=308)</td></tr>
<tr><th colspan="4">Supportive Efficacy Analysis Populations: NDA Resubmission Only</th></tr>
<tr><td colspan="3">ITT_histology
(N=1607)</td><td rowspan="2">Population Definition
All patients randomized, received at least 1 dose of investigational product by the DCO of 31 Dec 2021, and who had or were expected to have completed Month 18 Visit (including the Month 18 biopsy) per Protocol Version 8 (08 Jan 2019) or earlier[a]
NDA resubmission biopsies were read by Consensus Method.</td></tr>
<tr><td>Placebo
(n=536)</td><td>OCA 10 mg
(n=532)</td><td>OCA 25 mg
(n=539)</td></tr>
<tr><td colspan="3">ITT_all
(N=2187)</td><td rowspan="2">Population Definition
All patients who were randomized, received at least 1 dose of investigational product by the DCO of 31 Dec 2021, and have a post-baseline measurement.
Non-histologic efficacy analyses (liver biochemistry and imaging NITs)</td></tr>
<tr><td>Placebo
(n=728)</td><td>OCA 10 mg
(n=729)</td><td>OCA 25 mg
(n=730)</td></tr>
<tr><th colspan="4">Patients with Original Eligibility Baseline of Fibrosis Stage 1, 2, or 3</th></tr>
<tr><th colspan="4">Safety Analysis Population: Resubmission</th></tr>
<tr><td colspan="3">Safety_all (N=2477)</td><td rowspan="2">Population Definition
All patients randomized, received at least 1 dose of investigational product by the DCO of 31 Dec 2021.</td></tr>
<tr><td>Placebo
(n=825)</td><td>OCA 10 mg
(n=825)</td><td>OCA 25 mg
(n=827)</td></tr>
</table>

DCO=data cutoff; ITT=Intent-to-Treat; NDA=New Drug Application; NIT=noninvasive test; OCA=obeticholic acid

[a] Study protocol Version 8 (dated 08 Jan 2019) or earlier required a Month 18 biopsy. The study protocol was amended on 29 Jul 2019 (Version 9) upon the completion of the IA to remove the Month 18 biopsy assessment.

Figure 21: Study 303 Resubmission Analysis Populations



F1=fibrosis stage 1; F2=fibrosis stage 2; F3=fibrosis stage 3; IA=interim analysis; ITT=Intent-to-Treat
Note: Key efficacy and safety populations presented are shaded in blue.

3.3. Phase 2 FLINT

FLINT was a multicenter, randomized, DB, placebo-controlled, Phase 2b clinical study designed to evaluate the efficacy and safety of OCA in patients with biopsy-confirmed evidence of NASH (Figure 22). The primary endpoint was improvement in liver histology, as defined by no worsening of the fibrosis score and a decrease in NAS by at least 2 points. Worsening of the fibrosis score was defined as any numeric increase in the fibrosis score at the end of treatment (EOT) compared to baseline.

FLINT was sponsored by the NIDDK and designed and conducted by the NASH CRN at eight centers in the US. Grading and staging of biopsies for the purposes of enrollment were done by the NASH CRN pathologist at the site of enrollment using the NAS and fibrosis staging criteria established by the NASH CRN.

A "central read" was later conducted and scoring for both baseline and Month 18 biopsies were based on a consensus achieved by a team of 3 to 8 central NASH CRN pathologists. Other NASH CRN therapeutic and natural history studies were ongoing during the time FLINT was conducted and the central pathologists who read FLINT liver biopsies were blinded to study origin and treatment assignment.

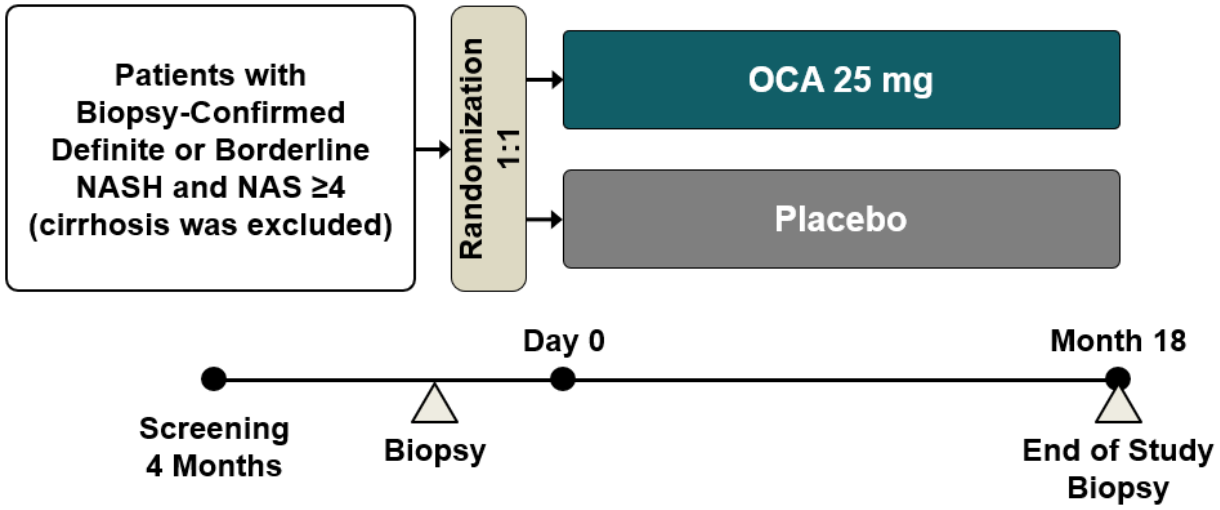
Eligible patients were randomized to receive either OCA 25 mg or placebo QD for 18 months. Randomization was stratified by diabetes status at baseline and study center. Patients returned

for safety assessments periodically throughout the study until completion of treatment at Month 18, when they underwent a final liver biopsy. To assess the reversibility of the therapeutic effects post treatment cessation, the study included a 6-month follow-up period after the EOT during which samples for assessment of ALT and other non-histologic assessments were collected at Month 24.

A total of 283 patients were randomized and received at least 1 dose of investigational product (ITT Population). The modified Intent-to-Treat (mITT) (N=218) population was the primary analysis population for the primary endpoint and second histological endpoints. This included all patients from the ITT population except those who did not receive an end-of-treatment biopsy due to protocol modification after the efficacy stopping criteria were met were included.

See Section 5.2 for FLINT study results.

Figure 22: FLINT Design



FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; NAS=NAFLD Activity Score; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid
Note: After Month 18 EOS biopsy, patients continued in a 6-month follow-up period after the end of treatment to assess the reversibility of the therapeutic effects post treatment cessation.

3.4. Phase 2 D8602001

Study 2001 was a Phase 2, exploratory, DB, placebo-controlled study in Japanese patients with NASH evaluating the effect of OCA on NASH histology. A total of 202 patients with biopsy-confirmed, noncirrhotic NASH (NAS ≥5) were randomized to once-daily treatment with placebo or OCA 10 mg, OCA 20 mg, or OCA 40 mg (approximately 50 patients per treatment group) for 72 weeks, with a subsequent follow-up period of 24 weeks. Safety assessments included AE monitoring, electrocardiogram (ECG) evaluation, physical examination, clinical laboratory assessments, and vital signs. Only data from the OCA 10 mg cohort has been included in the pooled safety analysis in this resubmission.

4. CLINICAL PHARMACOLOGY

The clinical pharmacology properties of OCA in healthy adults and in patients with pre-cirrhotic NASH (F1, F2 and F3) as well as patients with compensated cirrhosis (Child-Pugh A) were characterized in the Original Submission. Following multiple-dose administration of OCA 5, 10, and 25 mg QD for 14 days, systemic exposures of OCA increased dose proportionally. Exposures to the active conjugates, glyco-OCA and tauro-OCA, and total OCA (the molar sum of OCA and its 2 active conjugates) increased more than proportionally with dose due to accumulation. The steady-state systemic exposure (area under the concentration-time curve $[AUC]_{0\text{-}24h}$) of total OCA achieved on Day 14 was 4.2-, 6.6-, and 7.8-fold the systemic exposure ($AUC_{0\text{-}24h}$) achieved on Day 1 after 5, 10, and 25 mg QD dosing, respectively. Systemic exposure (AUC and peak [maximum] plasma concentration [C_{max}]) for total OCA in patients with NASH who had F2 and F3 appeared comparable to those in healthy patients in a cross-study comparison. The half-life of total OCA was similar between healthy patients and those with pre-cirrhotic NASH (approximately 4 days).

Results from the pharmacokinetic (PK) analyses in this resubmission confirmed that after single- or multiple-dose administration of OCA 10 mg or OCA 25 mg in patients with liver fibrosis due to NASH, exposure PK parameters (AUC values, predose plasma concentration at steady state [C_{trough}], and C_{max}) increased with increasing dose and a higher variability in plasma concentrations was observed for the OCA 25 mg group compared to the OCA 10 mg group. Newly collected sparse samples collected at visits after 04 May 2021 (post 18-month treatment) analyzed for this resubmission confirm that mean concentrations of OCA and conjugates increased with increasing dose.

Dose Selection

The optimized OCA doses for PBC and NASH were empirically determined in clinical studies. In terms of mechanism, it is likely that the presence of cholestasis in PBC results in higher liver OCA concentrations relative to NASH for the same dose, resulting in differential dosing requirements based on the pathophysiology of each indication. Thus, the approved doses for OCA in PBC are 5 mg daily uptitrated to 10 mg daily, as tolerated, by Month 3. Cholestasis, or reduced bile flow from the liver, results in accumulation of endogenous bile acids, and presumably OCA, in the liver, requiring lower doses to achieve similar exposures. In PBC, multiple studies showed there was no additional efficacy at doses higher than OCA 10 mg.

For the Phase 3 Study 303, the 25 mg OCA dose was included because it was efficacious, safe, and tolerated in the FLINT study. The 10 mg dose was included in Study 303 in order to evaluate the impact of a lower dose on efficacy, safety, and tolerability. As shown in Section 5.1.4, OCA 25 mg demonstrated higher efficacy than OCA 10 mg.

4.1. Intrinsic Factors

Previous cross-study analysis using single dose $AUC_{0\text{-}6h}$ found that body weight and NASH fibrosis stage were predictors of total OCA plasma exposure in patients with liver fibrosis due to NASH. However, total OCA exposure increased only modestly with F3 and markedly with F4.

Expanded results from Study 303 allowed a broader analysis of intrinsic factors than originally performed in the cross-study analysis presented in the original submission. Updated analysis of intrinsic factors within Study 303 (body weight, BMI, fibrosis stage, age, sex, race, and renal

function) using steady-state C_{trough} and AUC_{0-24h} found that most factors did not significantly alter the overall total OCA PK exposure. Only sex (higher exposures in female patients compared to male patients) influenced total OCA PK exposure. Review of Study 303 data indicated that no sex difference was apparent in exposure-response relationships and no clinically meaningful differences between male and female patients were observed for efficacy and safety results. Therefore, no dose adjustments are necessary for body weight, BMI, age, sex, race, F1-F3, and renal function (excluding severely impaired).

4.2. Extrinsic Factors

Food effect studies indicated that OCA may be administered without regard to meals.

Drug-drug interaction (DDIs) assessments indicated that no major DDIs are expected with OCA and the most common concomitant medications used in the NASH patients. Drug interactions observed are as follows:

- Warfarin: Potential for decreased international normalized ratio (INR); monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range.
- Cytochrome P (CYP)1A2 Substrates with Narrow Therapeutic Index (e.g., theophylline and tizanidine): Potential for increased exposure to CYP1A2 substrates; monitor drug concentrations of CYP1A2 substrates with narrow therapeutic index.
- Inhibitors of Bile Salt Efflux Pump (e.g., cyclosporine): Avoid use. If concomitant use is necessary, monitor serum transaminases and bilirubin.

4.3. Exposure-Response Relationships

The results from exposure-response (efficacy, pharmacodynamic [PD], and safety/tolerability) analyses are aligned with those of dose-response analyses: the primary efficacy endpoint of improvement of fibrosis by ≥1 stage with no worsening of NASH, C4 (a PD marker of FXR activation) and liver biochemistry (ALT and GGT), as well as AESIs pruritus and dyslipidemia indicated that higher plasma exposure (measured by either C_{trough} or AUC_{0-24h}) of total OCA at steady-state was associated with a higher proportion of the responses. However, no exposure-response relationships were apparent for hepatic disorder, renal disorder, urolithiasis, hyperglycemia, and CV AESIs consistent with the lack of dose-response observed.

5. CLINICAL EFFICACY

5.1. Phase 3 Study 303 (REGENERATE)

5.1.1. Histological Evaluation - New Biopsy Reading Method (Consensus Method)

For the Month 18 IA (Original Analysis), biopsies were read by 1 of 2 expert pathologists in a blinded manner (Central Method). Despite achieving the pre-specified primary endpoint for the Month 18 IA (N=931), inter-reader discordance at the individual patient level between the 2 pathologists that was in line with the discordance rates reported by the NASH CRN group (Kleiner 2005), led to FDA concern about uncertainty around the efficacy results.

To address this uncertainty, the Resubmission Analysis utilized a new, more rigorous biopsy scoring method that aims to increase inter-reader concordance. A re-evaluation of the effect of OCA on liver histology using a novel 2-stage consensus panel reading process for obtaining NASH CRN scores (Consensus Method) agreed upon with the Agency confirmed the antifibrotic effect of OCA demonstrated in the Original Analysis in the ITT_old (N=931) population.

Digital whole slide images of the stained liver biopsy samples were evaluated by 3 pathologists using the NASH CRN scoring system. The Consensus Method involved an independent read (Stage 1) and, if necessary, a blinded joint panel read (Stage 2). The pathologists were blinded to the patient identification (ID), site ID and location, and patient's treatment assignment. Separate panels of pathologists were assembled to read Trichrome and H&E-stained images. A schematic of the Consensus Method is provided in Figure 23.

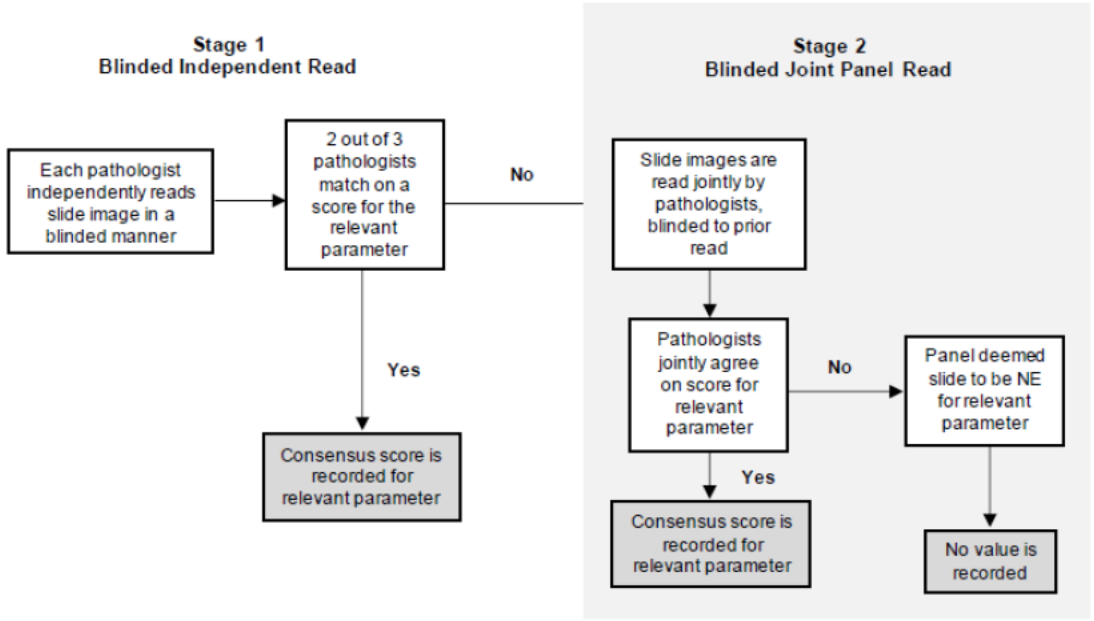
Stage 1

In Stage 1, each slide image was read independently by each of the 3 pathologists, and the interpretations were recorded in a validated, study-specific database. If the 2 primary readers agreed on each component score (steatosis, hepatocellular ballooning, lobular inflammation for H&E-stained biopsies, and NASH CRN fibrosis stage for Trichrome-biopsies), the score served as the final assessment. In the event the 2 primary pathologists did not agree on a specific component score, then the third pathologist's score served as the tie-breaker; if the tie-breaker's score agreed with the score of 1 of the 2 primary readers, this was recorded as the final component score.

Stage 2

If all 3 pathologists' scores for a specific component were fully discrepant (all 3 readers' scores differ for a specific component), then the image was flagged for a joint panel read (Stage 2). If the panel determined that the slide image was not evaluable (NE), then no consensus score was entered for the discordant component(s). Patients with nonevaluable consensus reads were imputed as "nonresponders" for the primary and secondary histological efficacy endpoints.

Figure 23: Consensus Method Process



Approach is repeated for each parameter: fibrosis stage, steatosis, hepatocellular ballooning, lobular inflammation

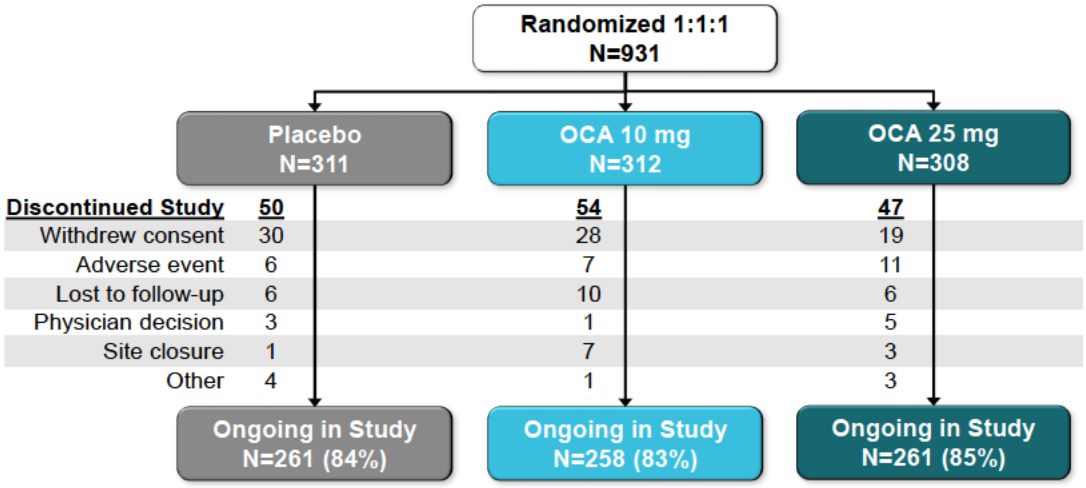
NE=not evaluable

5.1.2. Patient Disposition

Patient disposition at the time of the DCO for the original Month 18 IA (N=931) is presented in Figure 24.

The overall discontinuation rates were similar across the groups. A greater number of OCA-treated patients discontinued due to an AE while a greater number of those in the placebo and OCA 10 mg groups withdrew consent.

Figure 24: Patient Disposition: Study 303 ITT_old Population (N=931)



IA=interim analysis; ITT=Intent-to-Treat; OCA=obeticholic acid
Note: Patient disposition is based off the data cutoff for the original Month 18 IA (N=931).

5.1.3. Demographic and Baseline Characteristics

Clinical characteristics of the efficacy populations are reflective of a NASH population with pre-cirrhotic fibrosis seen in clinical practice, and therefore the study results can be extrapolated to the proposed population (Rinella 2023).

Efficacy populations supporting the Resubmission Analysis are defined in Table 4. The ITT_old Population included all 931 F2 and F3 patients that made up the original NDA submission and was used for Month 18 histology analyses. Long-term liver biochemistries and NITs were assessed up to Month 48 for the ITT_old (N=931), ITT_histology (N=1607), and ITT_all (N=2187) Populations.

Demographic and baseline characteristic results were generally similar between the ITT_old (N=931), ITT_histology (N=1607), and ITT_all (N=2187) Populations in Study 303 and across treatment groups within each respective population. Demographic and baseline characteristics of the ITT_old population are summarized in Table 5.

Table 5: Key Baseline Demographic and Clinical Characteristics: Study 303 ITT_old Population (N=931)

	303 Resubmission Analysis (ITT_old Population [N=931])		
	Placebo N=311	**OCA 10 mg N=312**	**OCA 25 mg N=308**
Age (years), Mean (Range)	55 (19-79)	55 (20-78)	55 (18-75)
<65 Years	79.1%	79.8%	81.5%
≥65 Years	20.9%	20.2%	18.5%
≥75 Years	0.6%	1.0%	0.6%
Female	60.1%	56.7%	56.8%
Male	39.9%	43.3%	43.2%
Race			
American Indian or Alaska Native	0.7%	0	1.7%
Asian	3.5%	5.9%	7.0%
Black or African American	1.1%	1.4%	3.5%
Native Hawaiian or Other Pacific Islander	0.4%	1.0%	0.7%
White	93.0%	91.3%	87.1%
Other	1.4%	0.3%	0
Hispanic or Latino	18.4%	14.7%	16.7%
Geographic Region			
Europe	22.2%	23.1%	22.1%
North America	72.7%	71.2%	74.0%
Rest of World	5.1%	5.8%	3.9%

	303 Resubmission Analysis (ITT_old Population [N=931])		
	Placebo N=311	**OCA 10 mg N=312**	**OCA 25 mg N=308**
BMI, Mean (kg/m^2)	34.1	33.6	33.8
≥30 kg/m^2	74.6%	72.8%	75.6%
≥35 kg/m^2	36.3%	36.5%	37.3%
Type 2 Diabetes	56%	55%	56%
Fibrosis stage 2	46%	42%	45%
Fibrosis stage 3	54%	58%	55%
NAS total score, mean	6.0	5.9	6.0
ALT (U/L), mean	79.7	75.6	80.4
AST (U/L), mean	59.0	56.6	57.1
Total Bilirubin (mg/dL), mean	0.64	0.65	0.69
ALP (U/L), mean	89.3	87.6	89.5
GGT (U/L), mean	101.9	99.6	95.6
Transient Elastography (kPa), mean	12.50	11.98	12.38
FIB-4, mean	1.62	1.63	1.63
ELF, mean	9.71	9.73	9.73
Lipid-lowering Medication	55.9%	54.2%	51.6%
Statins Only	46.3%	45.2%	40.9%
Anti-diabetic Medications	53.7%	54.8%	51.3%
GLP-1 agonists	7.4%	9.9%	6.8%
Thiazolidinedione only	1.6%	2.9%	1.3%
Vitamin E	13.5%	10.9%	10.4%

BMI=body mass index; ELF=enhanced liver fibrosis; FIB-4=fibrosis-4; ITT=Intent-to-Treat; NAS=NAFLD activity score; OCA=obeticholic acid

Key results of the ITT_old (N=931) population are as follows:

- The mean patient age was 54.7 years; 80% of patients were <65 years at baseline. A total of 57.9% of patients were female, 90.5% were white, and 83.4% were non-Hispanic.
- A total of 74.3% of patients had a BMI ≥30 kg/m^2 and 36.7% had a BMI ≥35 kg/m^2.
- Approximately 56% of patients had type 2 diabetes and ~53% were receiving antidiabetic drugs at baseline.
- Approximately 54% and 14% of patients were using lipid-lowering drugs and NASH-modifying agents (vitamin E or thiazolidinedione [TZD]), respectively, at baseline.
- Baseline ALT and AST values were elevated (>upper limit of normal [ULN], defined as 30 U/L and 35 U/L for ALT and AST, respectively) in approximately 60% and 74% of patients, respectively, while GGT was above normal limits in approximately 66% of patients.
- Baseline ALP was within the normal range for approximately 96% of patients. Over 92% of patients had normal bilirubin values.
- 44.1% of patients had a CRN fibrosis score of F2 and 55.9% had F3 at baseline (i.e., the eligibility screening read) by central reader.
- Across the 3 treatment groups, baseline markers of fibrosis were consistent with a study population with pre-cirrhotic fibrosis due to NASH:
  - Mean FIB-4 index ranged from 1.62 to 1.63.
  - Mean ELF ranged from 9.71 to 9.73.
  - Mean baseline liver stiffness values (assessed by TE in 675 patients) ranged from 11.98 kPa to 12.50 kPa.

5.1.4. Efficacy Results

This section summarizes the effects of OCA on the primary endpoints and the histologic fibrosis secondary and other endpoints measured in Study 303. The analysis populations in Study 303 Month 18 IA Resubmission are summarized in Section 3.2.1.

5.1.4.1. Evidence of OCA Efficacy on Histologic Endpoints

The Resubmission Analysis using the Consensus Method confirmed the dose-dependent antifibrotic effect of OCA demonstrated in the Original Analysis using the Central Method.

The robust antifibrotic effect demonstrated in Study 303 is clinically meaningful and reasonably likely to predict clinical benefit, given that clinically significant fibrosis without cirrhosis advanced fibrosis is highly predictive of liver-related outcomes and all-cause mortality in patients with NASH (Younossi 2011, Angulo 2015, Dulai 2017, Hagström 2017, Vilar-Gomez 2018, Sanyal 2021a).

5.1.4.1.1. Primary Endpoints

For the ITT_old population (N=931), results for the primary endpoint of improvement in fibrosis by ≥1 stage with no worsening of NASH at Month 18 based on the Consensus Method (Resubmission Analysis) are highly consistent with the Central Method (Original Analysis) (Figure 25a).

Using the Consensus Method, the statistically significant treatment effect of OCA 25 mg observed at Month 18 with the Original Analysis was confirmed with a doubling (2.3-fold increase) of the responder rate for OCA 25 mg compared to placebo in the Resubmission Analysis. Though OCA 10 mg showed a greater number of responders compared to placebo for the primary fibrosis endpoint, the difference did not reach statistical significance.

The primary endpoint of steatohepatitis at Month 18 based on the Consensus Method (Resubmission Analysis), which required hepatocellular ballooning of 0 and lobular inflammation of 0 or 1, was consistent with the Central Method (Original Analysis) in which proportions of responders were higher in both OCA groups; however, the treatment effect was not statistically significant (Figure 25a).

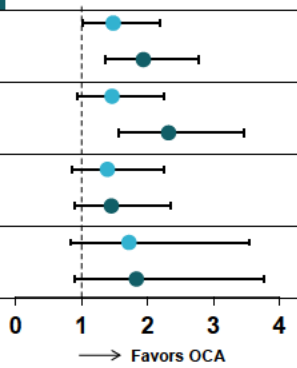
The primary efficacy endpoint results based on the Consensus Method for the ITT_old population (N=931) were also consistent with the ITT_histology population (N=1607) (Figure 25b). A dose-response was also observed in both populations.

Figure 25: Primary Efficacy Endpoints from Baseline to Month 18: Study 303 ITT_old (N=931) and ITT_histology (N=1607) Populations

a. ITT_old (N=931) Population: Central and Consensus Methods

Fibrosis Primary: Improvement in Fibrosis ≥1 Stage, No Worsening of NASH
NASH Primary: NASH Resolution, No Worsening of Fibrosis

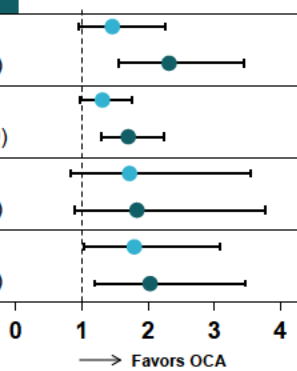
		Percent Responders			OCA vs. Placebo Odds Ratio (95% CI)	p-value
		Placebo	OCA 10 mg	OCA 25 mg		
Fibrosis Primary	Central Method	11.9% (37/311)	17.6% (55/312)	23.1% (71/308)	1.48 (1.01, 2.18)	0.0446
					1.94 (1.35, 2.78)	0.0002
	Consensus Method	9.6% (30/311)	14.1% (44/312)	22.4% (69/308)	1.46 (0.94, 2.26)	0.0863
					2.32 (1.56, 3.46)	<0.0001
NASH Primary	Central Method	8.0% (25/311)	11.2% (35/312)	11.7% (36/308)	1.39 (0.86, 2.25)	0.1814
					1.45 (0.90, 2.35)	0.1268
	Consensus Method	3.5% (11/311)	6.1% (19/312)	6.5% (20/308)	1.72 (0.83, 3.55)	0.1377
					1.83 (0.89, 3.77)	0.0926



b. ITT_old (N=931) and ITT_histology (N=1607) Populations: Consensus Method

Fibrosis Primary: Improvement in Fibrosis ≥1 Stage, No Worsening of NASH
NASH Primary: NASH Resolution, No Worsening of Fibrosis

		Percent Responders			Consensus Method OCA vs. Placebo Odds Ratio (95% CI)	p-value
		Placebo	OCA 10 mg	OCA 25 mg		
Fibrosis Primary	ITT_old (N=931)	9.6% (30/311)	14.1% (44/312)	22.4% (69/308)	1.46 (0.94, 2.26)	0.0863
					2.32 (1.56, 3.46)	<0.0001
	ITT_histology (N=1607)	12.3% (66/536)	16.2% (86/532)	21.0% (113/539)	1.31 (0.97, 1.76)	0.0736
					1.70 (1.29, 2.25)	0.0001
NASH Primary	ITT_old (N=931)	3.5% (11/311)	6.1% (19/312)	6.5% (20/308)	1.72 (0.83, 3.55)	0.1377
					1.83 (0.89, 3.77)	0.0926
	ITT_histology (N=1607)	3.5% (19/536)	6.4% (34/532)	7.2% (39/539)	1.79 (1.04, 3.09)	0.0341
					2.03 (1.19, 3.48)	0.0078



IA=interim analysis; ITT=Intent-to-Treat; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; TZD=thiazolidinedione

Notes: The Original Analysis used the Central Method to read liver biopsies. The Resubmission Analysis (ITT_old population [N=931]) used the Consensus Method to re-read the same liver biopsies; histology results in ITT_histology population (N=1607) are based on Consensus Method.
Any patient with a missing Month 18 biopsy was considered as a nonresponder.

OCA / Placebo Odds Ratio = Percentage of Responders in Active Treatment Arm / Percentage of Responders in Placebo, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no); the Mantel-Haenszel estimate of the common odds ratio and the associated asymptotic CIs are reported.

p-value versus Placebo: Using the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).

5.1.4.1.2. Secondary and Other Histological Endpoints

Results of the secondary and other fibrosis-related histological endpoints (i.e., improvement of fibrosis by ≥1 stage and by ≥2 stages and shifts in fibrosis by ≥1 stage) further support the robust clinically meaningful antifibrotic effect of OCA (reversal of fibrosis and fewer patients with worsening of fibrosis) beyond the primary endpoint. For all endpoints measuring improvement of fibrosis in the ITT_old population (N=931), the observed overall response rates were higher in the OCA 25 mg group relative to the OCA 10 mg group, and both were higher compared to placebo, confirming the dose-response.

Based on the Consensus Method, approximately twice as many patients had improvement of fibrosis by ≥1 stage and ≥2 stages in the OCA 25 mg group compared with placebo, independent of NASH. The proportion of patients attaining an improvement in fibrosis of ≥1 stage at Month 18, regardless of NASH, was 29.5% in the OCA 25 mg group compared with 15.8% in the placebo group. These results based on the Consensus Method (Resubmission Analysis) are highly consistent with the Central Method (Original Analysis) (Figure 26a).

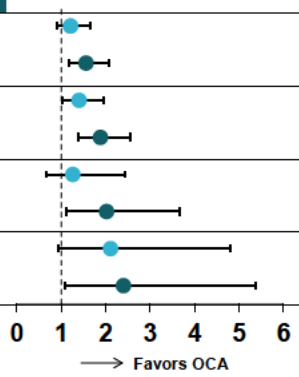
The results for the improvement of fibrosis by ≥1 stage or ≥2 stage based on the Consensus Method observed for the ITT_histology population (N=1607) were consistent with the ITT_old population (N=931) (Figure 26b).

Figure 26: Key Secondary Histology Endpoints from Baseline to Month 18: Study 303 ITT_old (N=931) and ITT_histology (N=1607) Populations

a. ITT_old (N=931) Population: Central and Consensus Methods

Fibrosis Secondary: Improvement in Fibrosis ≥1 Stage and ≥2 Stages

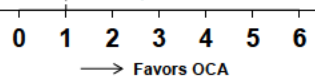
Improvement in:		Percent Responders: Placebo	OCA 10 mg	OCA 25 mg	OCA vs. Placebo Odds Ratio (95% CI)	p-value
≥1 Stage	Central Method	19.3% (60/311)	23.4% (73/312)	30.2% (93/308)	1.21 (0.90, 1.64)	0.2113
					1.56 (1.18, 2.07)	0.0016
	Consensus Method	15.8% (49/311)	22.1% (69/312)	29.5% (91/308)	1.40 (1.01, 1.95)	0.0435
					1.88 (1.38, 2.55)	<0.0001
≥2 Stages	Central Method	4.8% (15/311)	6.1% (19/312)	9.7% (30/308)	1.26 (0.65, 2.42)	0.4918
					2.02 (1.11, 3.66)	0.0183
	Consensus Method	2.6% (8/311)	5.4% (17/312)	6.2% (19/308)	2.11 (0.93, 4.79)	0.0685
					2.40 (1.07, 5.37)	0.0281



b. ITT_old (N=931) and ITT_histology (N=1607) Populations: Consensus Method

Fibrosis Secondary: Improvement in Fibrosis ≥1 Stage and ≥2 Stages

Improvement in:		Percent Responders: Placebo	OCA 10 mg	OCA 25 mg	Consensus Method: OCA vs. Placebo Odds Ratio (95% CI)	p-value
≥1 Stage	ITT_old (N=931)	15.8% (49/311)	22.1% (69/312)	29.5% (91/308)	1.40 (1.01, 1.95)	0.0435
					1.88 (1.38, 2.55)	<0.0001
	ITT_histology (N=1607)	18.5% (99/536)	24.1% (128/532)	28.2% (152/539)	1.30 (1.03, 1.64)	0.0264
					1.52 (1.22, 1.91)	0.0002
≥2 Stages	ITT_old (N=931)	2.6% (8/311)	5.4% (17/312)	6.2% (19/308)	2.11 (0.93, 4.79)	0.0685
					2.40 (1.07, 5.37)	0.0281
	ITT_histology (N=1607)	2.4% (13/536)	6.4% (34/532)	6.5% (35/539)	2.61 (1.40, 4.88)	0.0017
					2.64 (1.42, 4.91)	0.0013



IA=interim analysis; ITT=Intent-to-Treat; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; TZD=thiazolidinedione

Notes: The Original Analysis used the Central Method to read liver biopsies. The Resubmission Analysis (ITT_old population [N=931]) used the Consensus Method to re-read the same liver biopsies; histology results in ITT_histology population are based on Consensus Method (N=1607).

Any patient with a missing Month 18 biopsy was considered as a nonresponder.

OCA / Placebo Odds Ratio = Percentage of Responders in Active Treatment Arm/Percentage of Responders in Placebo, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no); the Mantel-Haenszel estimate of the common odds ratio and the associated asymptotic CIs are reported.

p-value versus Placebo: Using the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).

The analysis of shift in fibrosis stage is an additional supportive efficacy measure as it considers both improvement as well as worsening in fibrosis in patients with both baseline and post-baseline biopsies (e.g., excluding missing Month 18 biopsies).

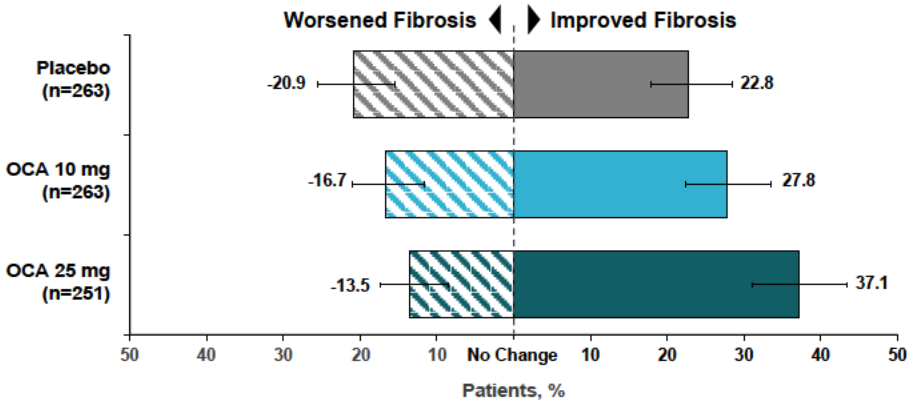
In the ITT_old population (N=931), based on the Consensus Method (Figure 27b), twice as many patients in the OCA 25 mg group achieved improved fibrosis (37.3%) as opposed to worsening fibrosis (17.6%), whereas, a similar percentage of patients achieved improvement (19.8%) versus worsening (23.8%) in the placebo group. Of note, a greater proportion of patients in the placebo group had a worsening of fibrosis stage at Month 18 compared to subjects in the OCA 25 mg group. Of the patients with F2 at baseline, 31% of patients from the placebo group progressed ≥1 stage at Month 18, compared to 20% of patients in the OCA 25 mg group. These results are clinically meaningful because patients with stable disease or reversal are less likely to progress to cirrhosis and experience adverse outcomes.

For patients with no change in fibrosis by ≥1 stage at Month 18, there was a trend towards improvement in transient elastography (TE) for OCA 25 mg compared to placebo (Section 5.1.4.2.2.1).

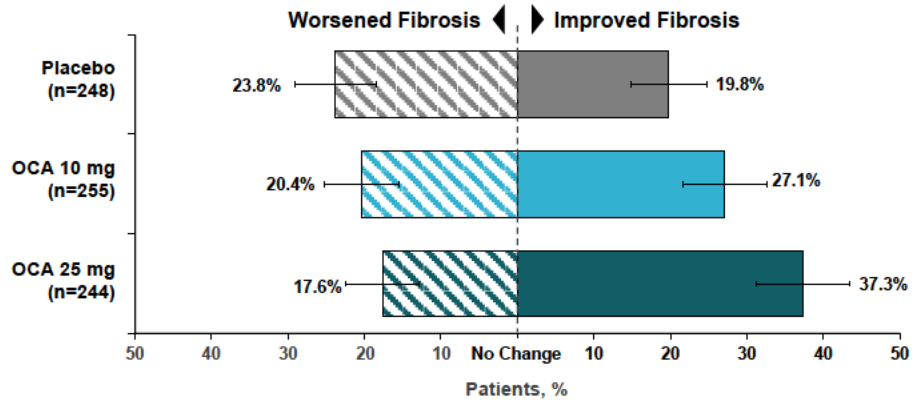
Similar results were observed for the ITT_old population (N=931) based on the Central Method (Original Analysis) (Figure 27a), as well as with the ITT_histology population (N=1607) (Figure 27c).

Figure 27: Fibrosis Shift Analysis from Baseline to Month 18 by Central and Consensus Methods: Study 303 ITT_old (N=931) and ITT_histology (N=1607) Populations, Baseline and Postbaseline

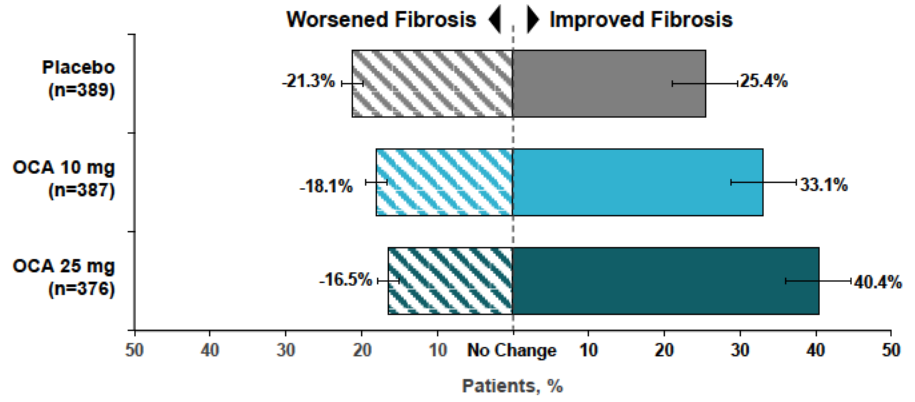
a. ITT old (N=931) Population: Central Method



b. ITT old (N=931) Population: Consensus Method



c. ITT histology (N=1607) Population: Consensus Method



IA=interim analysis; ITT=Intent-to-Treat; OCA=obeticholic acid

Notes: n indicates number of patients with both baseline and post-baseline biopsies, which is used for the denominator in calculating percentages.

Any patient with a missing Month 18 biopsy was considered as a nonresponder.

5.1.4.2. Additional Evidence from Non-Histologic Exploratory Endpoints

OCA improves liver biochemistries and noninvasive imaging assessments of fibrosis in a dose-dependent manner, reinforcing the totality of benefit of OCA.

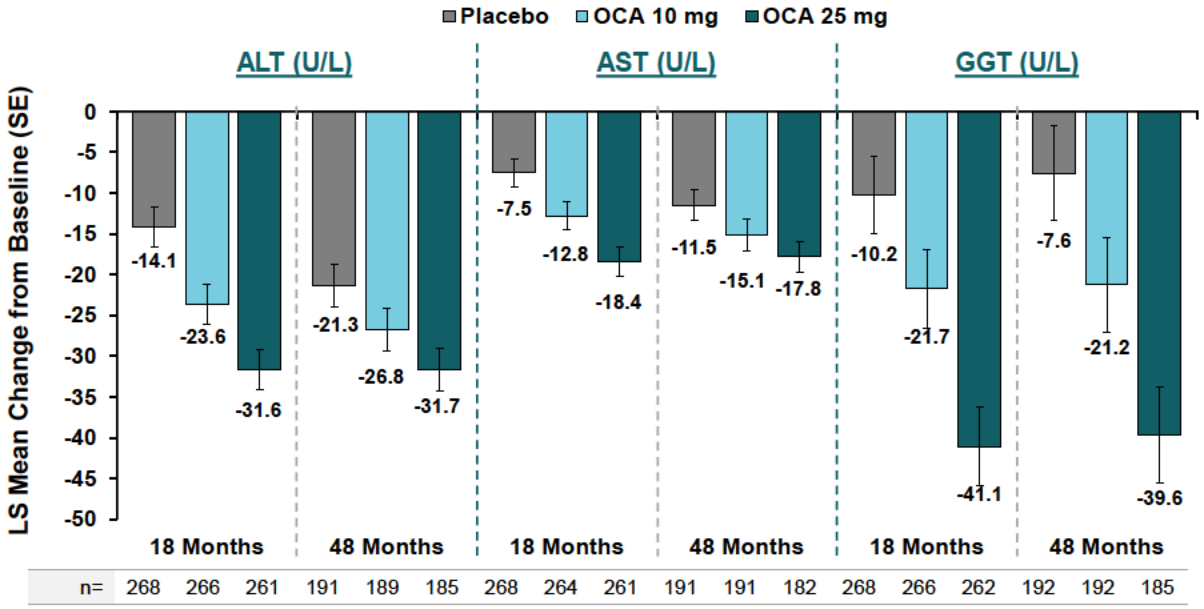
- Dose-dependent improvements in markers of hepatocellular injury (ALT, AST) and oxidative stress (GGT) at Month 18, that were sustained at Month 48, suggest long-term improvement and potentially a clinically meaningful impact on underlying liver injury. Observed improvements in NITs may predict improved outcomes in patients who were not considered histologic responders at Month 18.
- Improvements with OCA were also observed for multiple noninvasive markers of fibrosis, including imaging markers evaluating liver stiffness (TE) and serum-based composite markers (FIB-4, ELF, and APRI).
- In clinical practice, these NITs can supplement, and in many cases obviate, the need for histological assessment of fibrosis. All of these NITs can be measured repeatedly over time, allowing for greater ability to monitor change and therefore, provide information about disease progression.

5.1.4.2.1. Liver Biochemistry and Liver Function Over Time

In the ITT_old (N=931) population, OCA treatment produced dose-dependent reductions in mean ALT, AST, and GGT levels at Months 18 and 48 (Figure 28). In line with FXR agonist pharmacology (Patel 2020, Ratziu 2022a, Ratziu 2022b, Schramm 2022), increases in mean ALP levels were observed in patients treated with OCA 25 mg, and to a lesser extent OCA 10 mg, at Month 18, which were sustained at Month 48. Despite the increase observed with OCA 25 mg, mean ALP levels remained within normal limits. Mean total and direct bilirubin levels remained within normal limits at both timepoints (Month 18 and 48) across the 3 treatment groups (Table 6).

Similar trends in liver biochemistry and liver function assessments over time were observed for the ITT_all (N=2187) population (Appendix B).

Figure 28: LS Mean (SE) Change from Baseline in ALT, AST, and GGT at Months 18 and 48: Study 303 ITT_old Population (N=931)



ITT=intent-to-treat; LS=least squares; OCA=obeticholic acid; TE=transient elastography

Note: Patients with ALT assessments at baseline and Month 18 or Month 48.

Note: LSM and 95% CI were calculated using a mixed effect repeated measures model with an unstructured covariance structure and treatment group, visit, visit by treatment interaction, and stratification factors as fixed effects and baseline as a covariate.

Table 6: Liver Biochemistry and Liver Function at Month 18 and Month 48: Study 303 ITT_old Population (N=931)

	Placebo (N=311)		OCA 10 mg (N=312)		OCA 25 mg (N=308)	
	Month 18	**Month 48**	**Month 18**	**Month 48**	**Month 18**	**Month 48**
ALT (U/L)	268	191	266	189	261	185
Baseline Mean (SD)[a]	79.6 (56.67)		75.6 (46.96)		80.4 (56.74)	
LS Mean Change from Baseline[b] (SE)	-14.1 (2.44)	-21.3 (2.59)	-23.6 (2.45)	-26.8 (2.61)	-31.6 (2.46)	-31.7 (2.62)
95% CI of LSM	(-18.9, -9.3)	(-26.4, -16.2)	(-28.4, -18.8)	(-32.0, -21.7)	(-36.4, -26.8)	(-36.9, -26.6)
AST (U/L)	268	191	264	191	261	182
Baseline Mean (SD)[a]	58.9 (40.54)		56.6 (34.04)		57.1 (34.17)	
LS Mean Change from Baseline[b] (SE)	-7.5 (1.74)	-11.5 (1.90)	-12.8 (1.75)	-15.1 (1.91)	-18.4 (1.75)	-17.8 (1.93)
95% CI of LSM	(-10.9, -4.1)	(-15.3, -7.8)	(-16.2, -9.4)	(-18.9, -11.4)	(-21.8, -15.0)	(-21.6, -14.0)
GGT (U/L)	268	192	266	192	262	185
Baseline Mean (SD)[a]	101.9 (128.98)		99.6 (108.33)		95.6 (116.52)	
LS Mean Change from Baseline[b] (SE)	-10.2 (4.80)	-7.6 (5.80)	-21.7 (4.81)	-21.2 (5.82)	-41.1 (4.81)	-39.6 (5.87)
95% CI of LSM	(-19.6, -0.8)	(-19.0, 3.8)	(-31.1, -12.2)	(-32.6, -9.8)	(-50.6, -31.7)	(-51.1, -28.0)
ALP (U/L)	268	192	266	192	262	185
Baseline Mean (SD)[a]	89.3 (33.62)		87.6 (29.26)		89.5 (35.35)	
LS Mean Change from Baseline[b] (SE)	-1.4 (1.56)	-0.9 (1.80)	6.2 (1.56)	6.8 (1.80)	15.1 (1.56)	12.2 (1.82)
95% CI of LSM	(-4.5, 1.6)	(-4.4, 2.7)	(3.1, 9.3)	(3.2, 10.3)	(12.0, 18.2)	(8.7, 15.8)

	Placebo (N=311)		OCA 10 mg (N=312)		OCA 25 mg (N=308)	
	Month 18	**Month 48**	**Month 18**	**Month 48**	**Month 18**	**Month 48**
Total Bilirubin (mg/dL)	268	191	266	189	261	185
Baseline Mean (SD)[a]	0.640 (0.278)		0.649 (0.300)		0.689 (0.340)	
LS Mean Change from Baseline[b] (SE)	0.041 (0.0150)	0.035 (0.0181)	0.034 (0.0150)	0.013 (0.0182)	0.003 (0.0151)	-0.040 (0.0183)
95% CI of LSM	(0.012, 0.071)	(0.000, 0.070)	(0.004, 0.063)	(-0.023, 0.049)	(-0.026, 0.033)	(-0.076, -0.004)
Direct Bilirubin (mg/dL)	260	186	257	185	253	179
Baseline Mean (SD)[a]	0.250 (0.091)		0.254 (0.092)		0.264 (0.109)	
LS Mean Change from Baseline[b] (SE)	0.012 (0.0063)	0.018 (0.0064)	0.004 (0.0063)	0.015 (0.0064)	-0.002 (0.0063)	-0.005 (0.0064)
95% CI of LSM	(0.000, 0.024)	(0.006, 0.031)	(-0.008, 0.017)	(0.002, 0.027)	(-0.015, 0.010)	(-0.018, 0.008)

ITT=intent-to-treat; LS=least squares; LSM=least squares mean; OCA=obeticholic acid; SD=standard deviation

[a] Baseline was defined as the mean of all measurements prior to first dose of investigational product.

[b] LSM and 95% CI were calculated using a mixed effect repeated measures model with an unstructured covariance structure and treatment group, visit, visit by treatment interaction, and stratification factors as fixed effects and baseline as a covariate.

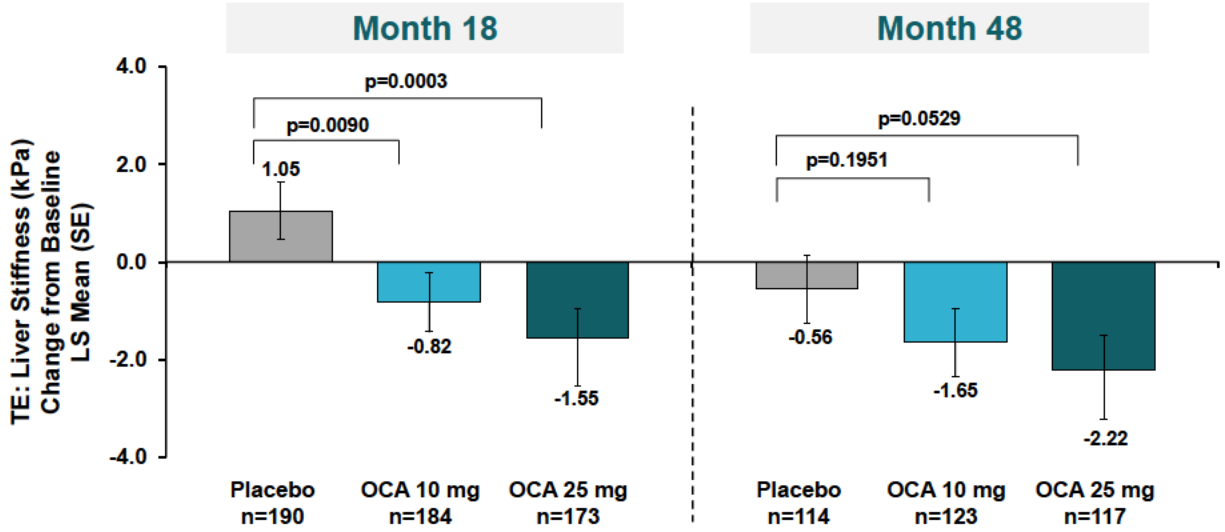
5.1.4.2.2. Imaging Based Marker of Fibrosis: Transient Elastography

Liver stiffness as measured by vibration-controlled TE (FibroScan®) is a noninvasive, point-of-care test providing reliable quantification of hepatic fibrosis in patients with chronic liver diseases (Eddowes 2019).

In the ITT_old population (N=931), mean baseline liver stiffness ranged from 11.98 to 12.50 kPa across treatment groups, consistent with pre-cirrhotic fibrosis (Table 5).

As shown in Figure 29, dose-dependent improvements in liver stiffness were observed with OCA treatment at Month 18 compared to placebo, which persisted at Month 48. At Month 18, the LS mean difference from placebo in liver stiffness values was -1.87 kPa (95% CI: -3.27, -0.47) for OCA 10 mg and -2.61 kPa (-4.03, -1.18) for OCA 25 mg. At Month 48, the LS mean difference from placebo in liver stiffness values was -1.09 kPa (95% CI: -2.75, 0.56) for OCA 10 mg and -1.66 kPa (-3.34, 0.02) for OCA 25 mg.

Figure 29: LS Mean (SE) Change from Baseline in Liver Stiffness (TE) at Month 18 and Month 48: Study 303 ITT_old Population (N=931)



ITT=intent-to-treat; OCA=obeticholic acid; TE=transient elastography

Similar results were observed for the ITT_histology (N=1607) and ITT_all (N=2187) populations.

5.1.4.2.2.1. Change from Baseline in Liver Stiffness by Fibrosis Responder Status at Month 18

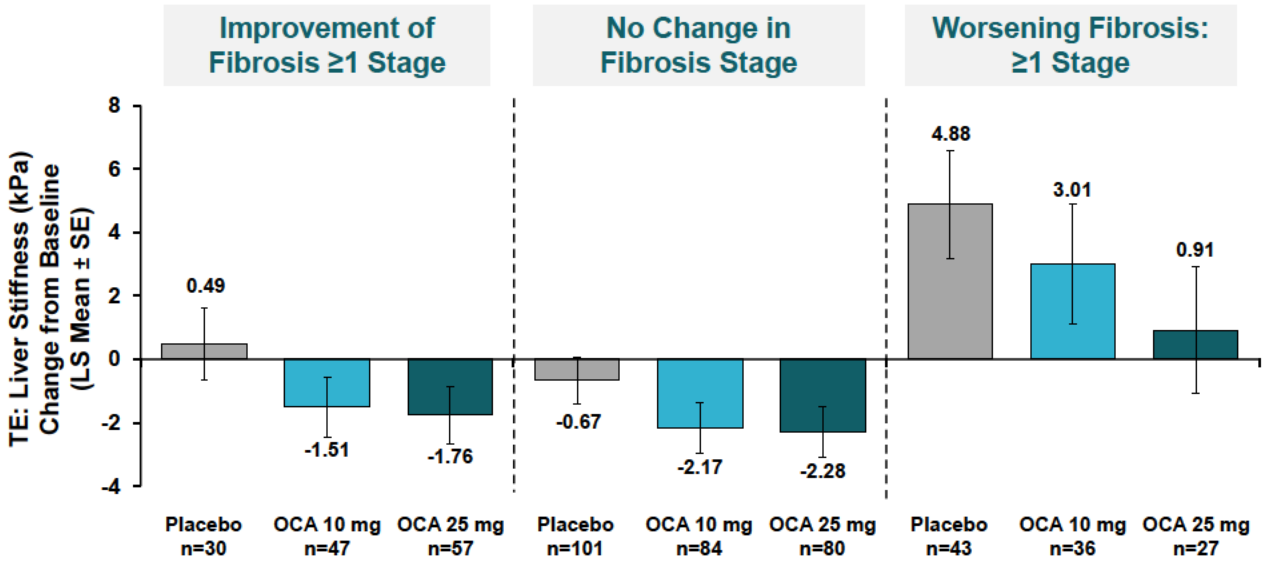
Change from baseline to Month 18 in liver stiffness (as measured by TE, Fibroscan®) was evaluated by histologic fibrosis responder status as measured by the Consensus Method in the ITT_old population (N=931). In this assessment, the liver biopsy responder analysis at Month 18 was subdivided into 3 categories:

- improvement (defined as improvement in fibrosis by ≥1 stage),
- worsening (defined as worsening in fibrosis by ≥1 stage), or
- no change in fibrosis.

Improvements in liver stiffness values at Month 18 relative to baseline were observed in patients with improvement in fibrosis (for both OCA groups) and with no changes in fibrosis (for all 3 treatment groups) (Figure 30). Liver stiffness values worsened at Month 18 in patients with worsening in fibrosis regardless of treatment group.

These results support a correlation between histologic change in fibrosis and a change in liver stiffness, as measured by TE, and highlight the loss of information when assessing endpoints on an ordinal scale such as the NASH CRN scoring. Even in patients with histologically "no change" in fibrosis, liver stiffness (and other NIT scores) were reduced in all treatment groups and reduced more in patients treated with OCA. Most notably, even in patients with worsening in fibrosis by ≥1 stage, subjects treated with OCA had less of an increase in liver stiffness than subjects treated with placebo.

Figure 30: LS Mean (SE) Change from Baseline in Liver Stiffness (TE) by Fibrosis Responder Status Based on Consensus Method at Month 18: Study 303 ITT_old Population (N=931)

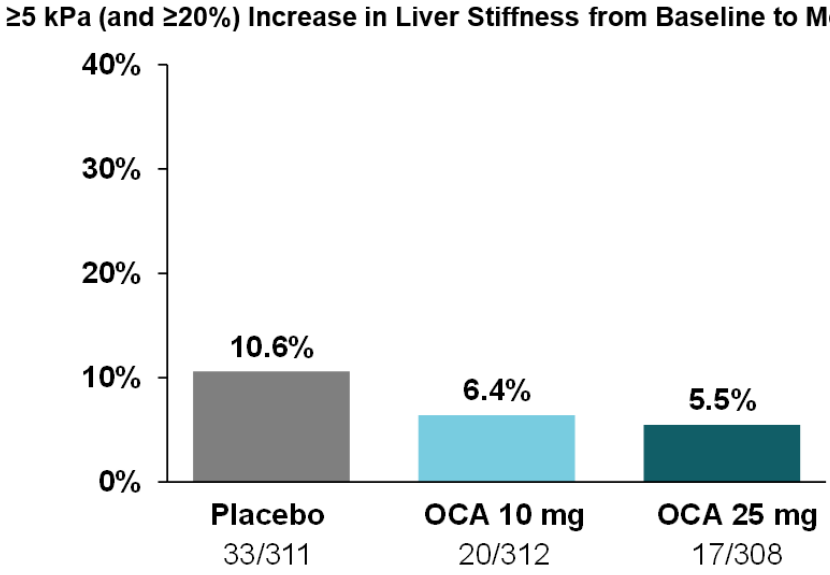


ITT=intent-to-treat; LS=least squares; OCA=obeticholic acid; TE=transient elastography

5.1.4.2.2.2. Evaluation of Worsening of Fibrosis Liver Stiffness Measurement by Transient Elastography as a Predictor of Progression to Cirrhosis

A recent peer-reviewed publication observed that an increase in liver stiffness of ≥5 kPa (and ≥20%), as measured by TE (FibroScan), is associated with an increased risk of progression to cirrhosis in patients with stage 3 (bridging) fibrosis due to NASH, with an adjusted hazard ratio of 1.98 (95% CI 1.20 to 3.26; p=0.008) (Loomba 2023). Applying this threshold to the Study 303 ITT_old population (N=931), nearly twice as many patients in the placebo group (10.6%) had a ≥5 kPa (and ≥20%) increase in liver stiffness compared to OCA 25 mg (5.5%) (Figure 31) further supporting that OCA 25 mg will reduce the number of patients with NASH progressing to cirrhosis.

Figure 31: Percent of Patients with ≥5 kPa and ≥20% Increase in Liver Stiffness (TE) at Month 18: Study 303 ITT_old Population (N=931)



ITT=intent-to-treat; LS=least squares; OCA=obeticholic acid; TE=transient elastography
Notes: A ≥5 kPa (and ≥20%) increase in liver stiffness (TE) is a strong independent predictor of progression to cirrhosis (Loomba 2023).

5.1.4.2.3. Serum-based Imaging Markers of Fibrosis: FIB-4, ELF, and APRI

OCA treatment was associated with improvements in several serum-based clinical markers (FIB-4, ELF, and APRI):

- Small dose-dependent improvements in FIB-4 were observed for OCA-treated patients at Month 18, while sustained improvement with OCA 25 mg was not observed at Month 48. Interpretation of changes in FIB-4 indices over time should be interpreted with caution as FIB-4 calculations can be confounded by advancing age.
- Improvements in ELF scores were observed for OCA-treated patients at Month 18 and for OCA 25 mg at Month 48 compared to worsening in placebo-treated patients. Decreases in ELF scores at Month 18 relative to baseline were observed in patients with improvement in fibrosis and no changes in fibrosis for all 3 treatment groups.
- Improvement in APRI over time was observed with OCA treatment, with the majority of response achieved within the first year.

5.1.5. Persistence of Efficacy and Potential Factors Affecting Treatment Effect

5.1.5.1. Persistence of Efficacy

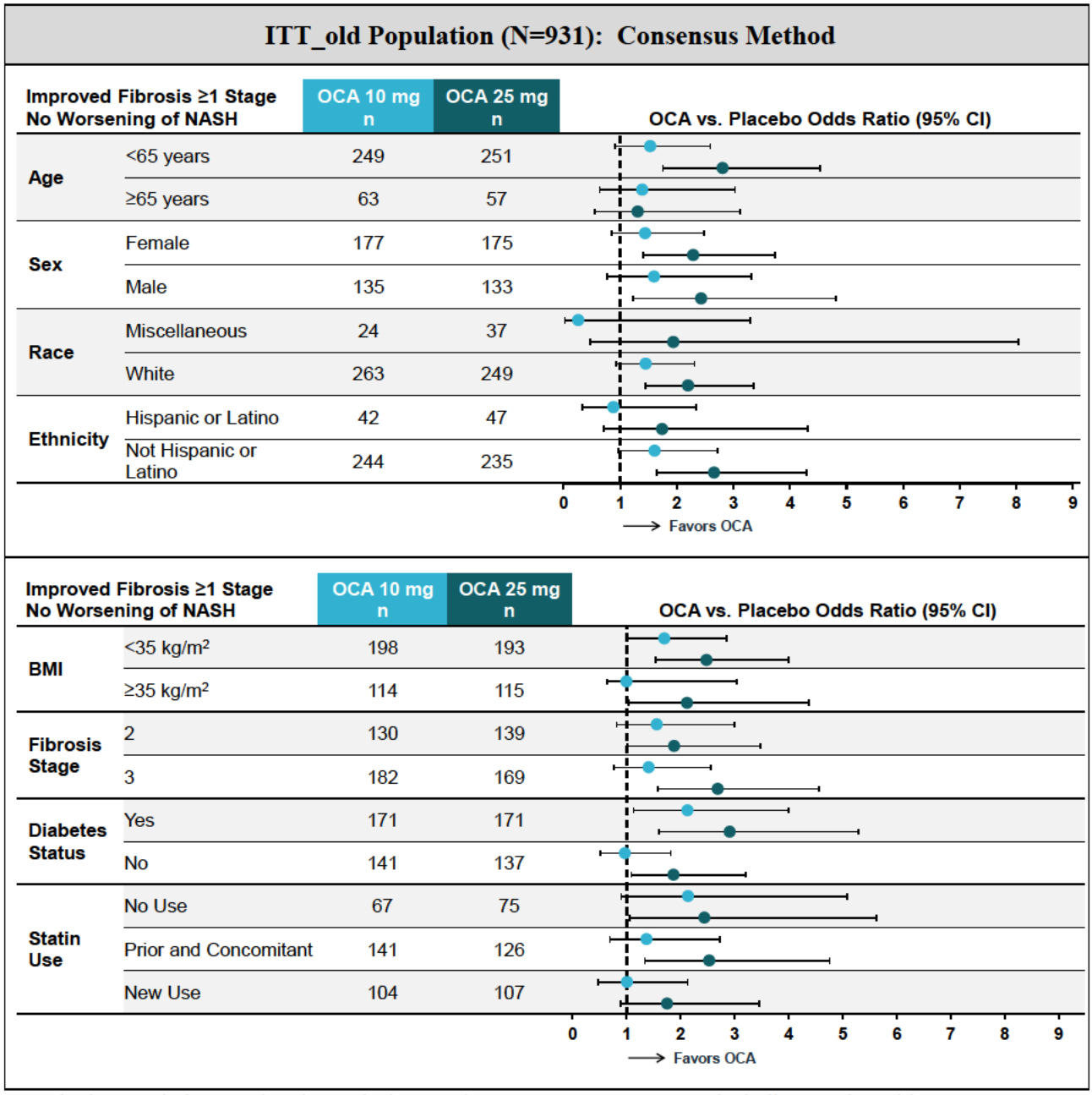
The Resubmission Analysis suggests persistent OCA benefits through Month 48. Long-term treatment benefits that OCA provides as shown with noninvasive markers of liver biochemistry (Section 5.1.4.2.1) and liver stiffness (Section 5.1.4.2.2) support the antifibrotic efficacy seen by histology after 18 months of treatment and supports the latter are reasonably likely to predict clinically meaningful benefits of OCA. The persistence of histologic response will continue to be evaluated as part of the EOS analysis for Study 303.

5.1.5.2. Potential Factors Affecting Treatment Effect

In Study 303, the primary efficacy endpoints were analyzed for a number of subgroups based on intrinsic (age, sex, race, ethnicity, BMI, fibrosis stage, and type 2 diabetes) and extrinsic factors (concomitant medication use for common comorbidities associated with NASH).

Results based on baseline intrinsic and extrinsic factor subgroups based on the Consensus Method (Resubmission Analysis) are summarized in Figure 32 for the ITT_old population (N=931). While interpretation of the results for some of the subgroups is limited by small sample sizes, where sufficient data exist for interpretation (e.g., sex, diabetes at baseline, baseline fibrosis stage, and statin use), the directionality and magnitude of response relative to placebo were generally consistent across a broad population of patients and when analyzed. The dose-response relationship observed in the overall population was also apparent within most of the subgroup analyses.

Figure 32: Subgroup Analysis of Primary Efficacy Fibrosis Endpoint at Month 18 by Consensus Method: Study 303 ITT_old Population (N=931)



BMI=body mass index; IA=interim analysis; ITT=intent-to-treat; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid

Note: For Race, Miscellaneous includes American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and Other.

For the Month 18 IA ITT_old population (N=931), the results based on the Consensus Method (Resubmission Analysis) are highly consistent with the results based on the Central Method (Original Analysis), as well as the results for the ITT_histology population (N=1607).

The totality of the results suggests that OCA shows benefit in the diverse population of patients with pre-cirrhotic fibrosis due to NASH.

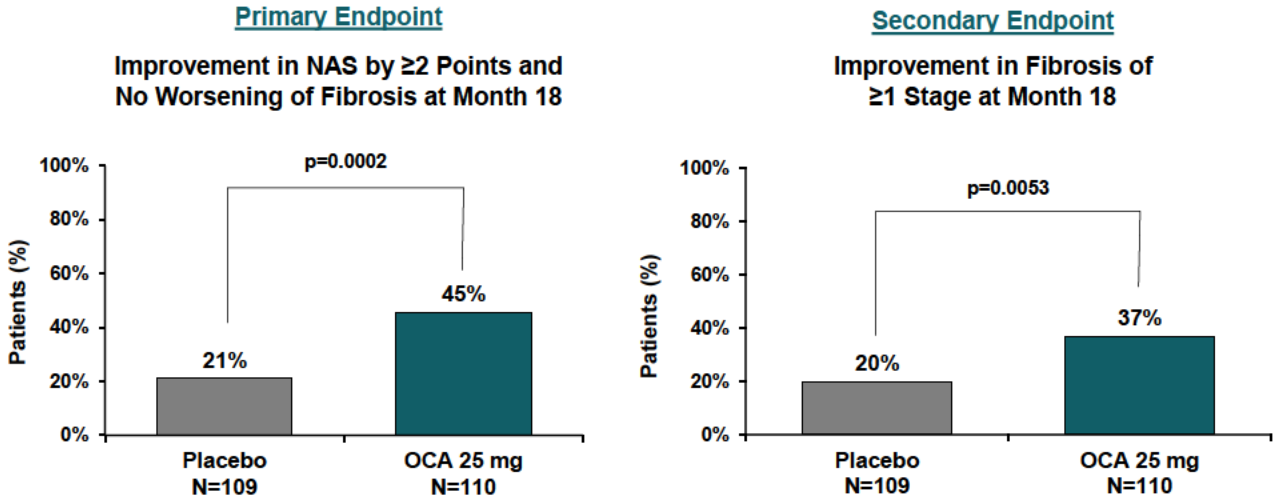
5.2. FLINT

FLINT was the first clinical study to demonstrate an improvement in fibrosis-related efficacy by pharmacologic intervention and led to Breakthrough Therapy designation being granted to OCA in NASH fibrosis in 2015. This randomized, DB, placebo-controlled, 18-month study included patients with biopsy-confirmed NASH and a NAS ≥4, with a broader spectrum of fibrosis stages (F1 to F4) compared to Study 303 Month 18 IA (F2 to F3).

FLINT was stopped early after a pre-specified IA demonstrated that OCA met the primary endpoint an improvement in NAS of ≥2 points with no worsening of fibrosis compared to placebo (Figure 33). Following 18 months of treatment, over twice as many OCA-treated patients had an improvement in the primary endpoint compared to placebo. The treatment difference with OCA 25 mg compared to placebo was nearly 25% (p=0.0002).

OCA 25 mg also improved fibrosis, a pre-specified secondary endpoint in FLINT, with 37% of patients treated with OCA showed ≥1-stage improvement in fibrosis, compared to 20% with placebo (p=0.0053) (Figure 33).

Figure 33: Improvement in NAS by ≥2 Points with No Worsening of Fibrosis at Month 18: FLINT mITT Population (N=219)



EOT=End-of-Treatment; NAFLD=nonalcoholic fatty liver disease; NAS=NAFLD Activity Score; OCA=obeticholic acid

Note: The mITT population (N=219) included all patients from the ITT population except those who did not receive an EOT biopsy due to protocol modification after the efficacy stopping criteria were met were included.

5.3. Summary of Clinical Efficacy and Clinical Utility of OCA

The primary fibrosis endpoint was achieved in Study 303, with the statistically significant effect of OCA 25 mg observed in the original analysis now confirmed using the Consensus Method, with a similar observed doubling of the responder rate compared to placebo. Consistent dose-related efficacy was observed across other fibrosis histologic endpoints, which suggests the antifibrotic effect of OCA includes both reversal of fibrosis and slowed progression of fibrosis. Liver

biochemistry and noninvasive markers further support the antifibrotic effect and demonstrate persistence of effect at Month 48, even in patients who did not meet histologic criteria for a full stage of antifibrotic benefit at Month 18. The clinically meaningful antifibrotic effect of OCA 25 mg was also demonstrated in FLINT.

The totality of efficacy evidence suggests that the benefit of OCA 25 mg for the primary histological endpoint is clinically significant and that a greater proportion of patients are likely to experience benefits beyond those captured by this primary endpoint. Collectively, the observed improvements in the histology and non-invasive endpoints are reasonably likely to predict clinical benefit to support accelerated approval of OCA 25 mg for the treatment of patients with pre-cirrhotic fibrosis due to NASH.

6. CLINICAL SAFETY

An updated Pooled Safety Population was used to assess overall safety data, including an integrated assessment of safety data all from the 3 long-term, DB, placebo-controlled studies in patients with liver fibrosis due to NASH (Study 303, FLINT, and 2001). The majority of updates to the integrated analysis are from the ongoing pivotal Phase 3 study (Study 303) with a DCO of 31 Dec 2021. The median duration of OCA exposure in the Pooled Safety Population was approximately 37 months (3.09 and 3.08 years in OCA 10 mg and OCA 25 mg groups, respectively), with approximately 700 patients across OCA treatment groups (including 335 patients in the OCA 25 mg group) having ≥4 years of exposure, which well exceeds the International Conference on Harmonisation (ICH) requirement for a therapeutic indicated for a chronic disease and is aligned with the projected exposure that was discussed during the pre-NDA meeting in July 2022.

The safety analysis included a robust evaluation of AESIs including included hepatic and gallstone-related events (including pancreatitis), CV safety (including the impact of lipids and glycemic markers), renal events (including urolithiasis), and pruritus. Additionally, 3 independent and blinded expert adjudication committees were utilized to evaluate CV events (CAC), hepatic safety/potential DILI events (HSAC), and renal safety/AKI events (RAC).

6.1. Extent of Exposure

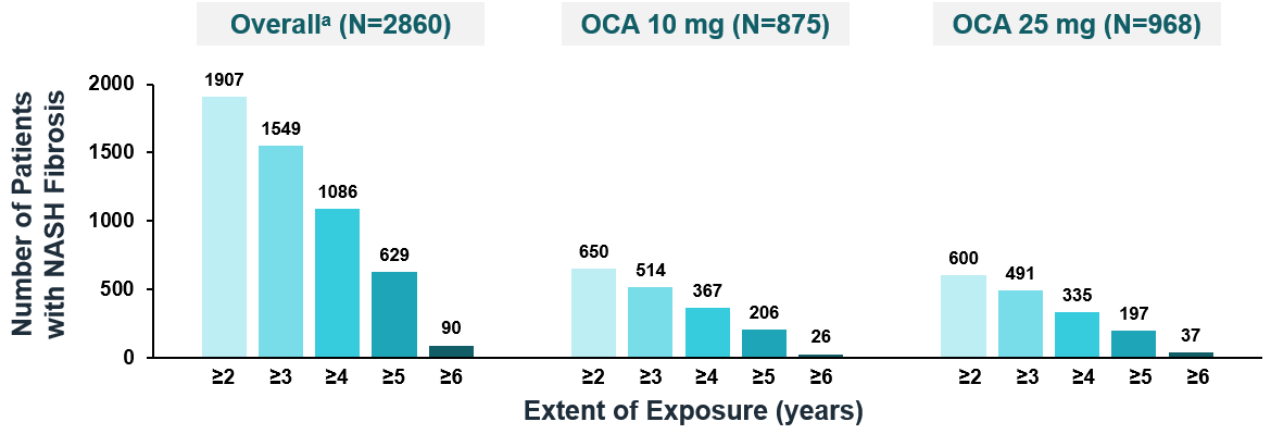
Study 303 represents the majority of safety data within the resubmission, including a total of 1652 patients with fibrosis due to NASH (825 patients and 827 patients in the OCA 10 mg and OCA 25 mg groups, respectively) who received at least a single dose of OCA. This represents an increase in exposure of more than 3-fold since the original NDA, which reported a total exposure of 2400 patient-years. The median duration of exposure in Study 303 was generally similar in the placebo (1238.0 days), OCA 10 mg (1177.0 days), and OCA 25 mg (1125.0 days) groups (i.e., approximately 39 months [3.25 years]). The total exposure excluding drug holidays, missed doses, and temporary interruptions was 7323 patient-years. Total exposure including drug holidays, missed doses, and temporary interruptions was 8054 patient-years overall, which was the calculation method used in the original NDA.

- The majority (≥59%) of patients had ≥36 months (i.e., 3 years) of exposure.
- Approximately 700 patients across OCA treatment groups (including 335 patients in the OCA 25 mg group) had ≥4 years of exposure, exceeding the ICH requirement for a therapeutic indicated for a chronic disease.
- At the highest dose (OCA 25 mg), 725 patients were treated for ≥6 months, 676 patients were treated for ≥12 months, 600 patients were treated for ≥2 years, 335 patients were treated for ≥4 years, 197 patients were treated for ≥5 years, and 37 patients were treated for ≥6 years.

In the Pooled Safety Population, a total of 1843 patients with fibrosis due to NASH received at least a single dose of OCA across the DB, placebo-controlled studies.

- A total of approximately 700 patients had ≥4 years of exposure across the OCA treatment groups (Figure 34).
- The median duration of OCA exposure was approximately 37 months (3.09 and 3.08 years in OCA 10 mg and OCA 25 mg groups, respectively) (Table 7).

Figure 34: Exposure: Pooled Safety Population (N=2860)



OCA=obeticholic acid
[a] Overall includes placebo, OCA 10 mg, and OCA 25 mg groups.

Table 7: Number of Days on Investigational Product: Pooled Safety Population (N=2860)

	Resubmission Analysis DCO 31DEC2021		
	Placebo	**OCA 10 mg**	**OCA 25 mg**
	N=1017 n (%)	**N=875 n (%)**	**N=968 n (%)**
Number of Days on Investigational Product[a]			
Mean (SD)	1131.7 (578.67)	1105.9 (570.31)	1065.8 (618.36)
Median	1185.0	1128.0	1125.0
(Q1, Q3)	627.0, 1646.0	563.0, 1618.0	524.0, 1611.0
Min, Max	1, 2200	2, 2197	1, 2201
Patient Exposure Years[b]			
Median	3.24	3.09	3.08

DCO=data cutoff; IP=investigational product; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid, SD=standard deviation; Q1=first quartile; Q3=third quartile

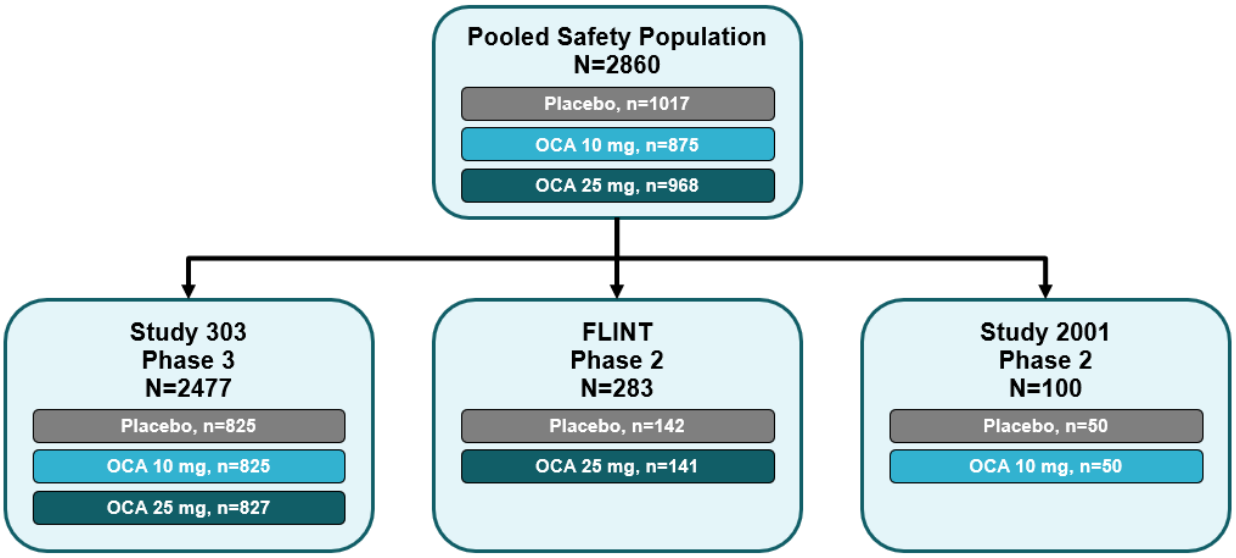
[a] Number of days on investigational product=Last dose date – First dose date + 1 – (Days on drug holiday, missed doses, or treatment interruption)

[b] Patient exposure years=Number of Days on IP/365.25

6.2. Safety Population

The Pooled Safety Population includes data from 2860 patients across 3 long-term, placebo-controlled studies in patients with pre-cirrhotic NASH (Figure 35).

Figure 35: Pooled Safety Population (N=2860)



FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; OCA=obeticholic acid

- Pooled safety data are provided when available; specific analyses have been provided based on safety data from Study 303 only (e.g., adjudicated CV and renal analyses). In general, no differences in the safety profile were observed between Study 303 and the Pooled Safety Population.
- Overall, the clinical characteristics of the Pooled Safety Population are reflective of a NASH population with pre-cirrhotic fibrosis seen in clinical practice (Rinella 2023); therefore, the study results can be extrapolated to the proposed population.
- Patients were predominantly White (85% to 89%), female (approximately 60%), and mean age was approximately 54 years, with 17% to 21% of patients ≥65 years of age.
- Most patients were obese, with approximately 70% having a BMI ≥30 kg/m^2.
- Approximately 60% of the patients had type 2 diabetes (61.1%, 62.6%, and 63.2% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively).
- Approximately 50% of patients were receiving antidiabetic medications at baseline.
- Approximately half of the patients were receiving lipid-lowering medications (including statins [52.5%, 49.8%, and 55.8%, in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively]) at baseline.
- Approximately 70% of patients had baseline eGFR values consistent with normal renal function/CKD stage G1 (74.5%, 75.0%, and 69.9% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively), approximately 24% with CKD stage G2 (22.9%, 22.7%, and 27.3% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively), and <3% with CKD stage G3a (2.3%, 2.3%, and 2.5% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively).
- As would be expected in a population with NASH fibrosis, mean baseline AST and ALT levels were elevated across treatment groups; approximately 55% to 62% of patients in each treatment group had ALT >ULN (with 5% to 9% being >3x ULN), and approximately 70% of patients had AST >ULN (with approximately 7% to 9% being >3x ULN).

6.3. General Safety Profile

An overview of TEAEs is presented in Table 8.

- The incidence rate of patients who reported a TEAE was similar across treatment groups, and the majority of TEAEs were mild to moderate in severity.
- The incidence rate of severe TEAEs was higher (27.2%) in the OCA 25 mg group compared with placebo (18.6%) and OCA 10 mg (21.0%) groups, with the difference mostly driven by pruritus.
- TEAEs leading to discontinuation of investigational product were higher in the OCA 25 mg group (21.6%) compared with the OCA 10 mg group (12.0%) and placebo (10.7%) and was largely driven by pruritus. The EAIR of TEAEs leading to discontinuation of investigational product was 3.34, 3.81, and 7.22 per 100 PYs in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively.

- An AE or suspected adverse reaction is considered "serious" by the FDA if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
  - The incidence rate of SAEs was 19.7% in the placebo group, 24.0% in the OCA 10 mg group, and 24.8% in the OCA 25 mg group. The EAIR of SAEs was 7.31, 8.67, and 10.14 per 100 PYs in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively. The numerically higher incidence rate of SAEs in the OCA 25 mg group was driven by the following PTs: pruritus (which was reported only in the OCA 25 mg group), cholecystitis, cholecystitis acute, cholelithiasis, AKI, and diabetes mellitus. Details for serious events are presented in Section 6.4.
- Twenty-nine patients experienced a TEAE leading to death (8 patients in the placebo group, 9 patients in the OCA 10 mg group, and 12 patients in the OCA 25 mg group). The EAIR of TEAEs leading to death was 0.26, 0.32, and 0.43 per 100 PYs in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively.
  - In the placebo group, 8 patients experienced TEAEs leading to death including: cardiac arrest, pneumonia viral (2 patients), bone cancer, small cell lung cancer, completed suicide (2 patients), and pancreatitis haemorrhagic.
  - In the OCA 10 mg group, 9 patients experienced TEAEs that led to death including: MI, congestive cardiomyopathy, coronavirus infection, HCC, lung adenocarcinoma, lung neoplasm, overdose of zolpidem, AKI, and completed suicide.
  - In the OCA 25 mg group, 12 patients experienced TEAEs that led to death including 1 patient with MI, myocardial ischemia, cardiac failure congestive, and acute respiratory distress syndrome; 1 patient each with cardiac arrest, cardio-respiratory arrest, acute hepatic failure, endometrial cancer metastatic, glioblastoma, and death; 1 patient with cerebrovascular accident and hypoxic-ischaemic encephalopathy; 2 patients with Corona Virus infection; and 2 patients with pneumonia viral.
  - All except 1 of the AEs leading to death were considered by the Investigator to be unlikely or not related to the investigational product. One patient, on OCA 25 mg, was found expired at home after several days by local authorities; the Investigator documented the case as unknown and possibly related to investigational product. This event was reported as verbatim term of "death" by the Investigator and has been queried to revise the reported term to the underlying event.
  - Since the Original Analysis, evidence continues to support the conclusion of no patterns between OCA and the underlying etiology of the events that led to death.
- The incidence rate of common TEAEs (affecting ≥10% of any treatment group) was generally similar across the 3 treatment groups with the exception of TEAEs in the Skin and subcutaneous tissue disorders SOC, where the incidence rate was dose-dependent, with the difference driven by events of pruritus. Common TEAEs of LDL increased in the SOC of Investigations and constipation in the SOC of Gastrointestinal disorders

were also generally more frequent with OCA as compared to placebo, but with no dose dependency.

- No clinically meaningful changes were observed for blood pressure, heart rate, or ECG. A modest decrease in body weight of 2 kg to 3 kg was observed with OCA treatment.

Table 8: Overall Summary of Treatment-Emergent Adverse Events: Pooled Safety Population (N=2860)

	Placebo N=1017 n (%)	OCA 10 mg N=875 n (%)	OCA 25 mg N=968 n (%)
Number (%) of Patients Reporting at Least One:			
TEAE	900 (88.5)	839 (95.9)	912 (94.2)
TEAE by Severity[a]			
Mild	194 (19.1)	173 (19.8)	134 (13.8)
Moderate	493 (48.5)	461 (52.7)	490 (50.6)
Severe	189 (18.6)	184 (21.0)	263 (27.2)
Life-Threatening	16 (1.6)	12 (1.4)	13 (1.3)
Death	8 (0.8)	9 (1.0)	12 (1.2)
Death (EAIR)	0.26	0.32	0.43
TEAE Leading to Discontinuation of IP[b]	94 (10.7)	105 (12.0)	179 (21.6)
TEAE Leading to Discontinuation of IP[b] (EAIR)	3.34	3.81	7.22
SAE	200 (19.7)	210 (24.0)	240 (24.8)
SAE (EAIR)	7.31	8.67	10.14

CTCAE=Common Terminology Criteria for Adverse Events; DCO=data cutoff; EAIR=exposure-adjusted incidence rate per 100 patient exposure years; FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; IP=investigational product; OCA=obeticholic Acid; SAE=serious adverse event; TEAE=treatment-emergent adverse event

[a] Patients reporting more than 1 adverse event were counted only once using the highest severity. Adverse events were graded for severity using CTCAE Version 4.03 as: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death.

[b] TEAE Leading to IP discontinuation information was not collected in FLINT.

6.4. Adverse Events of Special Interest

Specific events evaluated as AESIs based on mechanism of action (MOA), underlying comorbidities, and the known safety profile of OCA in PBC and the NASH clinical development program included:

- Hepatic safety
- CV safety (including the impact of lipids and glycemic markers)
- Renal events (including urolithiasis)
- Gallstone-related events (including pancreatitis)
- Pruritus

Pruritus and dyslipidemia were the most common AEs. Pruritus, dyslipidemia, and gallstone-related events were more likely to occur in the OCA treatment groups compared to placebo and are described as ADRs in the proposed label. A dose response was most notably observed for pruritus and gallstone-related events, as expected based on OCA's FXR agonism. No increased risk was observed for hyperglycemia, urolithiasis, or pancreatitis (Figure 10).

Rates of adjudicated CV, hepatic, and AKI events were low overall, but higher in the OCA groups compared to placebo (Figure 11).

6.4.1. Hepatic Safety

Due to an imbalance observed for hepatic events in the original NDA, with a higher incidence rate of SAEs in the OCA 25 mg group compared to placebo, a comprehensive evaluation for hepatic safety events was performed, including analysis of the following:

- Investigator-reported hepatic TEAEs (Section 6.4.1.1).
- Adjudicated hepatic safety events (Section 6.4.1.2). Hepatic events from the 2 Phase 2 studies (FLINT and Study 2001) were retrospectively adjudicated by the HSAC and pooled with adjudicated data from Study 303.
- Adjudicated hepatic safety events pre and post 2017 safety amendment (Section 6.4.1.3).
- Biochemical analyses, including eDISH (Section 6.4.1.4).

6.4.1.1. Hepatic TEAEs

Investigator-reported hepatic TEAEs are summarized in Table 9.

Table 9: Overview of Hepatic TEAEs: Pooled Safety Population (N=2860)

		Pooled		
Number of Patients with Any:		**Placebo N=1017**	**OCA 10 mg N=875**	**OCA 25 mg N=968**
Hepatic TEAEs	**n (%)**	199 (19.6)	199 (22.7)	172 (17.8)
	EAIR	7.44	8.26	6.89
Serious hepatic TEAE	**n (%)**	2 (0.2)	9 (1.0)	16 (1.7)
	EAIR	0.06	0.32	0.58
Related hepatic TEAE	**n (%)**	99 (9.7)	91 (10.4)	88 (9.1)
Hepatic TEAEs leading to withdrawal of IP	**n (%)**	25 (2.9)	26 (3.0)	22 (2.7)
Severe (Grade 3) hepatic TEAE	**n (%)**	12 (1.2)	20 (2.3)	16 (1.7)
Life-threatening (Grade 4) hepatic TEAE	**n (%)**	0	0	1 (0.1)
Hepatic TEAEs leading to death (Grade 5)	**n (%)**	0	1 (0.1)	1 (0.1)
Severe (≥Grade 3) hepatic TEAE	**n (EAIR)**	12 (0.39)	21 (0.76)	18 (0.65)

EAIR=exposure-adjusted incidence rate; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; SMQ=standardized MedDRA; TEAE=treatment-emergent adverse event

Note: Hepatic disorder TEAEs were defined as hepatic Disorders SMQ, excluding the following sub-SMQs: alcohol related, congenital, familial, neonatal, and genetic disorders of the liver, liver infections, pregnancy-related hepatic disorders.

- Of the 27 patients with Investigator-reported SAEs, 21 patients met a trigger and were referred to HSAC for adjudication. There were 16 patients whose case was consistent with potential acute liver injury.
  - 7 were adjudicated as either probably or possibly related to investigational product and 9 were unlikely related.
  - Of the 7 patients with probably or possibly related cases, 6 resolved after discontinuation of OCA and the remaining patient underwent liver transplantation (considered possibly related with diclofenac as a confounder).
- 6 of the 27 SAEs did not meet a trigger and thus were not referred to the HSAC. These events were due to disease progression (cirrhosis and HCC) rather than acute liver injury.
- Two hepatic disorder AESIs resulted in death, one in the 25 mg group (acute hepatic failure; patient presented with cholangitis, developed multisystem organ failure, and transitioned to palliative care) and one in the OCA 10 mg group (HCC). None of the fatal hepatic events were considered related to OCA treatment either by the Investigator or the independent HSAC.

6.4.1.2. Adjudicated Hepatic Safety Events: Pooled Safety Population

A rigorous adjudication process was performed to evaluate potential liver injury events in the context of drug-induced injury. Adjudication was conducted in a blinded manner by a committee that was comprised of independent hepatologists with expertise in DILI. Each case submitted for adjudication was reviewed to determine if the event met criteria for potential liver injury; then for each case, the severity of the event and relationship to investigation was assessed, adapted from the Drug Induced Liver Injury Network (DILIN) (LiverTox 2019, Rockey 2010).

Potential hepatic events were identified programmatically using SMQ searches of hepatic AEs, central and local laboratory data, and investigational product interruption records from the clinical database for hepatic injury. Hepatic AEs were defined as events included in the Hepatic Disorders SMQ, excluding the following sub-SMQs: alcohol related; congenital, familial, neonatal, and genetic disorders of the liver; liver infections; and pregnancy-related hepatic disorders. Events were reviewed in conjunction with evaluation of medical history, concomitant medications, vital signs, lab values, liver imaging and pathology reports (where available), and NITs.

The incidence rates of adjudicated hepatic events are summarized in Figure 36.

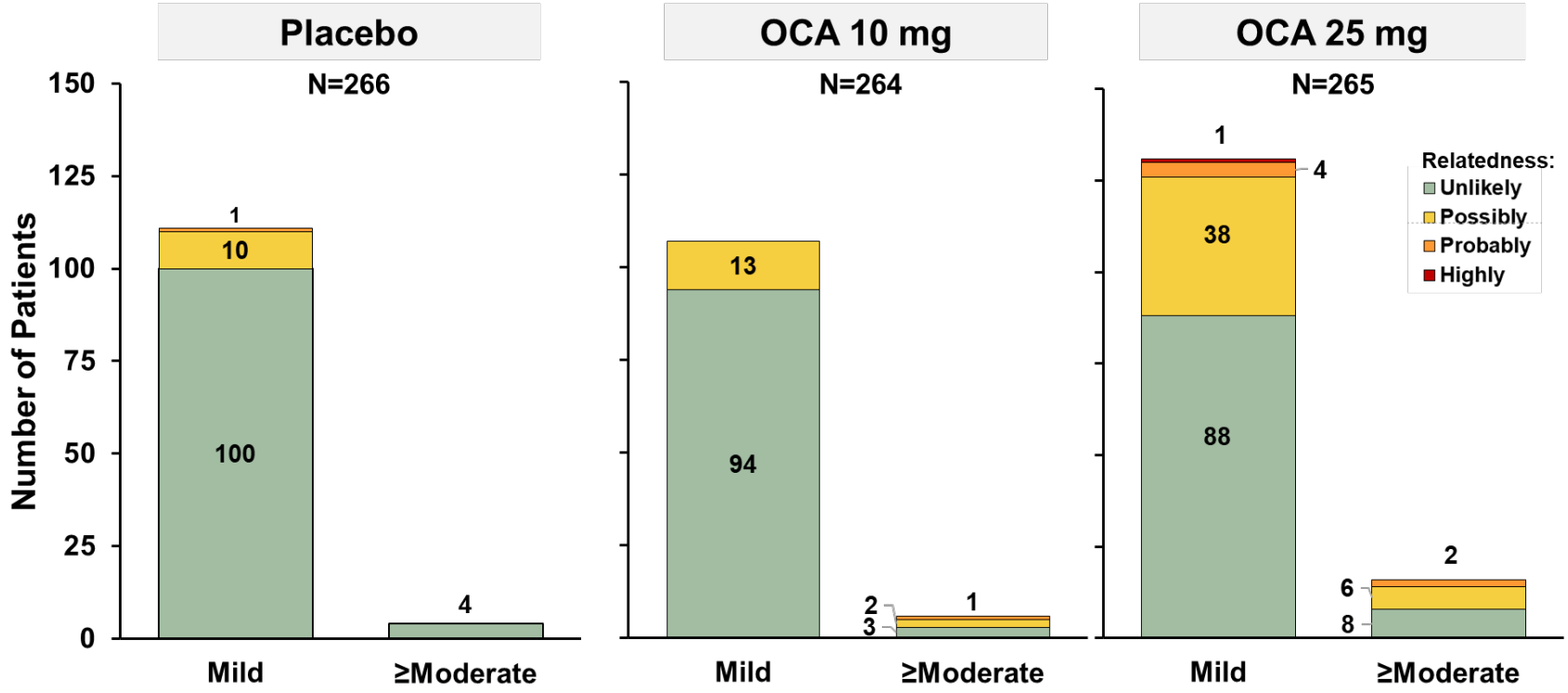
A total of 795 patients were referred for blinded adjudication by the HSAC, with a total of 367 patients experiencing an event adjudicated as consistent with potential liver injury, with a similar incidence across treatment groups (116 [11.4%], 113 [12.9%], and 138 [14.3%] in placebo, OCA 10 mg, and OCA 25 mg groups, respectively). For Study 303 alone, the incidence rate was 111 (13.5%), 110 (13.3%), and 130 (15.7%) in placebo, OCA 10 mg, and OCA 25 mg groups, respectively.

The majority of events in the Pooled Safety Population were adjudicated as mild in severity (338/367) and unlikely related to OCA (288/367). Approximately half of the mild and possibly related cases in the OCA 25 mg group reflected an isolated increase in serum ALP without concomitant increases in total or direct bilirubin or GGT and were not indicative of cholestasis but considered to be a direct PD effect of OCA.

Five patients experienced severe events on OCA (2 [0.2%] in OCA 10 mg and 3 [0.3%] in OCA 25 mg).

- 1 case assessed as probably related (OCA 10 mg): patient experienced an SAE of hyperbilirubinemia at 1 month and discontinued OCA. The SAE of hyperbilirubinemia, including liver biochemistries, resolved 2 months after OCA discontinuation and treatment with oral prednisone (no liver biopsy was performed).
- 1 case assessed as possibly related (OCA 25 mg): patient experienced a cholestatic liver injury approximately 5 months after initiating OCA and required liver transplantation approximately 1 month later. The adjudicators considered the event possibly related to OCA; however, the concomitant use of diclofenac was thought to have potentially contributed to the cause of injury, and the use of amlodipine and allopurinol may have been confounders.
- 3 cases were adjudicated as unlikely related by the expert committee:
  - OCA 25 mg: OCA was discontinued approximately 33 months after initiating treatment in response to imaging showing ascites. A follow-up MRI showed infiltrative HCC and portal vein thrombosis. The patient died 2 months later due to complications of HCC.
  - OCA 25 mg: OCA was discontinued approximately 34 months after initiating treatment due to jaundice, acute hepatitis, and acute renal failure in the setting of excessive alcohol use confirmed by family members. A biopsy confirmed a diagnosis of acute hepatitis with cholestasis. The patient recovered from the event.
  - OCA 10 mg: OCA was discontinued approximately 2 years after initiating treatment in response to hospitalization for new onset ascites. A biopsy confirmed cirrhosis and mild steatosis, leading to a diagnosis of Child-B cirrhosis due to NASH.
- Three fatal events were referred for hepatic adjudication: 1 on placebo (due to hemorrhagic pancreatitis) and 2 on OCA 25 mg (1 due to cholangitis with multi-organ failure and the other due to an infiltrative HCC). None of the fatal hepatic events were adjudicated by the expert committee as due to DILI.

Figure 36: Overall Summary of Adjudicated Treatment-Emergent Hepatic Safety (HSAC) Events: Pooled Safety Population (N=2680)



6.4.1.3. Safety Events Pre and Post 2017 Safety Amendment in Study 303

In September 2017, a major safety amendment was implemented for Study 303 (Protocol V6, 02 Oct 2017) based on previous safety findings, including 1 death in a patient with cirrhosis in Study 747-209 and 1 liver transplant in Study 303.

- The death in Study 747-209 occurred in a patient with baseline Child-Pugh Class A cirrhosis (CP-A) and thrombocytopenia (platelet count 82 $x10^9$/L) who received OCA 25 mg during the long-term safety extension (LTSE) phase. This patient experienced a severe and protracted illness prior to the onset of the serious hepatic AE (e.g., diarrhea and weight loss).
- The liver transplant in Study 303 occurred in a patient on OCA 25 mg who experienced a cholestatic liver injury, as adjudicated by the HSAC, approximately 5 months after initiating OCA. The patient developed ascites and encephalopathy, with liver transplantation at Month 6. The adjudicators considered the event possibly related to OCA; however, the concomitant use of diclofenac was thought to have potentially contributed to the cause of injury, and the use of amlodipine and allopurinol may have been confounders.

This amendment provided specific safety monitoring instructions, patient and provider education for prompt recognition of signs and symptoms of potential liver injury, and appropriate dosing adjustments, interruptions, and discontinuations in scenarios when liver injury or progression of disease was suspected. Algorithms based on liver biochemistries and NITs were provided to identify potential progression to cirrhosis (including assessment of Child-Pugh score) and suspected hepatic injury or decompensation. Hepatic safety events, as assessed by the independent HSAC, occurring prior to the 2017 amendment were compared to events occurring after the full implementation of the safety amendment to evaluate impact of the additional monitoring and management guidance.

Based on this analysis, a large reduction in the overall incidence rate of adjudicated hepatic events was observed for placebo and both OCA groups in the post amendment period, and no case resulting in a liver transplant or death due to DILI was reported in the post-amendment period.

Importantly, after implementation of the safety amendment, there was a 4-fold reduction in moderate to severe adjudicated events for the OCA 25 mg group. The EAIR of cases adjudicated as at least moderate in severity, regardless of causality, was 0.25 per 100 PYs in placebo patients, 0.0 per 100 PYs in OCA 10 mg, and 1.75 per 100 PYs in OCA 25 mg patients before the safety amendment, and 0.12 per 100 PYs in placebo patients, 0.24 per 100 PYs in OCA 10 mg, and 0.38 per 100 PYs in OCA 25 mg patients after implementation of the safety measures (Figure 12). In addition, the exposure adjusted incidence rate of cases deemed related (possible, probably, highly likely) to OCA decreased in both OCA treatment groups (from 1.45 per 100 PYs to 0.51 per 100 PYs in the OCA 10 mg group and from 4.49 per 100 PYs to 1.35 per 100 PYs in the OCA 25 mg group.

These data provide reassurance that the risk for clinically significant hepatic safety events can be managed with careful monitoring and drug interruption in cases where liver injury is suspected. Proposed labeling reflects the changes that were made in the 2017 safety amendment.

An analysis to assess demographics and baseline characteristics in patients with positively adjudicated potential liver injury events, including age, fibrosis stage, BMI, diabetes status, noninvasive markers of fibrosis (TE, FIB-4, ELF), and laboratory parameters (ALT, AST, GGT, ALP, total bilirubin) showed no difference between subjects enrolled pre and post safety amendment.

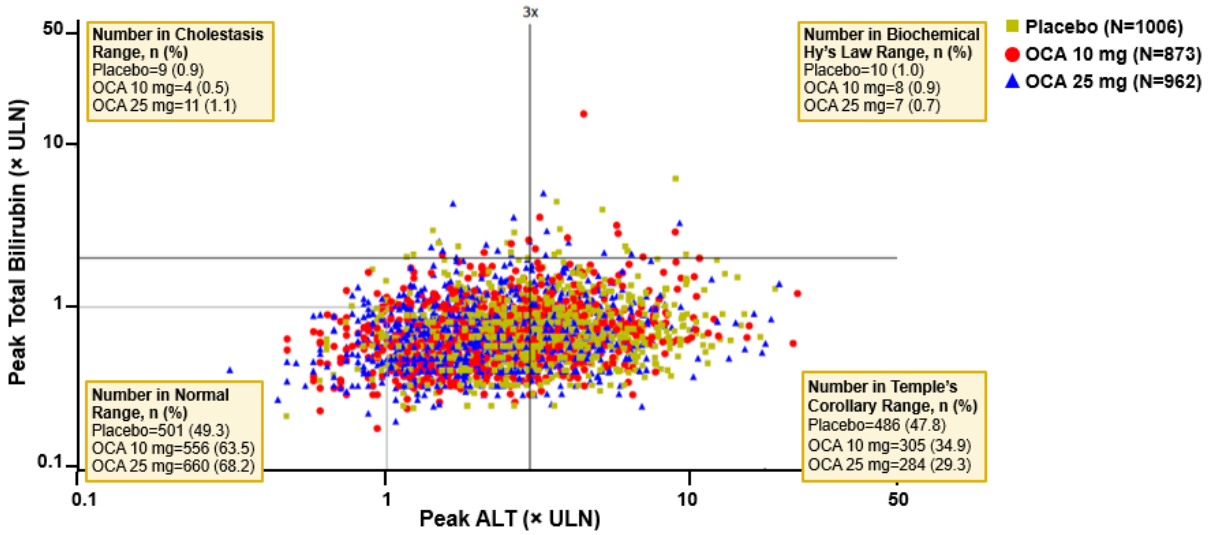
6.4.1.4. Laboratory Evaluations (eDISH and Biochemical Triggers)

The eDISH analyses are screening plots used for scanning large numbers of patients from clinical trials for extreme values, as indicators of hepatocellular or cholestatic injury by serum ALT or ALP and hepatic dysfunction by serum total bilirubin.

In the Pooled Safety Population:

- No difference was observed between placebo and OCA groups for lab excursions into the biochemical Hy's law range (peak ALT >3x ULN and peak total bilirubin >2x ULN), or cholestasis range (peak total bilirubin >2x ULN, and ALT <3x ULN). More patients in the placebo group are represented in the Temple's Corollary range (ALT >3x ULN and total bilirubin <2x ULN) than OCA groups, consistent with background NASH (Figure 37).
  - One subject in Study 303 with lab excursions into the right-upper quadrant on OCA 10 mg; event adjudicated as probably related to investigational product and resolved 2 months after OCA discontinuation and treatment with oral prednisone (no liver biopsy was performed). This patient is also described in Section 6.4.1.2.
  - Two subjects in Study 303 (1 placebo and 1 OCA 25 mg) with lab excursions into the right-upper quadrant; events adjudicated as possibly related to investigational product; the subject on OCA 25 mg was assessed as more likely related to Augmentin by the committee.
  - One subject in Study 303 experienced a cholestatic liver injury 5 months after initiating OCA 25 mg, which resulted in liver transplantation. The adjudicators considered the event possibly related to OCA; however, the concomitant use of diclofenac was thought to have potentially contributed. This patient is also described in Section 6.4.1.2 and Section 6.4.1.3.

Figure 37: Evaluation of Drug-Induced Serious Hepatotoxicity Total Bilirubin Versus ALT: Pooled Safety Population (N=2860)



FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid

Notes: For Study 303, the figure was based on data from central laboratory provided by ICON and local laboratory data.

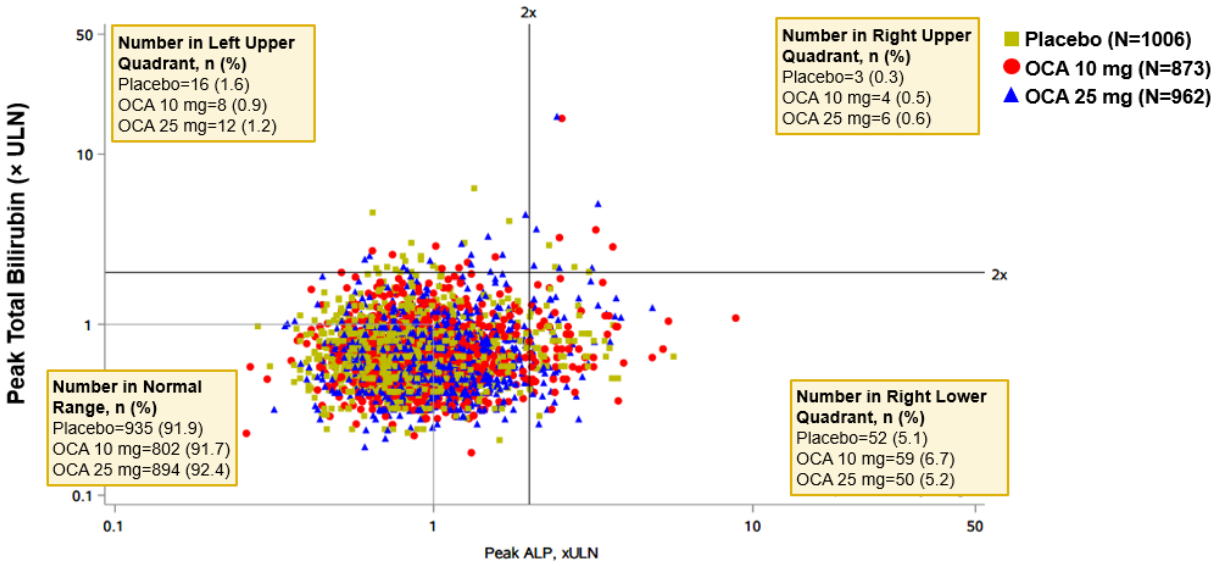
For completed studies FLINT and D8602001 all lab data was used.

The following ULN thresholds were used, ALT - 30 U/L, Total Bilirubin - 1.25 mg/dL.

An eDISH assessment for ALP was conducted in the Pooled Safety Population, with results as follows:

- The number of patients in the right-upper quadrant were low and similar across the treatments (3 patients, 4 patients, and 6 patients in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively). All patients with ALP eDISH excursions into the right upper quadrant had expert adjudication suggesting alternate etiologies as a more likely cause of the laboratory excursions; these included NASH disease, progression to cirrhosis, alcohol excess, and alternate drugs (e.g., Augmentin) (Figure 38).

Figure 38: Evaluation of Drug-Induced Serious Hepatotoxicity Total Bilirubin Versus ALP: Pooled Safety Population (N=2860)



FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid

Notes: For Study 303, the figure was based on data from central laboratory provided by ICON and local laboratory data.

For completed studies FLINT and D8602001 all lab data was used.

The following ULN thresholds were used, ALP - 120 U/L, Total Bilirubin - 1.25 mg/dL.

Biochemical Laboratory Triggers

In the Pooled Safety Population:

- There was no difference across treatment groups in the incidence rate of the 18 additional hepatic biochemical analyses requested by the Agency, regardless of baseline values (i.e., elevated or normal), with the exception of the combination of ALP ≥2x baseline (and >ULN) and direct bilirubin ≥2x baseline (and >ULN) in patients with elevated baseline values.
  - The absolute risk difference for this ALP trigger in patients with an elevated baseline was 1.2% (95% CI: 0.33, 1.98) in OCA 25 mg compared to placebo.
  - The majority of the ALP triggers were adjudicated by the HSAC as unlikely related to OCA and the majority of cases were mild in severity and reversible with discontinuation of OCA. Alternate etiologies for the lab excursions included progression to cirrhosis, HCC, concomitant medications (Augmentin, olanzapine, statins) and one case each of alcohol excess, common bile duct stone, and hip fracture.
  - A total of 3 events were adjudicated as at least probably related to investigational product, one from each treatment arm.

6.4.2. Cardiovascular Safety

6.4.2.1. Baseline Medical History

Consistent with the known comorbidities of patients with NASH, common medical history conditions in the Pooled Safety Population included hypertension (~65% patients), type 2 diabetes mellitus (~55% patients), obesity (~56% patients), and LDL≥100 mg/dL (~59% patients) (Table 10). Within Study 303, >85% of patients had clinical features of metabolic syndrome (87.2%, 88.5%, and 87.8% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively), >60% had a Framingham Risk Score >10% (61.7%, 65.2%, and 64.0% in placebo, OCA 10 mg, and OCA 25 mg, respectively), and ~12% patients had a 10-year ASCVD risk ≥20% (10.9%, 12.7%, and 14.6% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively).

Medical history of conditions included in the SOC of cardiac disorders was reported by 11.3%, 12.2% and 11.8% patients in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively in the Pooled Safety Population; coronary artery disease was the most frequently reported PT, in 2% to 3% of the patients.

In the Pooled Safety Population, the most common category of prior concomitant medications of interest were antihypertensive medications (62.6%, 59.5%, and 63.2% in the placebo, OCA 10 mg, and OCA 25 mg groups respectively). Approximately half of the patients were on prior concomitant antidiabetic medications, including TZDs (52.9%, 53.9%, and 55.2% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively) or lipid-lowering agents, including statins (52.5%, 49.8%, and 55.8% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively).

Table 10: Baseline Medical History: Pooled Safety Population (N=2860)

	Pooled		
	Placebo	**OCA 10 mg**	**OCA 25 mg**
Number (%) of Patients with Any Medical History Event	**N=1017 n (%)**	**N=875 n (%)**	**N=968 n (%)**
Type 2 diabetes mellitus	560 (55.1)	491 (56.1)	550 (56.8)
Obesity	535 (52.6)	528 (60.3)	533 (55.1)
LDL ≥100 mg/dL	583 (58.2)	508 (58.9)	567 (59.6)
Hypertension	659 (64.8)	569 (65.0)	624 (64.5)
Cardiac disorders	115 (11.3)	107 (12.2)	114 (11.8)

LDL=low-density lipoprotein; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid

6.4.2.2. Dyslipidemia

6.4.2.2.1. FXR Mediated Effects on Lipid Metabolism

Dyslipidemia was designated as an AESI due to the known FXR-mediated effects of OCA on lipid metabolism, including an increase in LDL cholesterol. FXR agonism has been shown to decrease hepatic sterol regulatory element-binding protein 1c (SREBP1c), leading to a decrease in LDL receptor protein and subsequent increase in LDL concentration (Nilsson 2007).

These effects have been observed in nonclinical studies in chimeric mice whose livers are mostly composed of human hepatocytes (Hambruch 2012, Papazyan 2018), as well as in clinical studies with healthy patients (Pencek 2016), patients with PBC (Nevens 2016), patients with presumed NAFLD and type 2 diabetes (Mudaliar 2013), and patients with NASH (Neuschwander-Tetri 2015, Younossi 2019).

6.4.2.2.2. Dyslipidemia TEAEs

Dyslipidemia TEAEs are summarized in Table 11.

- The overall incidence rate of dyslipidemia TEAEs was approximately 2-fold higher in the OCA groups, without a dose-dependent response (19.3%, 40.5%, and 40.4% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively).
- The most commonly reported dyslipidemia TEAEs by PT were LDL increased, hyperlipidaemia, blood cholesterol increased, hypercholesterolaemia, and dyslipidaemia, which occurred with a higher incidence rate in OCA treatment groups compared to the placebo group.
- The majority of these events were mild to moderate in severity. Few patients experienced severe dyslipidemia TEAEs, and the incidence rate was similar across treatment groups (≤0.5%).
- No patients reported a serious dyslipidemia TEAE in the OCA treatment groups and 1 (0.1%) patient in the placebo group reported a life-threatening, serious TEAE of hypertriglyceridemia. No dyslipidemia TEAEs resulting in death were reported.
- The incidence rate of dyslipidemia TEAEs leading to withdrawal of investigational product was low (<0.5%). While no dyslipidemia events leading to withdrawal of investigational product were recorded in the placebo group, a total of 4 patients in OCA treatment groups discontinued investigational product due to an TEAE of dyslipidemia (0.1% and 0.4% in the OCA 10 mg and OCA 25 mg groups, respectively).

Table 11: Overview of Dyslipidemia TEAEs: Pooled Safety Population (N=2860)

Number (%) of Patients with any:		Pooled		
		Placebo N=1017	OCA 10 mg N=875	OCA 25 mg N=968
Dyslipidemia TEAE[a]	**n (%)**	196 (19.3)	354 (40.5)	391 (40.4)
	n (EAIR)	196 (7.69)	354 (20.16)	391 (24.16)
Serious dyslipidemia TEAEs	**n (%)**	1 (0.1)	0	0
	n (EAIR)	1 (0.03)	0	0
Related dyslipidemia TEAEs	**n (%)**	129 (12.7)	276 (31.5)	307 (31.7)
Dyslipidemia TEAEs leading to withdrawal of IP	**n (%)**	0	1 (0.1)	3 (0.4)
Severe (Grade 3) dyslipidemia TEAEs	**n (%)**	3 (0.3)	4 (0.5)	3 (0.3)
Life-threatening (Grade 4) dyslipidemia TEAEs	**n (%)**	1 (0.1)	0	0
Dyslipidemia TEAEs leading to death (Grade 5)	**n (%)**	0	0	0
Severe (≥Grade 3) dyslipidemia TEAEs	**n (EAIR)**	4 (0.13)	4 (0.14)	3 (0.11)

EAIR=exposure-adjusted incidence rate; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; SMQ=standardized MedDRA query; TEAE=treatment-emergent adverse event

[a] Dyslipidemia TEAEs were defined as Dyslipidaemia SMQ.

6.4.2.3. Serum Chemistry Lipids

6.4.2.3.1. Pooled Safety Population

Mean lipid values and change from baseline to Month 54 are displayed for the Pooled Safety Population in Figure 39. Consistent with known FXR-related effects, and as previously observed in earlier phase studies of OCA, a larger proportion of patients treated with OCA compared to placebo showed an early increase in LDL cholesterol. The early increases in LDL decreased with continued treatment and returned to near baseline levels by Month 12.

At baseline, the mean value for each of the lipid parameters was similar across the 3 treatment groups. Mean (standard deviation [SD]) baseline values for LDL cholesterol were 115.9 mg/dL (37.77), 113.9 mg/dL (36.57), and 113.8 mg/dL (38.47) in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively.

A similar magnitude of an initial increase of 15-20 mg/dL in mean serum total cholesterol and LDL cholesterol was observed in the OCA groups. These initial increases occurred within the first days of initiation of OCA, peaked at Month 1, and diminished in magnitude with continued treatment, returning to approximately 3mg/dL above baseline at Month 18. Mean LDL cholesterol increased from 113.9 mg/dL (baseline) to a peak of 131.1 mg/dL (Month 1) before declining to 120.4 mg/dL (Month 12) and 107.9 mg/dL (Month 48) in the OCA 10 mg group and increased from 113.8 mg/dL (baseline) to a peak of 138.3 mg/dL (Month 1) before declining to 120.7 mg/dL (Month 12) and 112.0 mg/dl (Month 48) in the OCA 25 mg group. Mean LDL values decreased from 115.9 mg/dL (baseline) to 112.1 mg/dL (Month 1), 110.9 mg/dL (Month 12), and 103.8 mg/dL (Month 48) in the placebo group.

Mean high-density lipoprotein (HDL) decreased from 45.18 mg/dL (baseline) to 44.50 mg/dL (Month 1) and 45.55 mg/dL (Month 48) in the placebo group. Mean HDL cholesterol decreased from 45.27 mg/dL (baseline) to 43.29 mg/dL (Month 1), with a gradual return to 44.9 mg/dL (Month 48) in the OCA 10 mg group and decreased from 44.54 mg/dL (baseline) to 40.31 mg/dL (Month 1), with a gradual return to 42.93 mg/dL (Month 48) in the OCA 25 mg group.

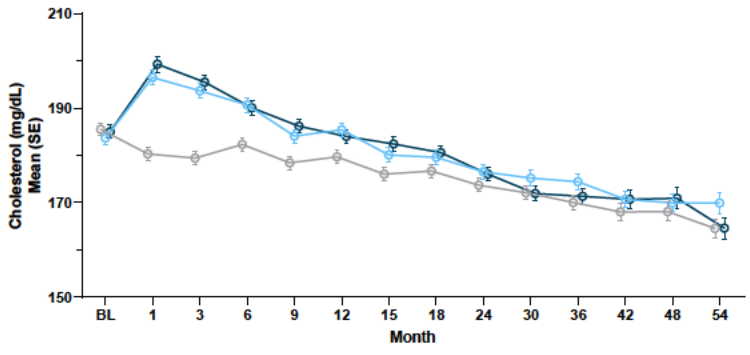
A progressive decrease from baseline in the mean triglyceride concentration was observed in the OCA groups. Mean triglycerides decreased from 176.9 mg/dL (baseline) to 165.1 mg/dL (Month 1), 154.3 mg/dL (Month 18), and 155.8 mg/dL (Month 48) in the OCA 10 mg group and decreased from 184.4 mg/dL (baseline) to 160.5 mg/dL (Month 1), 153.2 mg/dL (Month 18), and 150.1 mg/dL (Month 48) in the OCA 25 mg group. Mean triglycerides increased from 171.5 mg/dL (baseline) to 173.7 mg/dL (Month 1), followed by a decrease to 163.5 mg/dL (Month 18) and 163.4 mg/dL (Month 48) in the placebo group.

Mean very low-density lipoprotein (VLDL) cholesterol remained relatively unchanged in patients randomized to the placebo group through Month 48 (decrease from 32.5 mg/dL [baseline] to 31.3 mg/dL [Month 48]). A similar gradual decrease in the mean concentration of VLDL cholesterol was observed in the OCA groups through Month 48 (decreased from 34.0 mg/dL [baseline] to 31.9 mg/dL [Month 1] and 29.9 mg/dL [Month 48] in the OCA 10 mg group and decreased from 33.7 mg/dL [baseline] to 30.7 mg/dL [Month 1] and 28.8 mg/dL [Month 48] in the OCA 25 mg group), likely related to the effect of OCA on triglycerides, which are main components of VLDL.

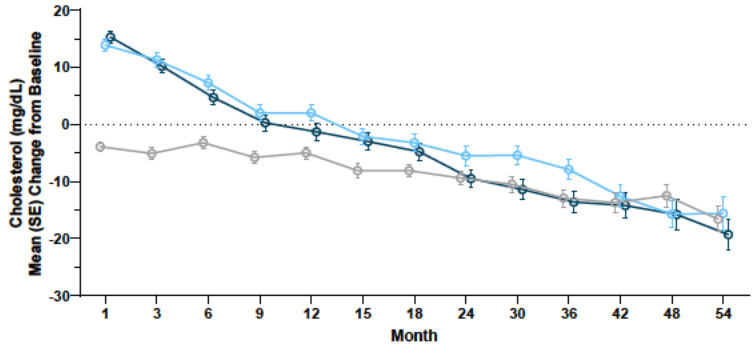
In Study 303, serum chemistry lipids were also evaluated in patients with any adjudicated CV event. Overall, the pattern of OCA-mediated effects on lipid parameters in patients with an adjudicated CV event was similar to that observed in the overall Safety_all Population.

Figure 39: Mean Serum Lipid Values and Change from Baseline Over Time: Pooled Safety Population (N=2860)

Total Cholesterol

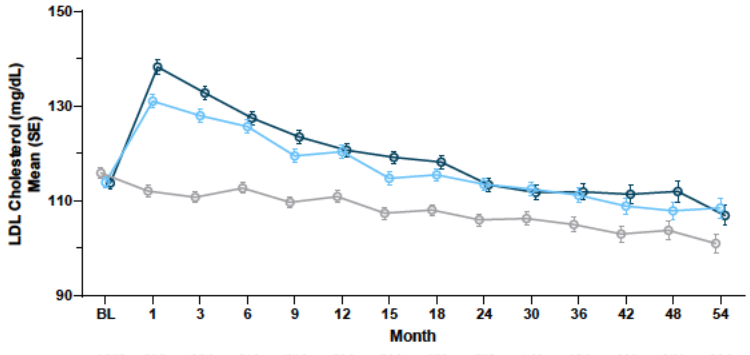


		BL	1	3	6	9	12	15	18	24	30	36	42	48	54
Placebo	n=	1006	808	932	966	885	920	848	895	788	642	546	461	376	315
OCA 10 mg	n=	862	814	810	834	762	793	716	758	691	648	541	451	362	305
OCA 25 mg	n=	958	812	933	896	857	833	819	815	770	628	523	426	349	297

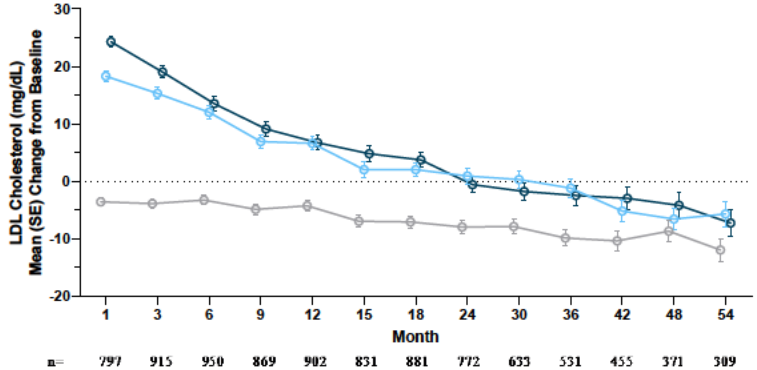


		1	3	6	9	12	15	18	24	30	36	42	48	54
Placebo	n=	798	923	958	875	910	838	885	779	634	540	456	371	310
OCA 10 mg	n=	801	798	822	750	781	704	746	680	637	533	443	356	300
OCA 25 mg	n=	803	923	886	847	823	810	805	761	619	515	420	345	294

LDL

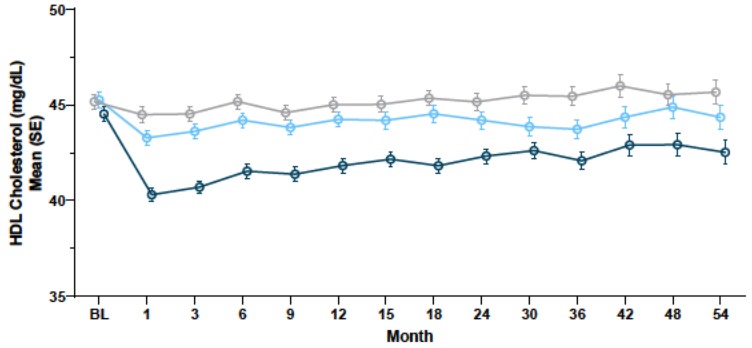


		BL	1	3	6	9	12	15	18	24	30	36	42	48	54
Placebo	n=	1002	808	927	961	883	914	844	893	783	641	537	460	376	314
OCA 10 mg	n=	862	814	810	834	760	792	715	755	690	646	529	450	362	304
OCA 25 mg	n=	951	812	929	889	851	830	810	809	760	627	513	425	349	294

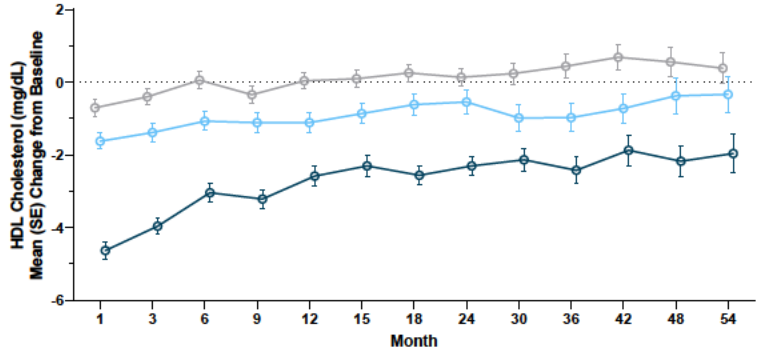


		1	3	6	9	12	15	18	24	30	36	42	48	54
Placebo	n=	797	915	950	869	902	831	881	772	633	531	455	371	309
OCA 10 mg	n=	801	798	822	748	780	703	743	679	636	521	442	356	299
OCA 25 mg	n=	803	915	876	837	815	799	792	750	618	505	419	345	291

HDL

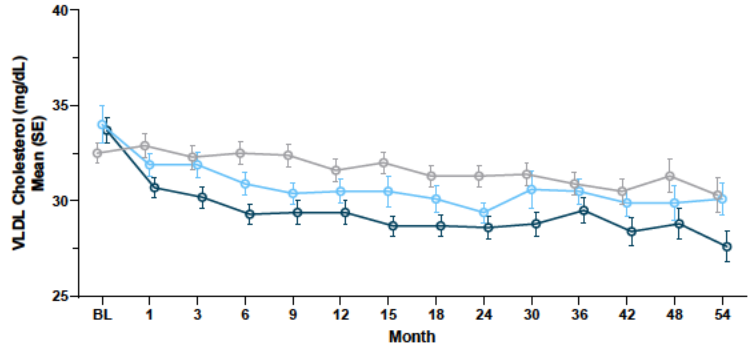


Placebo	n=	1004	807	931	964	883	919	843	891	785	638	544	459	375	314
OCA 10 mg	n=	860	813	809	831	759	793	715	754	689	645	541	451	357	305
OCA 25 mg	n=	957	812	931	896	855	833	817	814	768	626	519	421	347	295

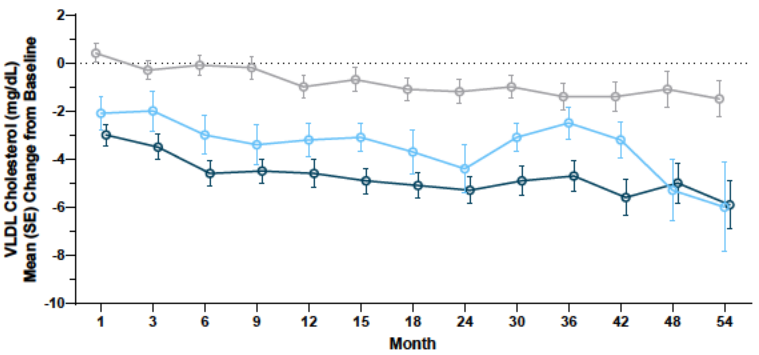


Placebo	n=	796	920	954	871	907	831	881	775	670	578	454	370	309
OCA 10 mg	n	798	795	817	746	779	701	740	676	633	531	443	351	300
OCA 25 mg	n	803	920	885	844	822	807	803	760	617	511	415	343	291

VLDL

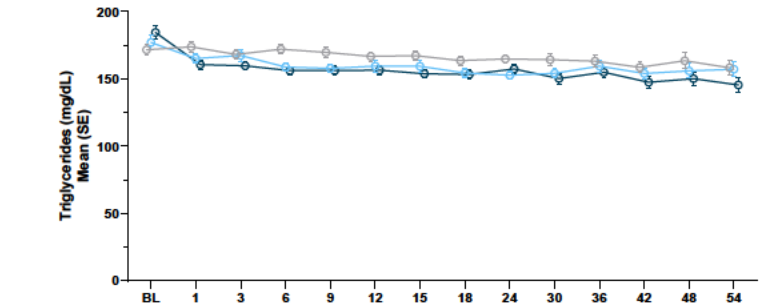


Placebo	n=	813	808	794	785	754	741	727	717	671	641	544	461	376	315
OCA 10 mg	n=	811	814	810	785	761	746	716	713	691	648	539	451	362	305
OCA 25 mg	n=	817	812	796	761	730	706	697	689	647	628	523	425	349	294

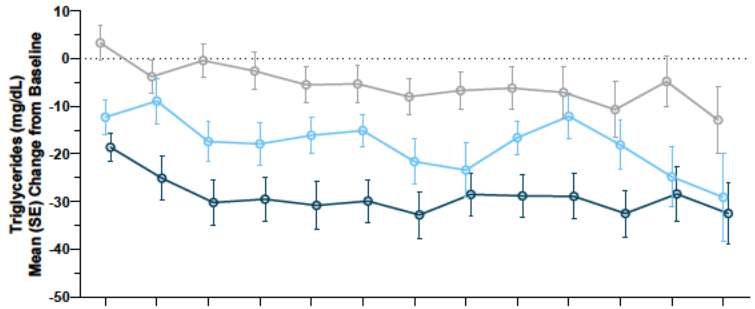


Placebo	n	797	784	776	743	730	716	707	662	603	538	456	371	310
OCA 10 mg	n=	800	797	772	748	733	703	700	679	637	530	442	355	299
OCA 25 mg	n=	803	786	751	720	696	688	679	638	619	515	419	345	291

Triglycerides



		BL	1	3	6	9	12	15	18	24	30	36	42	48	54
Placebo	n=	1005	808	932	966	885	920	846	895	788	641	545	461	376	315
OCA 10 mg	n=	861	814	810	834	761	793	716	757	691	647	540	451	362	305
OCA 25 mg	n=	958	812	932	896	857	833	819	815	770	628	523	425	349	295



		1	3	6	9	12	15	18	24	30	36	42	48	54
Placebo	n=	797	922	957	874	909	835	885	779	633	539	456	371	310
OCA 10 mg	n=	800	797	821	748	780	703	744	679	636	531	442	355	299
OCA 25 mg	n=	803	922	886	847	823	810	805	761	619	515	419	345	292

Placebo (N=1017) OCA 10 mg (N=875) OCA 25 mg (N=968)

HDL=high-density lipoprotein; LDL=low-density lipoprotein; NASH=nonalcoholic steatohepatitis; VLDL=very low density lipoprotein; OCA=obeticholic acid
Notes: Baseline is defined as the last fasted evaluation prior to the first administration of investigational product.
The summary is based on data from central laboratory provided by ICON in Study 303.

6.4.2.3.2. Apolipoprotein B and non-HDL: Study 303

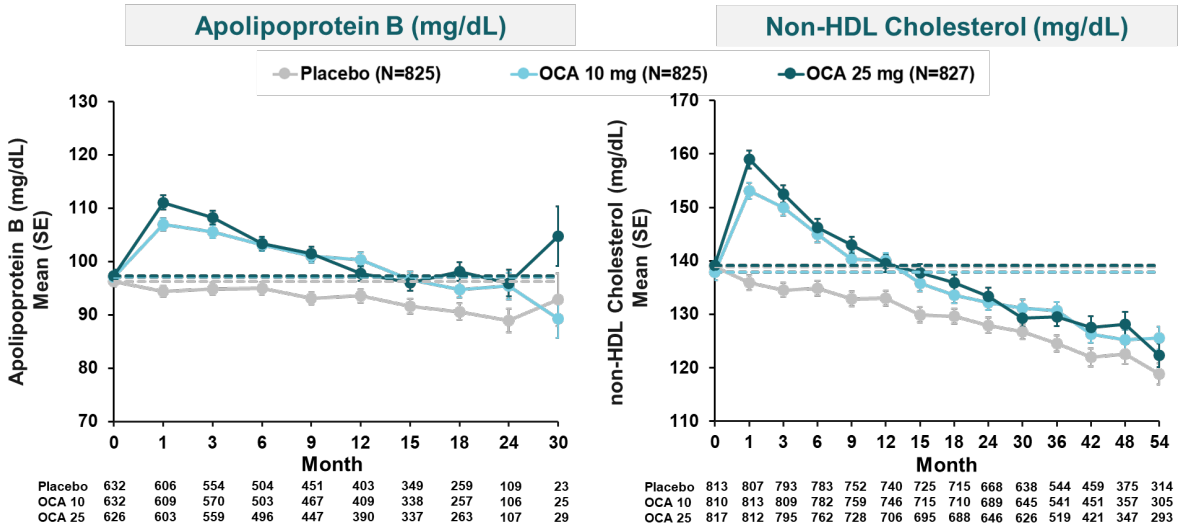
Apolipoprotein B and non-HDL levels were evaluated in Study 303. Although variability was observed in serum Apolipoprotein B levels due to a fewer number of patients sampled, a transient increase at Month 1 to Month 3 was observed in the OCA 10 mg and OCA 25 mg groups and diminished in magnitude with continued treatment, with values approaching baseline by Month 12.

The transient increase in Apolipoprotein B was of a lesser magnitude compared to the increase observed in LDL cholesterol (Figure 39), suggesting a shift from small dense LDL particles to large buoyant LDL particles as shown in a previous Phase 2 study with OCA treatment (Pockros 2019).

Non-HDL levels mirrored changes observed in LDL cholesterol, with a larger proportion of patients treated with OCA compared to placebo showing an early increase in non-HDL cholesterol. The early increases in non-HDL peaked at Month 1 and decreased with continued treatment, with values approaching baseline by Month 12.

These data for Apolipoprotein B and non-HDL cholesterol are of interest considering the high prevalence of metabolic syndrome in the NASH population, which might limit the accuracy of CV risk assessment based on LDL. Measures of non-HDL, Apolipoprotein B, and LDL particle concentrations might be more beneficial in assessing risk for CV events in this patient population (Virani 2011).

Figure 40: Mean Serum Apolipoprotein and Non-HDL Values Over Time: Study 303 Safety_all Population (N=2477)



HDL=high-density lipoprotein; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid
Notes: Baseline is defined as the last fasted evaluation prior to the first administration of investigational product.
The summary is based on data from central laboratory provided by ICON in Study 303.

6.4.2.3.3. Serum Chemistry Lipids and Statin Use: Study 303

The impact of statin use on serum chemistry lipids was evaluated in Study 303.

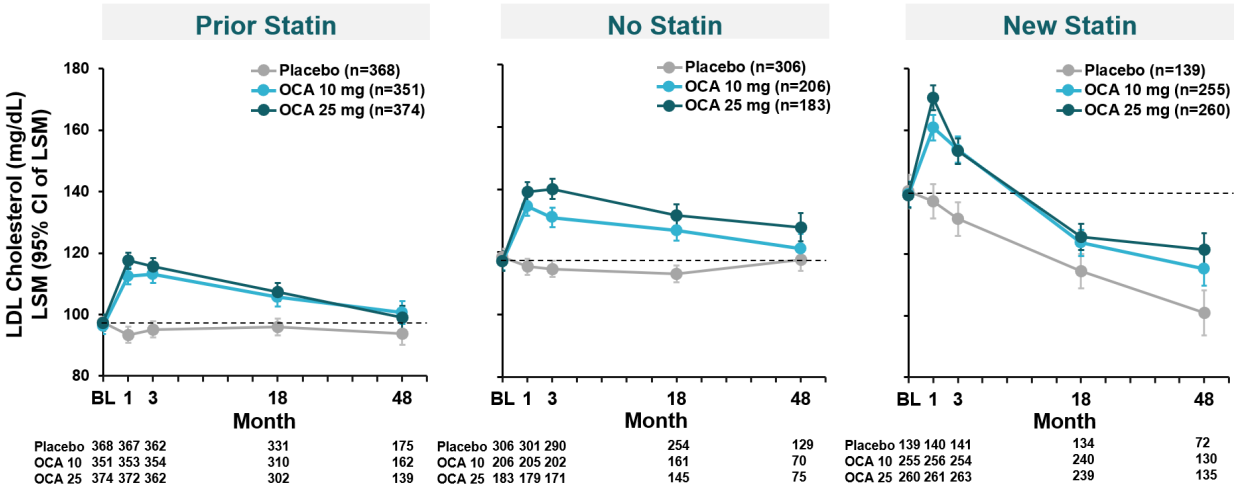
The mean LDL cholesterol at baseline ranged from 93.7 mg/dL to 98.1 mg/dL for patients who were using statins at the first dose of investigational product (prior and concomitant use), 114.8 mg/dL to 124.5 mg/dL for patients who never used statins during the course of the study, and from 137.2 mg/dL to 142.2 mg/dL for patients who initiated a statin during the study (new use). Of patients who initiated a statin during the study, the vast majority initiated use within the first 12 months of the study.

Early increases in LDL levels were observed at Month 1 in OCA-treated patients, regardless of statin subgroup (patients) who initiated statin treatment, never used a statin, or were using statins at baseline (Figure 41).

In the subgroup of patients on OCA treatment who initiated statin treatment during the study, LDL levels returned to baseline levels by Month 9-12 and further declined to below baseline levels by Month 18.

In the subgroups of patients on OCA treatment who never used a statin or were using statins at baseline, LDL levels declined over time, approaching baseline levels by Month 48.

Figure 41: Time Course of Mean LDL Absolute Values: Study 303 Safety_all Population (N=2477)



LDL=low-density lipoprotein; OCA=obeticholic acid

6.4.2.3.4. Statin Use: Pooled Safety Population

6.4.2.3.4.1. Lipid-Lowering Medications

Analyses of lipid-lowering medications, including statins, were conducted based on categories of no concomitant use, prior and concomitant use, and new use to evaluate proportion of patients with baseline (and concomitant use) versus proportion of patients who initiated a lipid-lowering agent or statin after Day 1.

6.4.2.3.4.2. Prior and Concomitant Use

The use of lipid-lowering medications (including statins) at baseline, and continued during the study, was approximately 55% (52.5%, 49.8%, and 55.8%, in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively).

In the Pooled Safety Population, across treatment groups, approximately 40% of patients were receiving statins at baseline (377 of 1017 patients in placebo, 359 of 875 patients in OCA 10 mg, and 377 of 968 patients in OCA 25 mg).

6.4.2.3.4.3. New Use

In the Pooled Safety Population, new use of lipid-lowering agents (including statins), defined as use that started after the initial dose of investigational product, occurred with a higher incidence rate in OCA treatment groups compared to placebo (17.4%, 29.8%, and 28.5% of patients in placebo, OCA 10 mg, and OCA 25 mg groups, respectively) (Table 12).

Table 12: Use of Lipid-Lowering Agents: Pooled Safety Population (N=2860)

Category of Interest Usage Criteria	Pooled Placebo N=1017 n (%)	Pooled OCA 10 mg N=875 n (%)	Pooled OCA 25 mg N=968 n (%)
Any Lipid-Lowering Agent, Including Statins			
No concomitant use at Baseline	306 (30.1)	178 (20.3)	152 (15.7)
Prior and concomitant use	534 (52.5)	436 (49.8)	540 (55.8)
New concomitant use	177 (17.4)	261 (29.8)	276 (28.5)

NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid

Notes: No Concomitant use indicated all patients who had no medication use at any time and for those who had concomitant medication prior and stopped before first dose of the investigational product. Prior concomitant medications were those medications started prior to and continued after the initial dose of investigational product. New concomitant medications were those medications that were started after the initial dose of investigational product. If it could not be determined whether the medication was concomitant due to a partial start or stop date of or the medication was taken on the same date as the initial dose of investigational product, then it was counted as a new concomitant medication.

No concomitant use, Prior Concomitant use, and New Concomitant use were mutually exclusive. If a patient had prior and new concomitant medication, prior concomitant medication was taken as the highest order.

Medication taken on Day 1 was considered as prior concomitant medication not new concomitant medication.

6.4.2.3.5. Study 747-209

Study 747-209, a Phase 2 study conducted to characterize OCA-mediated lipid changes, showed that statins can mitigate the increases in LDL observed with OCA in patients with NASH. At Baseline, the mean LDL concentration ranged from 120.6 mg/dL to 142.7 mg/dL across treatment groups. Consistent with results based on previous studies with OCA, LDL levels increased through Week 4 in the OCA treatment groups and remained stable in the placebo group (Figure 42). A clear and consistent relationship of increase in LDL to OCA dose was not apparent: the LS mean absolute changes from baseline in LDL at Week 4 were -5.94 mg/dL in

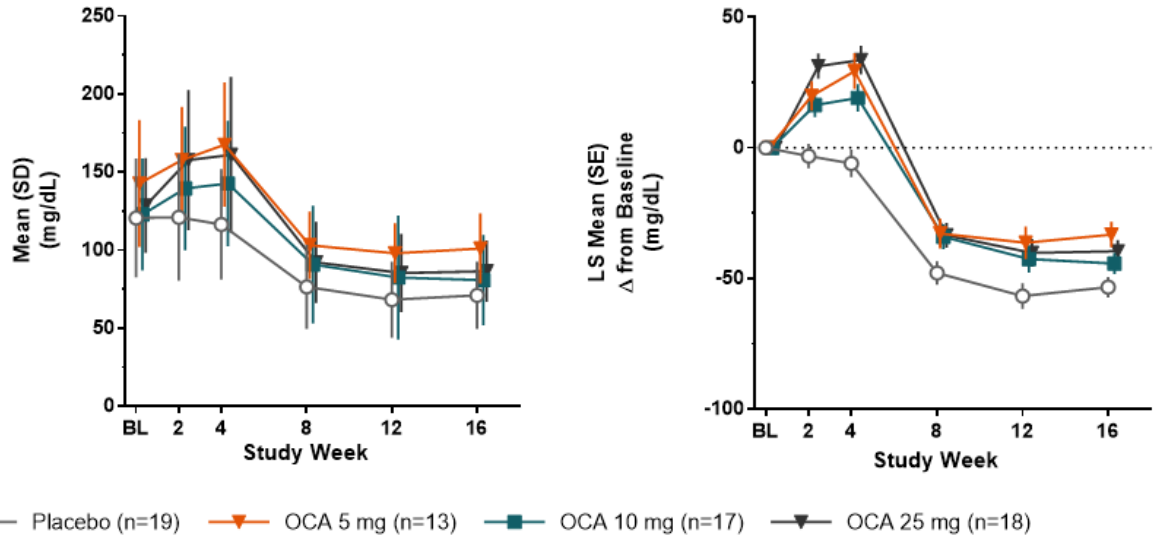
the placebo group and 29.40 mg/dL, 19.09 mg/dL, and 33.63 mg/dL in the 5 mg, 10 mg, and 25 mg OCA treatment groups, respectively.

At Week 8, after 4 weeks of 10 mg atorvastatin treatment with continued blinded (OCA or placebo) treatment, substantial reductions in LDL to below baseline values were observed in all treatment groups (Figure 42). The LS mean absolute changes from baseline at Week 8 were -47.91 mg/dL in the placebo group and -32.83 mg/dL, -34.04 mg/dL, and -33.48 mg/dL in the 5 mg, 10 mg, and 25 mg OCA treatment groups, respectively.

After an additional 4 weeks of atorvastatin treatment, which had been titrated up to 20 mg (for most patients; 9 patients received only the 10 mg dose, 1 patient titrated up to 30 mg, 4 patients titrated up to 40 mg, and 8 patients had dose reductions), patients in all 4 treatment groups showed either maintenance or further reduction in LDL. Reductions were maintained between Week 12 and Week 16, when patients may have titrated to 10 mg, 20 mg, or 40 mg atorvastatin while continuing their blinded treatment on OCA or placebo (Figure 42). At Week 16, the LS mean change from baseline for LDL was -33.20 mg/dL, -44.27 mg/dL, and -39.54 mg/dL in the 5 mg, 10 mg, and 25 mg OCA treatment groups, respectively, and -53.33 mg/dL in the placebo group. At Week 16, LDL mean values were within reference range (71.1 mg/dL, 101.0 mg/dL, 80.8 mg/dL, and 86.5 mg/dL in the placebo, 5 mg, 10 mg, and 25 mg OCA treatment groups, respectively).

Overall, the results showed that the OCA-associated increase in LDL could be mitigated by the addition of atorvastatin (lowest dose level), irrespective of OCA dose level.

Figure 42: LDL Concentration Absolute and Mean Change from Baseline: Study 747-209 (N=67)



BL=baseline; LDL=low-density lipoprotein; LS=least-square; OCA=obeticholic acid; SD=standard deviation; SE=standard error

Through Week 4, mean HDL levels decreased in the OCA 10 mg and OCA 25 mg treatment groups and increased in the 5 mg OCA and placebo treatment groups. By week 12, a decrease in HDL concentration was observed in all treatment groups after the initiation of atorvastatin. In patients randomized to OCA 25 mg during the DB Phase, HDL levels were generally unchanged

during the LTSE Phase. Those patients randomized to OCA 10 mg during the DB Phase experienced an increase in HDL concentrations back to DB Baseline levels. Patients who either initiated or uptitrated OCA during the LTSE Phase showed a modest decrease in HDL levels, which approached DB Baseline by Month 12 of the LTSE Phase. Triglyceride concentrations decreased in the OCA 5 mg and OCA 25 mg groups by Week 4, with further decreases apparent across all groups following initiation of atorvastatin. Reductions in triglycerides were maintained during the LTSE Phase.

6.4.2.4. Hyperglycemia

6.4.2.4.1. Hyperglycemia TEAEs

Hyperglycemia TEAEs are summarized in Table 13.

- The incidence rate of hyperglycemia TEAEs in the Pooled Safety Population was generally similar across the 3 treatment groups (19.3%, 25.8%, and 21.0% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively).
- The most frequently occurring hyperglycemia TEAE by PT was diabetes mellitus (7.6%, 10.6%, and 8.8% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively). The incidences of other frequently reported hyperglycemia TEAEs (type 2 diabetes mellitus, glycosylated hemoglobin increased, blood glucose increased, and hyperglycemia) were also generally similar between the OCA and placebo treatment groups.
- The majority of these TEAEs were mild to moderate in severity. Few patients experienced severe (Grade 3) hyperglycemia TEAEs, and the incidence rate was ≤1.0% in all treatment groups. Hyperglycemia was the most common severe (Grade 3) hyperglycemia TEAE, occurring in 2 (0.2%) patients in the placebo group, 0 patients in the OCA 10 mg group, and 3 (0.3%) patients in the OCA 25 mg group. Other severe (Grade 3) hyperglycemia TEAEs that occurred in >1 patient in either OCA treatment group included diabetes mellitus, diabetes mellitus inadequate control, and diabetic ketoacidosis (DKA).
- Serious hyperglycemia TEAEs occurred in <1.5% of patients across all treatment groups. The imbalance between placebo and OCA 25 mg groups was driven by SAEs related to hospitalization for management of worsening glycemic control in patients with underlying diabetes mellitus. The majority of the serious events were mild to moderate. SAEs related to worsening diabetes control were reported by 1 patient in the placebo group, 4 patients in the OCA 10 mg group, and 10 patients in the OCA 25 mg group, with the majority of events reported in patients with a history of diabetes. None of these SAEs led to discontinuation of investigational product.
- DKA reported as an SAE occurred in 1 (0.1%), 2 (0.2%), and 2 (0.2%) patients in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively. The patient with DKA in the placebo group was diagnosed with type 2 diabetes on Day 1. Both patients with DKA in the OCA 10 mg group had no history of diabetes at baseline. DKA was presumed to be triggered by hypertriglyceridemia in one of these two patients; the other patient had reported a TEAE of skin infection preceding the DKA event. The

DKA events in the OCA 25 mg group were reported by patients who had a prior history of diabetes; one of these patients had a urinary tract infection and was using concomitant semaglutide; the other patient was using concomitant empagliflozin and reported DKA of mild severity.

- In terms of other non-serious, clinically significant hyperglycemia events, 1 patient in the OCA 10 mg group with a history of diabetes reported a nonserious TEAE of diabetic metabolic decompensation, which occurred in the setting of acute infectious diarrhea, and 1 patient in the OCA 25 mg without a history of diabetes at baseline reported a mild, nonserious TEAE of ketoacidosis, which was related to change in diet. In the patient that reported ketoacidosis, HbA1c ranged between 4.9% and 5.1%.
- Hyperglycemia TEAEs that led to discontinuation of investigational product were rare, occurring in 2 patients in the OCA 10 mg group.
- No life-threatening hyperglycemia TEAEs or deaths resulting from hyperglycemia events were reported.

Table 13: Overview of Hyperglycemia: Pooled Safety Population (N=2860)

Number (%) of Patients with Any:		Pooled		
		Placebo N=1017	OCA 10 mg N=875	OCA 25 mg N=968
Hyperglycemia TEAEs[a]	n (%)	196 (19.3)	226 (25.8)	203 (21.0)
	n (EAIR)	196 (7.61)	226 (10.45)	203 (9.09)
Serious hyperglycemia TEAEs	n (%)	2 (0.2)	6 (0.7)	12 (1.2)
	n (EAIR)	2 (0.06)	6 (0.22)	12 (0.44)
Related hyperglycemia TEAEs	n (%)	20 (2.0)	42 (4.8)	35 (3.6)
Hyperglycemia TEAEs leading to withdrawal of IP	n (%)	0	2 (0.2)	0
Severe (Grade 3) hyperglycemia TEAEs	n (%)	3 (0.3)	3 (0.3)	10 (1.0)
Life-threatening (Grade 4) hyperglycemia TEAEs	n (%)	0	0	0
Hyperglycemia TEAEs leading to death (Grade 5)	n (%)	0	0	0
Severe (≥Grade 3) hyperglycemia TEAEs	n (EAIR)	3 (0.10)	3 (0.11)	10 (0.36)

EAIR=exposure-adjusted incidence rate; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; SMQ=standardized MedDRA query; TEAE=treatment-emergent adverse event

[a] Hyperglycaemia TEAEs were defined as Hyperglycaemia narrow SMQ/new onset diabetes mellitus.

6.4.2.4.2. Glycemic Markers

Summaries of glycemic markers by visit are provided in Figure 43.

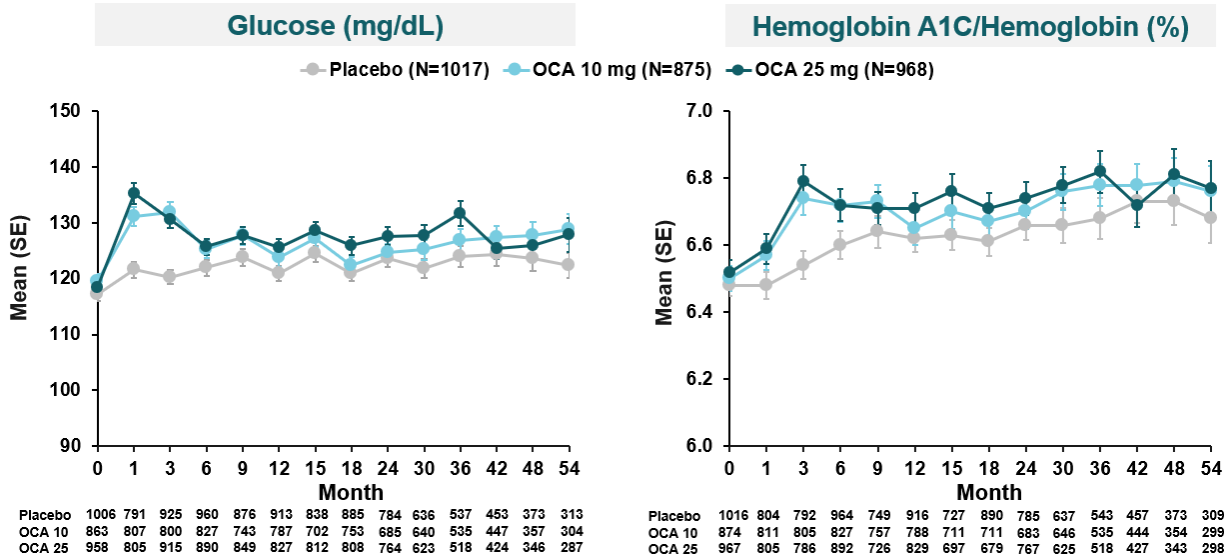
Mean baseline glucose levels were similar across treatment groups (117.1 mg/dL, 119.5 mg/dL, and 118.4 mg/dL in placebo, OCA 10 mg, and OCA 25 mg groups, respectively). Increases from baseline in mean fasting plasma glucose concentrations were evident early in the course of treatment, with the majority of such increases occurring between Months 1 and 3 in all treatment

groups, and greater increases observed in OCA treatment groups (mean change from baseline to Month 1 of 4.3 mg/dL, 11.0 mg/dL, and 16.5 mg/dL in placebo, OCA 10 mg, and OCA 25 mg groups, respectively, and mean change from baseline to Month 3 of 3.1 mg/dL, 12.1 mg/dL, and 12.7 mg/dL in placebo, OCA 10 mg, and OCA 25 mg groups, respectively). Mean fasting plasma glucose concentrations in the OCA 25 mg and OCA 10 mg groups were similar to those in the placebo group by Month 6 (122.0 mg/dL, 125.3 mg/dL, and 125.7 mg/dL in placebo, OCA 10 mg, and OCA 25 mg groups, respectively). By Month 48, the mean change from baseline to last postbaseline (high) was similar across all treatment groups, including placebo.

An early mean increase in HbA1c was observed from baseline to Month 3 (0.03%, 0.21%, and 0.27% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively). Mean change from baseline in HbA1c values were similar to those in the placebo group by Month 9 (0.15%, 0.20%, and 0.22% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively). Over a longer duration of treatment through Month 48, no clinically meaningful difference across treatment groups were observed in the mean change from baseline to last postbaseline value between placebo and the OCA 25 mg treatment group for the well-established marker of long-term glycemic control (0.15%, 0.20%, and 0.15% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively).

Mean fasting serum insulin concentrations showed high variability with no clear trend between the placebo and OCA treatment groups.

Figure 43: Change in Serum Markers of Glycemic Control Over Time: Pooled Safety Population (N=2860)



HbA1c=hemoglobin A1C; IP=investigational product; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid
Note: Baseline of HbA1c was defined as the mean of all measurements prior to first dose of IP in Study 303. For other parameters and studies, baseline was defined as the last fasted evaluation prior to first dose of IP.
The summary was based on data from central laboratory provided by ICON in Study 303. For Glucose values from ICON, all were considered fasting (including those missing fasting status due to i.e., data issues).

There are several lines of preclinical evidence to suggest that OCA-mediated FXR activation may have beneficial effects on glucose homeostasis (Claudel 2005). Consistent with these nonclinical findings, a Phase 2 study demonstrated that OCA treatment improved insulin sensitivity in patients with presumed NAFLD and type 2 diabetes, assessed by the hyperinsulinemic euglycemic glucose clamp method (Mudaliar 2013).

Data for other glycemic markers evaluated in Study 303, including C-peptide and homeostasis model of assessment of insulin resistance (HOMA-IR) showed significant variability at all timepoints and across all treatment groups without a clear trend, thereby making any conclusions of limited value.

6.4.2.4.3. Change of Antidiabetic Medication Use

A summary of antidiabetic medication use in patients with or without diabetes mellitus is presented in Table 14.

Results in the Pooled Safety Population were mostly driven by the results in Study 303. Approximately half of the patients across the treatment groups were on antidiabetic medication at baseline. During the study, an additional 3% of patients in the OCA 25 mg group compared to placebo increased the number of antidiabetic medications (28.4% vs 25.4%). The incidence rate of patients maintaining the number of medications was approximately 55% across the treatment groups. The incidence rate of patients who initiated antidiabetic medications was generally similar in both OCA groups (each 26.0%) compared to placebo (24.6%).

Table 14: Summary of Change for Antidiabetic Medication Use In Patients with Diabetes Mellitus or Non-Diabetes Mellitus: Pooled Safety Population (N=2860)

	Pooled		
	Placebo	**OCA 10 mg**	**OCA 25 mg**
	N=1017 n (%)	**N=875 n (%)**	**N=968 n (%)**
Baseline			
On Medication	460	464	461
Not on Medication	415	411	366
During study, n (%)			
Increased number of medications[a]	117 (25.4)	114 (24.6)	131 (28.4)
Maintained number of medications[a]	254 (55.2)	257 (55.4)	252 (54.7)
Decreased number medications[a]	89 (19.3)	93 (20.0)	78 (16.9)
Initiated medications[b]	102 (24.6)	107 (26.0)	95 (26.0)

FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid

[a] Denominator for percentages should be based on the number of patients receiving antidiabetics at baseline. On-study changes in antidiabetic use could not be determined for FLINT because dates for concomitant medications were not collected.

[b] Denominators for percentages should be based on the number of patients not receiving antidiabetics at baseline.

6.4.2.5. CV Events

Treatment-emergent CV events (Investigator-reported and adjudicated) were summarized in the resubmission. Since the resubmission, analyses for on-study CV AESIs and adjudicated events have been performed. On-study analyses, highlighted below, are considered more clinically relevant since there is a potential for a lag in the development of CV events. Definitions used for "treatment-emergent" and "on-study" events are described below:

- Treatment-emergent events are defined as AEs that occurred from the first dose date until 30 days after last dose date in Study 303 and were defined as AEs that occurred from the first dose date in FLINT and Study 2001.
- On-study events are defined as AEs occurred between start date of first dose and earliest date of EOS, death, or DCO (31DEC2021) in Study 303 and are defined as AEs that occurred from the first dose date in FLINT and Study 2001.

While a larger number of events are captured in the on-study analyses, no meaningful differences were observed between the treatment-emergent and on-study data.

This section includes the following analyses:

- Investigator-reported on-study CV AEs (Section 6.4.2.5.1)
- Treatment-emergent and on-study adjudicated CV events (Section 6.4.2.5.2.2)

6.4.2.5.1. On-Study CV AEs

- On-study CV AEs are summarized in Table 15.
- The incidence rate of CV AEs was generally similar across the three treatment groups in the Pooled Safety Population (5.7% in the placebo group, 6.6% in the OCA 10 mg group, and 8.0% in the OCA 25 mg group) and without evidence of a clear dose-response.
- The incidence rates of individual CV AE PTs were also generally balanced across treatment groups. Of all CV AE PTs, angina pectoris and coronary artery disease were the CV events that occurred in ≥1.0% of patients in any treatment group. Angina pectoris occurred in 9 (0.9%), 15 (1.7%), and 16 (1.7%) patients in placebo, OCA 10 mg, and OCA 25 mg groups, respectively, while coronary artery disease occurred in 10 (1.0%), 5 (0.6%), and 11 (1.1%) patients in placebo, OCA 10 mg, and OCA 25 mg groups, respectively.
- The majority of CV AEs were rated as mild to moderate in severity by the Investigators, and the incidence rate of severe or life-threatening CV AEs was low and similar across treatment groups.
- The incidence rate of serious CV events was numerically higher in the OCA treatment groups (2.5%, 3.1%, and 3.8% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively). The higher incidence rate of serious CV AEs in the OCA 25 mg group was mainly driven by the PTs of myocardial infarction (MI), acute MI, and cerebrovascular accident. For patients in Study 303, for which adjudication data is available, all MI, acute MI, and cerebrovascular accident SAEs (11 total) were

positively adjudicated in the OCA 25 mg group, while 3 of 4 events in the OCA 10 mg group and all events in the placebo group (4 total) were positively adjudicated. The adjudicated outcome of CV events based on a broad search strategy provides a more rigorous CV risk assessment (Section 6.4.2.5.2).

- A total of 3 patients experienced CV AEs leading to death (1 patient in the OCA 10 mg group and 2 patients in the OCA 25 mg group).
  - One patient from Study 303 in the OCA 10 mg group experienced an event of MI (as reported by the Investigator) that led to death; this event was adjudicated as a death of undetermined cause.
  - Two patients in the OCA 25 mg group experienced CV AEs that led to death (1 patient with events of MI and myocardial ischemia; 1 patient with events of cerebrovascular accident and hypoxic-ischemic encephalopathy). Both patients had participated in FLINT; of note, CV events were not adjudicated in the earlier Phase 2 studies.
- CV AEs that led to discontinuation of investigational product occurred with a low and similar incidence rate in all three treatment groups: 0.3% in the placebo group and 0.1% in both OCA treatment groups.

Table 15: Overview of On-Study Cardiovascular AEs: Pooled Safety Population (N=2860)

Number (%) of Patients with any:		Pooled		
		Placebo N=1017	OCA 10 mg N=875	OCA 25 mg N=968
CV AE[a]	n (%)	58 (5.7)	58 (6.6)	77 (8.0)
Serious CV AEs	n (%)	25 (2.5)	27 (3.1)	37 (3.8)
Related CV AEs	n (%)	5 (0.5)	3 (0.3)	5 (0.5)
CV AEs Leading to Withdrawal of IP	n (%)	3 (0.3)	1 (0.1)	1 (0.1)
Severe CV AEs	n (%)	15 (1.5)	16 (1.8)	26 (2.7)
Life-threatening CV AEs	n (%)	7 (0.7)	1 (0.1)	6 (0.6)
CV AEs Leading to Death	n (%)	0	1 (0.1)	2 (0.2)

AE=adverse event; CNS= central nervous system; CV=cardiovascular; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; SMQ=standardized MedDRA query

Notes: On-study AEs are defined as AEs that occurred between start date of first dose and earliest date of end of study date, death date or Data cutoff date (31DEC2021) in Study 303 and are defined as AEs occurred from the first dose date in studies FLINT and D8602001.
AEs Leading to Withdrawal of IP information was not collected in FLINT. Denominators for Pooled doses exclude FLINT patients.

[a] CV AEs were defined as Embolic and thrombotic events broad SMQ, Ischemic heart disease broad SMQ, or CNS vascular disorders narrow SMQ.

6.4.2.5.2. Adjudicated CV Events (Study 303)

6.4.2.5.2.1. Adjudication Process

As agreed with the FDA, a systematic approach to the surveillance and management of CV risk was undertaken. A broad category of CV events was evaluated through a rigorous, standardized adjudication process.

Potential events were identified programmatically using searches for fatal events, hospitalizations, and SMQ based searches for CV TEAEs. SMQ trigger events included ischaemic heart disease, cardiac failure, Torsade de pointes/QT prolongation, arrhythmia related investigations, signs and symptoms, cardiac arrhythmia terms [including bradyarrhythmias and tachyarrhythmias], and central nervous system haemorrhages and cerebrovascular conditions. Events were reviewed in conjunction with evaluation of medical history, concomitant medications, vital signs, prespecified lab values, and ECGs. Adjudication committee members remained blinded to investigational product treatment assignment (CAC Charter, Version 7).

A panel of up to 7 independent, blinded CV experts (in groups of 3) adjudicated a broad set of suspected CV events and hospitalizations while blinded to study treatment assignment. Endpoints assessed by the CV adjudication committee included non-fatal MI, non-fatal stroke, CV death, hospitalization for unstable angina, all causes of death, transient ischemic attack, coronary/peripheral revascularization procedures, arrhythmias, or hospitalization/urgent visit for heart failure. Event adjudication required agreement between at least two reviewers; independent review was conducted by the third member if the initial two members were not in agreement. No changes to the adjudication process have been made since the original NDA.

6.4.2.5.2.2. Adjudication Results

On-study adjudicated CV events are summarized in Table 16.

- Analyses of adjudicated on-study CV events were conducted for Core MACE (defined as CV death, non-fatal MI, non-fatal stroke), 4-point MACE (defined as CV death, non-fatal MI, non-fatal stroke + hospitalization for unstable angina), and 5-point MACE (defined as CV death, non-fatal MI, non-fatal stroke + hospitalization for unstable angina + hospitalization/urgent visit for heart failure).
  - The on-study incidence rate for positively adjudicated events for Core MACE was 11 (1.3%), 5 (0.6%), and 15 (1.8%) patients in placebo, OCA 10 mg, and OCA 25 mg groups, respectively. Of note, the incidence rate for treatment-emergent adjudicated events for Core MACE was 10 (1.2%), 5 (0.6%), and 11 (1.3%) patients in placebo, OCA 10 mg, and OCA 25 mg groups, respectively.
  - On-Study 4-point MACE incidence rates were 13 (1.6%), 9 (1.1%), and 18 (2.2%) and 5-point MACE incidence rates were 16 (1.9%), 9 (1.1%), and 18 (2.2%) patients in placebo, OCA 10 mg, and OCA 25 mg groups, respectively. Of note, treatment-emergent adjudicated 4-point MACE incidence rates were 12 (1.5%), 8 (1.0%), and 13 (1.6%) and 5-point MACE incidence rates were 15 (1.8%), 8 (1.0%), and 13 (1.6%) patients in placebo, OCA 10 mg, and OCA 25 mg groups, respectively.

- A broader category of CV events was also adjudicated which included the following events: death from any cause, transient ischemic attack, coronary revascularization procedures, peripheral revascularization procedures, and hospitalization for clinically significant arrhythmias.

As a majority of patients enrolled in Study 303 reported comorbidities, including hypertension, type 2 diabetes, and hypercholesterolemia, an additional analysis controlling for baseline 10-year ASCVD risk was conducted. On-study adjudicated CV events occurred at similar rates in the three treatment groups in both the low risk (10-year ASCVD risk <20%) and high risk (10-year ASCVD risk ≥20%) categories (Figure 13).

As might be expected, a higher proportion of adjudicated events were reported in subjects with a 10-year ASCVD risk ≥20% across all treatment groups, including placebo, indicating that the risk is more likely related to underlying comorbidities in this patient population.

Table 16: Summary of On-Study Adjudicated Cardiovascular Events: Study 303 Safety_all Population (N=2477)

Cardiovascular Events		**Placebo (N=825) n (%)**	**OCA 10 mg (N=825) n (%)**	**OCA 25 mg (N=827) n (%)**
Number of Patients with at Least 1 Event				
Core MACE[a]	n (%)	11 (1.3)	5 (0.6)	15 (1.8)
	n (EAIR)[d]	10 (0.34)	5 (0.17)	15 (0.52)
4-point MACE[b]	n (%)	13 (1.6)	9 (1.1)	18 (2.2)
	n (EAIR)[d]	12 (0.41)	9 (0.31)	18 (0.63)
5-point MACE[c]	n (%)	16 (1.9)	9 (1.1)	18 (2.2)
	n (EAIR)[d]	15 (0.51)	9 (0.31)	18 (0.63)
Death				
From any cause		9 (1.1)	10 (1.2)	11 (1.3)
Cardiovascular death		1 (0.1)	1 (0.1)	1 (0.1)
Noncardiovascular death		7 (0.8)	7 (0.8)	9 (1.1)
Undetermined death		1 (0.1)	2 (0.2)	1 (0.1)
Nonfatal MI		**6 (0.7)**	**1 (0.1)**	**11 (1.3)**
Nonfatal stroke		**4 (0.5)**	**3 (0.4)**	**4 (0.5)**
Hospitalization for unstable angina		**2 (0.2)**	**4 (0.5)**	**3 (0.4)**
Transient ischemic attack		**1 (0.1)**	**0**	**4 (0.5)**
Revascularization procedure		**8 (1.0)**	**12 (1.5)**	**11 (1.3)**
Coronary		7 (0.8)	10 (1.2)	10 (1.2)
Peripheral		1 (0.1)	3 (0.4)	1 (0.1)

Cardiovascular Events	Placebo (N=825) n (%)	OCA 10 mg (N=825) n (%)	OCA 25 mg (N=827) n (%)
Heart failure	**4 (0.5)**	**1 (0.1)**	**3 (0.4)**
Hospitalization	3 (0.4)	0	1 (0.1)
Missing	1 (0.1)	1 (0.1)	2 (0.2)
Hospitalization for clinically significant arrhythmias	**3 (0.4)**	**4 (0.5)**	**9 (1.1)**

CV=cardiovascular; EAIR=exposure-adjusted incidence rate; IP=investigational product; MACE=major adverse cardiovascular events; MI=myocardial infarction; OCA=obeticholic acid

Notes: On-study defined as date of adjudicated event that occurred between start date of receipt of IP and earliest date of end of study date, death date, or data cutoff date (31DEC2021).

[a] Core MACE: CV death, non-fatal MI, non-fatal stroke

[b] 4-point MACE: CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina

[c] 5-point MACE: CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization/urgent visit for heart failure

[d] Trigger event for one placebo patient occurred slightly after the data cutoff date and is included in the cumulative incidence but not EAIR calculation since the exposure time was censored at the earliest of (treatment end date + 30 days, end of study or data cutoff date [31DEC2021]).

6.4.3. Renal Safety

Intercept performed a comprehensive evaluation of renal safety, including analyses of the following:

- Investigator-reported renal TEAEs (Section 6.4.3.1)
- Adjudicated renal events (Section 6.4.3.2)
- Renal function parameters (Section 6.4.3.3)

6.4.3.1. Renal TEAEs

Investigator-reported renal disorder TEAEs are summarized in Table 17.

- The incidence rate of renal TEAEs in the Pooled Safety Population was 9.3%, 11.7%, and 11.1% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively.
- The most frequently reported renal event in all treatment groups was blood creatinine increased (3.8%, 5.8%, and 4.4% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively), which may have been related to the protocol driven trigger for an increase in creatinine (≥0.3 mg/dl or ≥1.5 x Baseline).
- AKI was reported in 0.4% of patients in the placebo group, 0.9% of patients in the OCA 10 mg group, and 2.2% of patients in the OCA 25 mg group.
- The majority of renal TEAEs were mild or moderate in severity across treatment groups. A higher incidence rate of severe renal TEAEs, most commonly AKI, was reported for the OCA 25 mg group (0.2%, 0.7%, and 1.5% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively).

- A higher incidence rate of serious renal disorder TEAEs was reported in the OCA 25 mg group (0.3%, 0.7%, and 1.3% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively).
  - The imbalance in the incidence rate of serious renal disorder TEAEs was mainly attributed to events with the PT AKI, which was higher in the OCA 25 mg group (0.1%, 0.6%, and 1.1% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively).
  - A patient level review of the serious cases showed that the majority involved multiple confounding factors, including severe intercurrent illness such as sepsis, volume depletion, or exposure to ACE inhibitors, ARBs, or diuretics, all known to be associated with fluctuations in serum creatinine and possibly contributing to AKI. In the majority of cases, renal function improved after resolution of the acute event, with resumption of investigational product.
- The incidence rate of renal TEAEs leading to withdrawal of investigational product was low (<1.5%) across all treatment groups (1.1% each in the placebo and OCA 10 mg groups and 0.7% in the OCA 25 mg group).
- One renal TEAE was life-threatening and occurred in the placebo group (AKI), and one renal event led to death in the OCA 10 mg group (related to a case of sepsis, uremia, and AKI, resulting in a fatal outcome).

Table 17: Overview of Renal TEAEs: Pooled Safety Population (N=2477)

Number (%) of Patients with Any		Pooled		
		Placebo N=1017	**OCA 10 mg N=875**	**OCA 25 mg N=968**
Renal TEAE[a]	**n (%)**	95 (9.3)	102 (11.7)	107 (11.1)
	n (EAIR)	95 (3.26)	102 (3.94)	107 (4.18)
Serious renal TEAEs	**n (%)**	3 (0.3)	6 (0.7)	13 (1.3)
	n (EAIR)	3 (0.10)	6 (0.22)	13 (0.47)
Related renal TEAEs	**n (%)**	26 (2.6)	34 (3.9)	30 (3.1)
Renal TEAEs leading to withdrawal of IP	**n (%)**	10 (1.1)	10 (1.1)	6 (0.7)
Severe (Grade 3) renal TEAEs	**n (%)**	2 (0.2)	6 (0.7)	15 (1.5)
Life-threatening (Grade 4) renal TEAEs	**n (%)**	1 (0.1)	0	0
Renal TEAEs leading to death (Grade 5)	**n (%)**	0	1 (0.1)	0
Severe (≥Grade 3) renal TEAEs	**n (EAIR)**	3 (0.10)	7 (0.25)	15 (0.54)

CKD=chronic kidney disease; EAIR=exposure-adjusted incidence rate; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; SMQ=standardized MedDRA query; TEAE=treatment-emergent adverse event

[a] Renal disorders were defined as Acute renal failure broad SMQ, CKD broad SMQ, Proteinuria broad SMQ, Renovascular disorders broad SMQ, Tubulointerstitial diseases broad SMQ.

6.4.3.2. Adjudicated Renal Events in Study 303

Potential events were identified programmatically using the Acute Renal Failure SMQ searches of TEAEs as well as changes in central and local laboratory creatinine data. The definition of AKI specified in the RAC charter was based on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines (KDIGO 2012). Episodes where a patient experienced an increase within 7 days of previous values (i.e., prior value) in serum creatinine by ≥1.5x prior value, an increase within 48 hours of previous values (i.e., prior value) in serum creatinine by ≥0.3 mg/dl (≥26.5 µmol/l), or a decline within 48 hours of previous values (i.e., prior value) of serum creatinine by ≥0.3 mg/dl (≥26.5 µmol/l) were identified for evaluation. These triggered events were reviewed by the RAC, in conjunction with evaluation of medical history, concomitant medications, vital signs, and prespecified lab values and assessed for the presence or absence of injury, its severity, and whether or not the event could be attributed to investigational product according to the charter and the strength of the evidence available to RAC. The RAC remained blinded to investigational product allocation.

A summary of adjudicated AKI events in Study 303, as determined by the RAC, is presented in Table 18. Many cases had potential etiological confounding factors which the adjudication committee considered.

- The number of patients with events referred for adjudication were balanced across treatment groups, with events submitted from 38 (4.6%) patients in the placebo group, 46 (5.6%) in the OCA 10 mg group, and 44 (5.3%) in the OCA 25 mg group.
- The number of events adjudicated with evidence of AKI was low overall, but higher in the OCA 25 mg group.
- The number of patients with events adjudicated with evidence of AKI were 7 (0.8%) in the placebo group, 11 (1.3%) in the OCA 10 mg group, and 12 (1.5%) in the OCA 25 mg groups. Most events were adjudicated by the committee as mild (Stage 1).
- No patients in the placebo group, 2 patients in the OCA 10 mg group, and 0 patients in the OCA 25 mg group were adjudicated as Stage 2 AKI.
- One patient in the placebo group, 2 patients in the OCA 10 mg group, and 4 patients in the OCA 25 mg group were adjudicated as Stage 3 AKI (Table 18). All seven patients with Stage 3 AKI across the treatment groups were using a concomitant ACE inhibitor/ARB and a statin. OCA was resumed in 3 of the 6 patients with AKI in the OCA groups after resolution of the acute underlying illness.

Table 18: Adjudicated Treatment-Emergent Acute Kidney Injury Events: Study 303 Safety_all Population (N=2477)

Acute Kidney Injury Events	Placebo (N=825) n (%)	OCA 10 mg (N=825) n (%)	OCA 25 mg (N=827) n (%)
Number of Patients Submitted for Adjudication	**38 (4.6)**	**46 (5.6)**	**44 (5.3)**
Number of Patients Adjudicated with Evidence of AKI[a]	**7 (0.8)**	**11 (1.3)**	**12 (1.5)**
Number of Patients Adjudicated with Potential AKI Cases: By Severity of AKI			
Stage 1	6 (0.7)	7 (0.8)	8 (1.0)
Stage 2	0	2 (0.2)	0
Stage 3	1 (0.1)	2 (0.2)	4 (0.5)
Insufficient Data	0	0	0
Number of Patients Adjudicated with Potential AKI Case by Causal Association of AKI with Study Treatment[b]			
Insufficient Data	0	0	0
Not Related	4 (0.5)	1 (0.1)	4 (0.5)
Unlikely	1(0.1)	1 (0.1)	4 (0.5)
Possible	1 (0.1)	6 (0.7)	2 (0.2)
Probable	1 (0.1)	3 (0.4)	2 (0.2)
Highly Likely	0	0	0
Number (%) of Patients Adjudicated with Potential AKI Case with Highly Likely Drug-Related[a]	**0**	**0**	**0**
Number (%) Patients Adjudicated with Potential AKI Case with Probable Drug-Related by the Severity of AKI[a]	**1 (0.1)**	**3 (0.4)**	**2 (0.2)**
Stage 1	1 (0.1)	2 (0.2)	1 (0.1)
Stage 2	0	1 (0.1)	0
Stage 3	0	0	1 (0.1)
Insufficient Data	0	0	0

Acute Kidney Injury Events	Placebo (N=825) n (%)	OCA 10 mg (N=825) n (%)	OCA 25 mg (N=827) n (%)
Number (%) Patients Adjudicated with Potential AKI Case with Possible Drug-Related by the Severity of AKI[a]	**1 (0.1)**	**6 (0.7)**	**2 (0.2)**
Stage 1	1 (0.1)	5 (0.6)	1 (0.1)
Stage 2	0	1 (0.1)	0
Stage 3	0	0	1 (0.1)
Insufficient Data	0	0	0
Number (%) Patients Adjudicated with Potential AKI Case with Unlikely Drug-Related by the Severity of AKI[a]	**1 (0.1)**	**2 (0.2)**	**4 (0.5)**
Stage 1	1 (0.1)	1 (0.1)	3 (0.4)
Stage 2	0	0	0
Stage 3	0	1 (0.1)	1 (0.1)
Insufficient Data	0	0	0
Number of Patients with Potential AKI Case with Not Related by the Severity of AKI[a]	**5 (0.6)**	**1 (0.1)**	**4 (0.5)**
Stage 1	4 (0.5)	0	3 (0.4)
Stage 2	0	0	0
Stage 3	1 (0.1)	1 (0.1)	1 (0.1)
Insufficient Data	0	0	0

AKI=acute kidney injury; OCA=obeticholic acid; RAC=renal adjudication committee
Note: The adjudicated cases with missing relationship were counted in the 'Probable Related' group.
[a] Patients with more than 1 potential adjudicated event were counted only once using the highest stage. The adjudicated cases were assessed by RAC for severity according to RAC Charter (v4.0, 15 Feb 2022). Each adjudicated case could be determined by evaluating multiple renal triggers.
[b] Patients with more than 1 potential adjudicated case were counted only once using the closest relationship to investigational product. The adjudicated cases were assessed by RAC for relationship to investigational product according to RAC Charter (v4.0, 15 Feb 2022). Each adjudicated case could be determined by evaluating multiple renal triggers.

6.4.3.3. Renal Function Parameters

Serum markers of renal function included eGFR, serum creatinine, and urinary albumin to creatinine ratio. No difference was observed between placebo and the OCA groups for renal function parameters over time.

In the Pooled Safety Population, mean urine albumin to creatinine ratio was in the normal range in all treatment groups at both baseline (43.34 g/kg, 44.89 g/kg, and 40.41 g/kg in placebo, OCA 10 mg, and OCA 25 mg groups, respectively) and Month 18 (42.82 g/kg, 51.27 g/kg, and 41.63 g/kg in placebo, OCA 10 mg, and OCA 25 mg groups, respectively), and no clinically meaningful changes from baseline were observed across treatment groups at Month 18. At

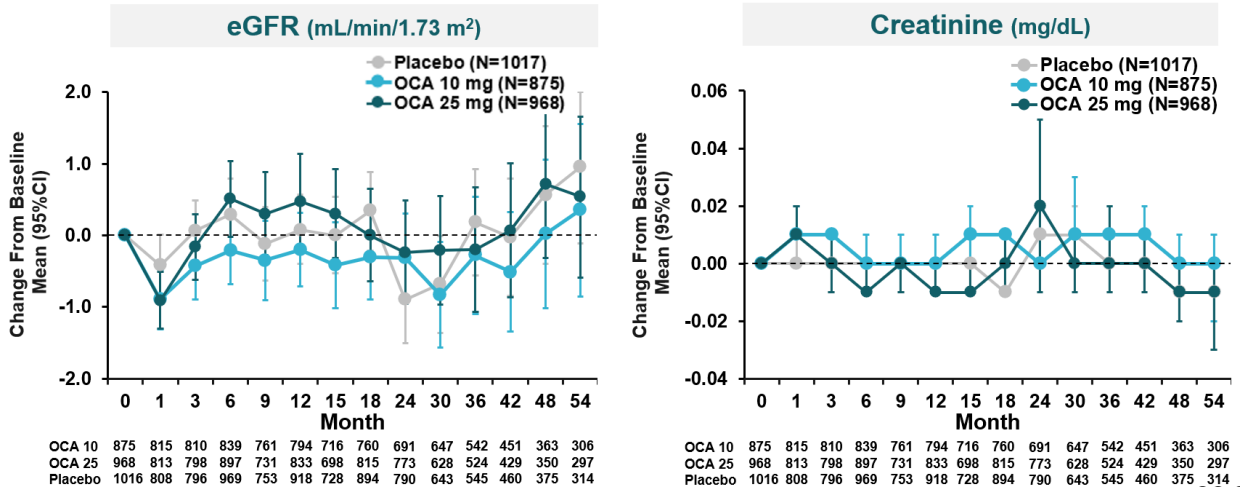
Month 48, the placebo group had a numerically higher, but not clinically significant, increase in mean urine albumin to creatinine ratio (72.09 g/kg, 54.67 g/kg, and 63.33 g/kg in placebo, OCA 10 mg, and OCA 25 mg groups, respectively).

6.4.3.3.1. eGFR and Serum Creatinine

No clinically significant changes over time or across treatment groups were observed with respect to eGFR or serum creatinine in the Pooled Safety Population (Figure 44).

The proportion of patients remaining in study with existing and missing eGFR or serum creatinine data differed at individual visits; however, the overall proportion of patient data was similar amongst treatment groups.

Figure 44: Mean Change from Baseline Over Time in eGFR and Creatinine: Pooled Safety Population (N=2860)



eGFR=estimated glomerular filtration rate; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid
Note: The summary was based on data from central laboratory provided by ICON.

6.4.3.4. Urolithiasis

The incidence rate of Investigator-reported urolithiasis TEAEs, including serious TEAEs, was similar across treatment groups in the Pooled Safety Population (Table 19).

- The overall incidence rate of urolithiasis TEAEs was similar across the treatment groups (3.2%, 3.7%, and 3.5% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively).
- The majority of urolithiasis TEAEs were mild to moderate in severity. The incidence rate of severe and serious urolithiasis TEAE events was low (<1.0%) in all treatment groups,

Table 19: Overview of Urolithiasis TEAEs: Pooled Safety Population (N=2860)

Number (%) of Patients with any:		Pooled		
		Placebo N=1017	OCA 10 mg N=875	OCA 25 mg N=968
Urolithiasis TEAE[a]	**n (%)**	33 (3.2)	32 (3.7)	34 (3.5)
	n (EAIR)	33 (1.10)	32 (1.18)	34 (1.26)
Serious urolithiasis TEAEs	**n (%)**	5 (0.5)	8 (0.9)	6 (0.6)
	n (EAIR)	5 (0.16)	8 (0.29)	6 (0.22)
Related urolithiasis TEAEs	**n (%)**	1 (0.1)	5 (0.6)	1 (0.1)
Urolithiasis TEAEs leading to withdrawal of IP	**n (%)**	0	1 (0.1)	0
Severe (Grade 3) urolithiasis TEAEs	**n (%)**	4 (0.4)	7 (0.8)	7 (0.7)
Life-threatening (Grade 4) urolithiasis TEAEs	**n (%)**	0	0	0
Urolithiasis TEAEs leading to death (Grade 5)	**n (%)**	0	0	0
Severe (≥Grade 3) urolithiasis TEAEs	**n (EAIR)**	4 (0.13)	7 (0.25)	7 (0.25)

EAIR=exposure-adjusted incidence rate; IP=investigational product; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; SOC= system organ class; TEAE=treatment-emergent adverse event

[a] Urolithiases (Nephrolithiasis) was defined as High-level group term Urolithiases (under the SOC Renal and Urinary Disorders).

6.4.4. Gallstone-Related Events

6.4.4.1. Gallstone-Related TEAEs

Investigator-reported gallstone-related TEAEs are summarized in Table 20.

- The incidence rate of overall gallstone-related TEAEs was low and dose-dependent, with a higher incidence rate in the OCA groups compared with placebo.
- The incidence rate of serious gallstone TEAEs was higher in the OCA groups compared with placebo (risk difference [95% CI] of 0.21 [-0.60, 1.02] and 1.68 [0.59, 2.76] in OCA 10 mg and OCA 25 mg groups, respectively), mainly driven by cholecystitis and cholelithiasis, consistent with the known MOA of FXR-agonists related increased bile lithogenicity.
- The overall rate of investigational product discontinuation due to gallstone-related TEAEs was similar across the 3 treatment groups (0.1%, 0.5%, and 0.4% patients in the placebo, OCA 10 mg, and OCA 25 mg group, respectively).

Table 20: Overview of Gallstone-Related TEAEs: Pooled Safety Population (N=2860)

Number of Patients with Any:		Pooled		
		Placebo N=1017	OCA 10 mg N=875	OCA 25 mg N=968
Gallstone-related TEAE	**n (%)**	34 (3.3)	44 (5.0)	65 (6.7)
	n (EAIR)	34 (1.13)	44 (1.63)	65 (2.48)
Serious gallstone-related TEAE	**n (%)**	7 (0.7)	8 (0.9)	23 (2.4)
	n (EAIR)	7 (0.23)	8 (0.29)	23 (0.84)
Related gallstone-related TEAE	**n (%)**	15 (1.5)	20 (2.3)	17 (1.8)
Gallstone-related TEAE leading to discontinuation of IP	**n (%)**	1 (0.1)	4 (0.5)	3 (0.4)
Severe (Grade 3) gallstone-related TEAE	**n (%)**	6 (0.6)	5 (0.6)	18 (1.9)
Life-threatening (Grade 4) gallstone-related TEAE	**n (%)**	0	0	0
Gallstone-related TEAE leading to death (Grade 5)	**n (%)**	0	0	0
Severe (≥Grade 3) gallstone-related TEAE	**n (EAIR)**	6 (0.20)	5 (0.18)	18 (0.66)

EAIR=exposure-adjusted incidence rate; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; PT=preferred term; SMQ= standardized MedDRA query; TEAE=treatment-emergent adverse event

[a] Gallstone-related events were defined as Gallbladder related disorders narrow SMQ, Gallstone-related disorders narrow SMQ, Additional PTs of Biliary abscess, Biliary sepsis, Biliary tract infection, Gallbladder abscess, Gallbladder empyema, Bile duct necrosis, Bile duct obstruction, Bile duct stenosis, Biliary colic, Cholangitis, Cholangitis acute, Cholangitis chronic, Cholecystocholangitis, or Perforation bile duct.

6.4.4.2. Cholecystectomy

In the pooled analysis, there were 216 (21.2%) patients in the placebo group, 194 (22.2%) patients in OCA 10 mg group, and 226 (23.3%) patients in the OCA 25 mg group with a history of a prior cholecystectomy at baseline (prior to Day 1).

In the Pooled Safety Population, the incidence rate of patients undergoing cholecystectomy during the study was low overall (1.7%, 1.7%, and 3.9% in the placebo, OCA 10 mg, and OCA 25 mg groups), with a risk difference [95% CI] of 0.03% [-1.14, 1.19] and 2.26% [0.81, 3.72] in OCA 10 mg and OCA 25 mg groups, respectively, compared to placebo (Table 21). All patients reporting a cholecystectomy were from Study 303.

Table 21: Post-Baseline Cholecystectomy: Study 303 Safety_all Population (N=2477) and Pooled Safety Population (N=2860)

	Placebo	OCA 10 mg	OCA 25 mg
Study 303 Safety_all Population	**N=825**	**N=825**	**N=827**
Patients with Post-Baseline Cholecystectomy[a] n (%)	17 (2.1)	15 (1.8)	38 (4.6)
Risk Difference (95% CI)	-	-0.25 (-1.58, 1.08)	2.54 (0.82, 4.27)
Pooled Safety Population	**N=1017**	**N=875**	**N=968**
Patients with Post-Baseline Cholecystectomy[a] n (%)	17 (1.7)	15 (1.7)	38 (3.9)
Risk Difference (95% CI)	-	0.03 (-1.14, 1.19)	2.26 (0.81, 3.72)

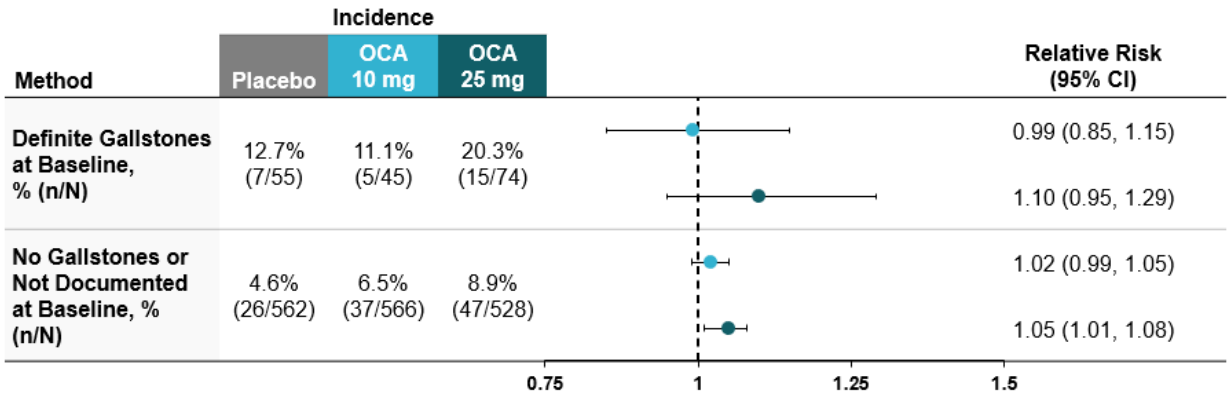
IP=investigational product; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; TZD=thiazolidinedione
Note: Denominators for percentages are based on N, the number of patients in the population.
Risk difference= Percentage of patients with at least one event in each treatment group – Percentage of patients with at least one event in placebo group, stratified by use of TZDs or vitamin E at baseline (yes/no); the Cochran-Mantel-Haenszel method is used to construct the confidence intervals.
[a] Patients with procedure after IP dose by searching standard procedure name ='Cholecystectomy' in Procedure.

In Study 303, 17 (2.1%), 15 (1.8%), and 38 (4.6%) of patients in placebo, OCA 10 mg, and OCA 25 mg groups, respectively, underwent a cholecystectomy on-study.

In patients who resumed or maintained investigational product after a post-baseline cholecystectomy in Study 303 (14 [1.7%], 12 [1.5%], and 33 [4.0%] in placebo, OCA 10 mg, and OCA 25 mg groups, respectively), only 2 patients experienced a gallstone-related TEAE: 1 (0.1%) in the placebo group and 1 (0.1%) on OCA 10 mg. No patient who resumed or maintained investigational product after a post-baseline cholecystectomy experienced a pancreatitis-related TEAE.

The rate of gallstone-related events by baseline gallstone status (prior cholecystectomy, gallstones present at baseline, no gallstones or not documented at baseline) in Study 303 is displayed in Figure 45. No difference in the proportionate risk was observed for OCA 25 mg relative to placebo, regardless of baseline gallstone-related status.

Figure 45: Gallstone-Related Events by Gallstone Status: Study 303 Safety_all Population (N=2477)



OCA=obeticholic acid

6.4.4.3. Pancreatitis Events

The incidence rate of Investigator-reported pancreatitis TEAEs, including severe and serious TEAEs, was balanced across treatment groups (Table 22).

- The overall incidence rate of pancreatitis TEAEs was balanced across treatment groups: 0.9% in the placebo group, 0.6% OCA 10 mg group, and 0.8% in the OCA 25 mg group.
- The incidence rate of severe pancreatitis TEAEs was 0.4%, 0.1%, and 0.4% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively.
- One (0.1%) patient in the OCA 10 mg group experienced a life-threatening (Grade 4) event of pancreatitis acute.
- The incidence rate of serious pancreatitis TEAEs, including severe and serious pancreatitis and biliary pancreatitis TEAEs, was balanced across treatment groups (0.5% in the placebo group, 0.6% in the OCA 10 mg group, and 0.6% in the OCA 25 mg group). One (0.1%) patient in the placebo group experienced a serious AE of pancreatitis hemorrhagic with a fatal outcome.
- The incidence rate of pancreatitis acute TEAEs that led to withdrawal of investigational product was balanced across the treatment groups, with 0.8% in the placebo group, 0.2% in the OCA 10 mg group, and 0.6% in the OCA 25 mg group.
- The EAIR of ≥Grade 3 pancreatitis TEAEs was similar across treatment groups and occurred in 5 (0.16 per 100 PY) patients in the placebo group, 2 (0.07 per 100 PY) patients in the OCA 10 mg group, and 4 (0.14 per 100 PY) patients in the OCA 25 mg group.

Table 22: Overview of Pancreatitis TEAEs: Pooled Safety Population (N=2860)

		Pooled		
Number (%) of Patients with Any		**Placebo N=1017**	**OCA 10 mg N=875**	**OCA 25 mg N=968**
Acute Pancreatitis TEAE	**n (%)**	9 (0.9)	5 (0.6)	8 (0.8)
	n (EAIR)	9 (0.29)	5 (0.18)	8 (0.29)
Serious pancreatitis TEAE	**n (%)**	5 (0.5)	5 (0.6)	6 (0.6)
	n (EAIR)	5 (0.16)	5 (0.18)	6 (0.22)
Related pancreatitis TEAE	**n (%)**	5 (0.5)	3 (0.3)	4 (0.4)
Pancreatitis TEAE leading to withdrawal of IP	**n (%)**	3 (0.3)	2 (0.2)	4 (0.5)
Pancreatitis acute TEAE leading to withdrawal of IP	**n (%)**	7 (0.8)	2 (0.2)	5 (0.6)
Severe pancreatitis TEAEs	**n (%)**	4 (0.4)	1 (0.1)	4 (0.4)
Life-threatening pancreatitis TEAEs	**n (%)**	0	1 (0.1)	0
Pancreatitis TEAE leading to death	**n (%)**	1 (0.1)	0	0
Severe (≥Grade 3) pancreatitis TEAEs	**n (EAIR)**	5 (0.16)	2 (0.07)	4 (0.14)

EAIR=exposure-adjusted incident rate; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; SMQ=standardized MedDRA query; TEAE=treatment-emergent adverse event

Note: Pancreatitis is defined as Acute pancreatitis narrow SMQ.

6.4.5. Pruritus

6.4.5.1. Pruritus TEAEs

Pruritus was the most frequently reported Investigator-reported AE in DB NASH studies for OCA and is identified as an ADR in the labeling of Ocaliva for PBC. The majority of pruritus events were mild to moderate and occurred within the first 3 months of treatment. Pruritus TEAEs are summarized in Table 23.

- The overall incidence rate of pruritus TEAEs was dose-dependent and highest in the OCA 25 mg group (23.2%, 34.3%, and 53.3% in placebo, OCA 10 mg, and OCA 25 mg groups, respectively).
- The incidence rate of serious pruritus TEAEs was low across all treatment groups (<1%); 7 patients in the OCA 25 mg group reported an SAE of pruritus. In all 7 cases, pruritus resolved after discontinuing treatment with OCA.
- Pruritus TEAEs that led to discontinuation of investigational product were observed only in Study 303 and occurred with a higher incidence rate in the OCA 25 mg group (12.1%) compared with the OCA 10 mg (1.6%) or placebo (0.9%) groups; approximately half of the discontinuations were protocol-mandated discontinuations for ≥Grade 3 (severe) pruritus, which limits an accurate assessment of tolerability.

Table 23: Overview of Pruritus TEAEs: Pooled Safety Population (N=2860)

		Pooled		
Number (%) of Patients with Any:		**Placebo N=1017**	**OCA 10 mg N=875**	**OCA 25 mg N=968**
Pruritus TEAE[a]	**n (%)**	236 (23.2)	300 (34.3)	516 (53.3)
	n (EAIR)	236 (9.50)	300 (15.11)	516 (34.51)
Serious pruritus TEAEs	**n (%)**	0	0	7 (0.7)
	n (EAIR)	0	0	7 (0.25)
Related pruritus TEAEs	**n (%)**	178 (17.5)	240 (27.4)	474 (49.0)
Pruritus TEAEs leading to withdrawal of IP	**n (%)**	8 (0.9)	14 (1.6)	100 (12.1)
Severe pruritus TEAEs	**n (%)**	3 (0.3)	10 (1.1)	60 (6.2)
Life-threatening pruritus TEAEs	**n (%)**	0	0	0
Pruritus TEAEs leading to death	**n (%)**	0	0	0
Severe (≥Grade 3) pruritus TEAEs	**n (EAIR)**	3 (0.10)	10 (0.36)	60 (2.18)

EAIR=exposure-adjusted incidence rate; HLT=high level term; IP=investigational product; NASH=nonalcoholic steatohepatitis; NEC=Not Elsewhere Classified; OCA=obeticholic acid; PT=preferred term; TEAE=treatment-emergent adverse event

Note: AESIs leading to IP discontinuation information was not collected in FLINT. Denominators for Pooled doses excluded FLINT subjects.

[a] Pruritus TEAEs were defined as any PT within the Pruritus NEC HLT or including 'prur'.

6.4.5.2. Management Strategies

An assessment of management strategies for pruritus was conducted in Study 747-303 (Table 24); results are as follows:

- A Grade 3 or higher TEAE of pruritus required mandatory discontinuation of investigational product (Protocol 747-303 Safety Amendment; 19 Sep 2017).
- No dose modification was reported in 24.7%, 31.2%, and 44.3% of patients who reported pruritus in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively.
- Drug interruption (i.e., a drug holiday) to manage pruritus was reported in 2.1%, 4.1%, and 16.1% of patients in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively. Most patients who reported a drug interruption for pruritus experienced a single interruption.
- When evaluating intervention for Grade ≤2 severity pruritus events, a medication was used to manage pruritus in 7.4%, 15.8%, and 35.8% of patients in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively, with an antihistamine used most frequently.
- Most pruritus events were mild to moderate and managed with temporary interruption of OCA treatment or use of medications such as antihistamines.

Table 24: Summary of Management Strategies for Pruritus: Study 303 Safety_all Population (N=2477)

	Placebo (N=825) n (%)	OCA 10 mg (N=825) n (%)	OCA 25 mg (N=827) n (%)
Action Taken with Study Medication for Pruritus (all Grades of Severity)[a]			
Drug Interrupted	17 (2.1)	34 (4.1)	133 (16.1)
Dose Not Changed	204 (24.7)	257 (31.2)	366 (44.3)
Dose Adjustment	0	2 (0.2)	9 (1.1)
Dose Frequency Change	4 (0.5)	4 (0.5)	38 (4.6)
Drug Withdrawn	8 (1.0)	14 (1.7)	100 (12.1)
Unknown	0	0	1 (0.1)
NA	3 (0.4)	9 (1.1)	13 (1.6)
Action Taken for Pruritus (≤Grade 2 Severity)[a]			
Non-drug Treatment	0	2 (0.2)	3 (0.4)
Patient Discontinued from Study	1 (0.1)	1 (0.1)	21 (2.5)
Medication Given	61 (7.4)	130 (15.8)	296 (35.8)
Emergency Room Visit	5 (0.6)	2 (0.2)	7 (0.8)
Other	14 (1.7)	18 (2.2)	46 (5.6)

	Placebo (N=825) n (%)	OCA 10 mg (N=825) n (%)	OCA 25 mg (N=827) n (%)
Medication Initiated for Pruritus (≤Grade 2 Severity)			
Bile Acid Sequestrants	10 (1.2)	22 (2.7)	101 (12.2)
Antihistamines	36 (4.4)	87 (10.5)	220 (26.6)
Corticosteroids	9 (1.1)	22 (2.7)	56 (6.8)
Other	16 (1.9)	27 (3.3)	76 (9.2)

OCA=obeticholic acid
[a] Patients who reported more than 1 action with multiple occurrences for Pruritus were counted only once.

7. SAFETY IN SPECIAL POPULATIONS AND GROUPS

7.1. Intrinsic and Extrinsic Factors

TEAEs from patients with NASH treated with OCA or with placebo in the long-term, DB, placebo-controlled studies were evaluated for differences based on age group, sex, race, baseline fibrosis stage, and baseline diabetes status. Overall, review of TEAEs by subgroups did not indicate any clinically meaningful differences, and trends across subgroups appeared to be generally similar.

7.1.1. Age Group

An overview of TEAEs by age (<65 years, ≥65 years to <75 years, or ≥75 years) occurring in the Pooled Safety Population is shown in Table 25. Overall, the pattern of TEAEs was similar across age groups. The incidence rate of SAEs and TEAEs leading to discontinuation was higher in patients ≥65 years to <75 years compared to those <65 years of age.

For age group ≥75 years, SAEs were reported by 4 (33.3%) patients in the placebo group, 1 (7.1%) in the OCA 10 mg group, and 4 (36.4%) in the OCA 25 mg group. The TEAEs leading to discontinuation of investigational product was reported in 2 (20.0%) patients in the OCA 25 mg group. Since there are only 37 patients in the Pooled Safety Population ≥75 years, any differences in the pattern and rate of events should be interpreted with caution.

The rate of common TEAEs was generally similar across age groups. No meaningful age dependent effect was observed on the overall pattern of TEAEs by PT.

Table 25: Overall Summary of Treatment-Emergent Adverse Events by Age Group: Pooled Safety Population (N=2860)

	Age Group <65 Years			Age Group ≥65 to <75 Years			Age Group ≥75 Years		
	Placebo	OCA 10 mg	OCA 25 mg	Placebo	OCA 10 mg	OCA 25 mg	Placebo	OCA 10 mg	OCA 25 mg
	N=1017 n (%)	N=875 n (%)	N=968 n (%)	N=1017 n (%)	N=875 n (%)	N=968 n (%)	N=1017 n (%)	N=875 n (%)	N=968 n (%)
N	842	705	769	175	170	199	12	14	11
Number (%) of Patients Reporting at Least One:									
TEAE	743 (88.2)	675 (95.7)	720 (93.6)	157 (89.7)	164 (96.5)	192 (96.5)	11 (91.7)	12 (85.7)	10 (90.9)
TEAE by Severity[a]									
Mild	165 (19.6)	145 (20.6)	114 (14.8)	29 (16.6)	28 (16.5)	20 (10.1)	2 (16.7)	4 (28.6)	2 (18.2)
Moderate	407 (48.3)	367 (52.1)	395 (51.4)	86 (49.1)	94 (55.3)	95 (47.7)	6 (50.0)	7 (50.0)	4 (36.4)
Severe	153 (18.2)	146 (20.7)	196 (25.5)	36 (20.6)	38 (22.4)	67 (33.7)	3 (25.0)	1 (7.1)	4 (36.4)
Life-Threatening	12 (1.4)	10 (1.4)	9 (1.2)	4 (2.3)	2 (1.2)	4 (2.0)	0	0	0
Death	6 (0.7)	7 (1.0)	6 (0.8)	2 (1.1)	2 (1.2)	6 (3.0)	0	0	0
TEAE Leading to Discontinuation of IP[b]	71 (10.0)	77 (10.9)	116 (18.0)	23 (14.2)	28 (16.5)	63 (34.4)	0	0	2 (20.0)
SAE	157 (18.6)	163 (23.1)	171 (22.2)	43 (24.6)	47 (27.6)	69 (34.7)	4 (33.3)	1 (7.1)	4 (36.4)

CTCAE=Common Terminology Criteria for Adverse Events; FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; IP=investigational product; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Notes: Denominators for percentages were based on N, the number of patients in the population.

Adverse events with missing severity were counted in the 'Severe' group.

[a] Patients who reported more than one adverse event were counted only once using the highest severity. Adverse events were graded for severity using CTCAE Version 4.03 as: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death.

[b] TEAE Leading to IP discontinuation information was not collected in FLINT. Denominators for Pooled doses excluded FLINT patients.

7.1.2. Sex

An overview of TEAEs by sex occurring in the Pooled Safety Population is shown in Table 26. Overall, the pattern of TEAEs was similar across males and females. Overall, more females than males experienced SAEs and severe TEAEs. TEAEs leading to discontinuation of investigational product also occurred with a higher incidence rate in female than male patients in OCA treatment groups.

In the analysis of the Pooled Safety Population, the overall pattern of common TEAEs by PT was similar across groups regardless of sex.

Table 26: Overall Summary of Treatment-Emergent Adverse Events by Sex: Pooled Safety Population (N=2860)

	Male			Female		
	Placebo	OCA 10 mg	OCA 25 mg	Placebo	OCA 10 mg	OCA 25 mg
	N=1017 n (%)	N=875 n (%)	N=968 n (%)	N=1017 n (%)	N=875 n (%)	N=968 n (%)
N	436	385	376	581	490	592
Number (%) of Patients Reporting at Least One:						
TEAE	379 (86.9)	368 (95.6)	344 (91.5)	521 (89.7)	471 (96.1)	568 (95.9)
TEAE by Severity[a]						
Mild	90 (20.6)	84 (21.8)	58 (15.4)	104 (17.9)	89 (18.2)	76 (12.8)
Moderate	212 (48.6)	208 (54.0)	189 (50.3)	281 (48.4)	253 (51.6)	301 (50.8)
Severe	67 (15.4)	62 (16.1)	89 (23.7)	122 (21.0)	122 (24.9)	174 (29.4)
Life-Threatening	5 (1.1)	8 (2.1)	1 (0.3)	11 (1.9)	4 (0.8)	12 (2.0)
Death	5 (1.1)	6 (1.6)	7 (1.9)	3 (0.5)	3 (0.6)	5 (0.8)
TEAE Leading to Discontinuation of IP[b]	43 (11.2)	42 (10.9)	60 (18.0)	51 (10.4)	63 (12.9)	119 (24.1)
SAE	82 (18.8)	88 (22.9)	85 (22.6)	118 (20.3)	122 (24.9)	155 (26.2)

CTCAE=Common Terminology Criteria for Adverse Events; FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; IP=investigational product; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Notes: Denominators for percentages were based on N, the number of patients in the population.
Adverse events with missing severity were counted in the 'Severe' group.

[a] Patients who reported more than one adverse event were counted only once using the highest severity. Adverse events were graded for severity using CTCAE Version 4.03 as: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death.

[b] TEAE Leading to IP discontinuation information was not collected in FLINT. Denominators for Pooled doses excluded FLINT patients.

7.1.3. Race

An overview of TEAEs by sex occurring in the Pooled Safety Population is shown in Table 27. The majority of the patients were White, with 88.1%, 96.9%, and 93.6% of the patients receiving placebo, OCA 10 mg, and OCA 25 mg, respectively. The overall rate of TEAEs was not affected by race; the majority of patients who received placebo, OCA 10 mg, and OCA 25 mg reported at least one TEAE. Most TEAEs were of mild or moderate severity, regardless of race. The rate of life threatening TEAEs was low in all treatment groups, regardless of race.

Regardless of race, the overall rate of SAEs was higher in the OCA treatment groups compared with placebo.

Table 27: Overall Summary of Treatment-Emergent Adverse Events by Race: Pooled Safety Population (N=2860)

	White			Other Races			Missing		
	Placebo	OCA 10 mg	OCA 25 mg	Placebo	OCA 10 mg	OCA 25 mg	Placebo	OCA 10 mg	OCA 25 mg
	N=1017 n (%)	N=875 n (%)	N=968 n (%)	N=1017 n (%)	N=875 n (%)	N=968 n (%)	N=1017 n (%)	N=875 n (%)	N=968 n (%)
N	796	679	797	126	120	90	95	76	81
Number (%) of Patients Reporting at Least One:									
TEAE	701 (88.1)	658 (96.9)	746 (93.6)	107 (84.9)	109 (90.8)	88 (97.8)	92 (96.8)	72 (94.7)	78 (96.3)
TEAE by Severity[a]									
Mild	132 (16.6)	117 (17.2)	109 (13.7)	41 (32.5)	43 (35.8)	14 (15.6)	21 (22.1)	13 (17.1)	11 (13.6)
Moderate	397 (49.9)	371 (54.6)	410 (51.4)	48 (38.1)	50 (41.7)	48 (53.3)	48 (50.5)	40 (52.6)	32 (39.5)
Severe	154 (19.3)	153 (22.5)	206 (25.8)	15 (11.9)	14 (11.7)	25 (27.8)	20 (21.1)	17 (22.4)	32 (39.5)
Life-Threatening	12 (1.5)	9 (1.3)	12 (1.5)	2 (1.6)	2 (1.7)	1 (1.1)	2 (2.1)	1 (1.3)	0
Death	6 (0.8)	8 (1.2)	9 (1.1)	1 (0.8)	0	0	1 (1.1)	1 (1.3)	3 (3.7)
TEAE Leading to Discontinuation of IP[b]	68 (9.9)	83 (12.2)	133 (19.7)	5 (5.1)	11 (9.2)	15 (20.0)	21 (23.1)	11 (14.5)	31 (39.7)
SAE	162 (20.4)	167 (24.6)	195 (24.5)	16 (12.7)	18 (15.0)	17 (18.9)	22 (23.2)	25 (32.9)	28 (34.6)

CTCAE=Common Terminology Criteria for Adverse Events; FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; IP=investigational product; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Notes: Denominators for percentages were based on N, the number of patients in the population.

Adverse events with missing severity were counted in the 'Severe' group.

Other races included American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and Other.

[a] Patients who reported more than one adverse event were counted only once using the highest severity. Adverse events were graded for severity using CTCAE Version 4.03 as: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death.

[b] TEAE Leading to IP discontinuation information was not collected in FLINT. Denominators for Pooled doses excluded FLINT patients.

7.1.4. Baseline Fibrosis Stage

7.1.4.1. Overall Adverse Events

In the analysis of the Pooled Safety Population, the rate of patients with baseline F2 or F3 who reported a TEAE was similar across treatment groups: approximately 90%, 96%, and 95% of patients in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively.

An overall summary of TEAEs by baseline fibrosis stage in the Pooled Safety Population is presented in Table 28.

Table 28: Overall Summary of Treatment-Emergent Adverse Events by Baseline Fibrosis Stage: Pooled Safety Population (N=2860)

	F1			F2			F3		
	Placebo	OCA 10 mg	OCA 25 mg	Placebo	OCA 10 mg	OCA 25 mg	Placebo	OCA 10 mg	OCA 25 mg
	N=171 n (%)	N=116 n (%)	N=135 n (%)	N=343 n (%)	N=301 n (%)	N=338 n (%)	N=494 n (%)	N=452 n (%)	N=483 n (%)
Total Number of TEAEs	1336	1036	1167	2661	2918	3186	4103	4447	4521
Total Number of SAEs	46	47	40	101	117	164	167	172	246
Number (%) of Patients Reporting at Least One:									
TEAE	145 (84.8)	113 (97.4)	124 (91.9)	307 (89.5)	285 (94.7)	319 (94.4)	443 (89.7)	436 (96.5)	461 (95.1)
TEAE by Severity[a]									
Mild	38 (22.2)	30 (25.9)	18 (13.3)	66 (19.2)	56 (18.6)	50 (14.8)	88 (17.8)	85 (18.8)	66 (13.7)
Moderate	77 (45.0)	56 (48.3)	79 (58.5)	174 (50.7)	165 (54.8)	163 (48.2)	241 (48.8)	237 (52.4)	242 (50.1)
Severe	25 (14.6)	24 (20.7)	25 (18.5)	58 (16.9)	55 (18.3)	99 (29.3)	105 (21.3)	105 (23.2)	137 (28.4)
Life-Threatening	4 (2.3)	2 (1.7)	1 (0.7)	5 (1.5)	4 (1.3)	5 (1.5)	6 (1.2)	6 (1.3)	7 (1.4)
Death	1 (0.6)	1 (0.9)	1 (0.7)	4 (1.2)	5 (1.7)	2 (0.6)	3 (0.6)	3 (0.7)	9 (1.9)
TEAE Leading to Discontinuation of IP[b]	9 (7.4)	11 (9.5)	26 (26.8)	34 (11.2)	38 (12.6)	47 (15.7)	51 (11.3)	56 (12.4)	106 (24.7)
SAE	27 (15.8)	33 (28.4)	19 (14.1)	66 (19.2)	63 (20.9)	86 (25.4)	105 (21.3)	113 (25.0)	134 (27.7)

F1=fibrosis stage 1; F2=fibrosis stage 2; F3=fibrosis stage 3; IP=investigational product; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Notes: Denominators for percentages were based on N, the number of patients in the population.

Adverse events with missing severity were counted in the 'Severe' group.

Fibrosis stage for Study 303 is based on the original central read biopsy slides (ie, the unpaired screening read). Fibrosis stage for study Flint is based on the local read biopsy slides.

[a] Patients who reported more than one adverse event were counted only once using the highest severity. Adverse events were graded for severity using CTCAE Version 4.03 as: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death.

[b] TEAE Leading to IP discontinuation information was not collected in FLINT. Denominators for Pooled doses excluded FLINT patients.

7.1.4.2. Hepatic Events

A higher number of patients experienced Investigator-reported hepatic SAEs with increasing baseline fibrosis stage (F3>F2>F1) (Table 29). Similar to the overall population, the incidence rate of SAEs was higher in the OCA 25 mg group compared to placebo, regardless of fibrosis stage.

Table 29: Serious Hepatic Treatment-Emergent Adverse Events by Fibrosis Stage: Pooled Safety Population (N=2860)

	F1			F2			F3		
	Placebo	OCA 10 mg	OCA 25 mg	Placebo	OCA 10 mg	OCA 25 mg	Placebo	OCA 10 mg	OCA 25 mg
	N=171 n (%)	N=116 n (%)	N=135 n (%)	N=343 n (%)	N=301 n (%)	N=338 n (%)	N=494 n (%)	N=452 n (%)	N=483 n (%)
Total Number of Hepatic SAEs	0	1 (0.9)	1 (0.7)	2 (0.6)	1 (0.3)	4 (1.2)	0	7 (1.5)	11 (2.3)

F1=fibrosis stage 1; F2=fibrosis stage 2; F3=fibrosis stage 3; OCA=obeticholic acid; SAE=serious adverse event

7.1.5. Baseline Diabetes Status

In the pooled analyses, the majority of patients (approximately 60%) had diabetes at baseline. Although the overall incidence rate of TEAEs was not affected by baseline diabetes status, the incidences of SAEs, severe TEAEs, TEAEs leading to discontinuation of the investigational product, and TEAEs leading to death were higher among patients with diabetes compared to patients without diabetes. Among patients with diabetes, the incidence rate of SAEs was generally higher in the OCA treatment groups, and those of severe TEAEs and TEAEs leading to discontinuation of the investigational product were higher in the OCA 25 mg group compared to the placebo and OCA 10 mg groups and were mostly driven by pruritus. In the OCA groups, the incidence rate of pruritus was similar between patients with and without diabetes at baseline.

Table 30: Overall Summary of Treatment-Emergent Adverse Events by Baseline Diabetes Status: Pooled Safety Population (N=2860)

	Baseline Diabetes Status = Yes			Baseline Diabetes Status = No		
	Placebo N=1017 n (%)	OCA 10 mg N=875 n (%)	OCA 25 mg N=968 n (%)	Placebo N=1017 n (%)	OCA 10 mg N=875 n (%)	OCA 25 mg N=968 n (%)
N	621	548	612	396	327	356
Total Number of TEAEs	5353	5447	5645	2776	2976	3260
Total Number of SAEs	233	250	328	90	87	123
Number (%) of Patients Reporting at Least One:						
TEAE	560 (90.2)	526 (96.0)	584 (95.4)	340 (85.9)	313 (95.7)	328 (92.1)
TEAE by Severity[a]						
Mild	103 (16.6)	94 (17.2)	84 (13.7)	91 (23.0)	79 (24.2)	50 (14.0)
Moderate	303 (48.8)	295 (53.8)	293 (47.9)	190 (48.0)	166 (50.8)	197 (55.3)
Severe	135 (21.7)	121 (22.1)	187 (30.6)	54 (13.6)	63 (19.3)	76 (21.3)
Life-Threatening	12 (1.9)	9 (1.6)	10 (1.6)	4 (1.0)	3 (0.9)	3 (0.8)
Death	7 (1.1)	7 (1.3)	10 (1.6)	1 (0.3)	2 (0.6)	2 (0.6)
TEAE Leading to Discontinuation of IP[b]	67 (12.4)	69 (12.6)	130 (24.3)	27 (8.1)	36 (11.0)	49 (16.7)
SAE	141 (22.7)	150 (27.4)	172 (28.1)	59 (14.9)	60 (18.3)	68 (19.1)

CTCAE=Common Terminology Criteria for Adverse Events; FLINT=Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; IP=investigational product; HbA1c=hemoglobin A1c; OCA=obeticholic acid; SAE=serious adverse event; TEAE=treatment emergent adverse event

Notes: Denominators for percentages were based on N, the number of patients in the population.

Adverse events with missing severity were counted in the 'Severe' group.

Presence of Diabetes at Baseline: yes (medical history of diabetes, or baseline use of antidiabetic medication with a diabetes indication, or HbA1c ≥6.5%), no (no medical history of diabetes, no baseline use of antidiabetic medication with a diabetes indication, and HbA1c <6.5%).

[a] Patients who reported more than one adverse event were counted only once using the highest severity. Adverse events were graded for severity using CTCAE Version 4.03 as: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death.

[b] TEAE Leading to IP discontinuation information was not collected in FLINT. Denominators for Pooled doses excluded FLINT patients.

7.2. Post-Marketing Safety Experience

OCA was granted accelerated approval for PBC by the US FDA on 27 May 2016. Conditional approvals in the European Union and Canada were granted on 12 Dec 2016 and on 24 May 2017, respectively. As of 26 May 2022, OCA, under the tradename Ocaliva has been approved in 43 countries.

No postmarketing data are available for patients with liver fibrosis due to NASH, as OCA is not approved in this indication. OCA (Ocaliva®) is approved for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. As of 26 May 2022, the estimated cumulative patient exposure from marketing experience is 28,358 patient-years.

The postmarketing data demonstrate that the benefit-risk balance of OCA is positive for appropriate patients with PBC.

8. RISKS AND RISK MANAGEMENT

Based on greater exposure and longer-term follow-up to investigational product, the safety profile of OCA 25 mg is well characterized. The Pooled Safety Population of the integrated analysis across 3 studies (Study 303, FLINT, and Study 2001) served as the primary source of evidence for this risk analysis and includes 2860 patients across treatment groups. The median duration of OCA exposure in the Pooled Safety Population was approximately 37 months (3.09 and 3.08 years in OCA 10 mg and OCA 25 mg groups, respectively), with approximately 700 patients across OCA treatment groups (including 335 patients in the OCA 25 mg group) having ≥4 years of exposure, which represents a significantly longer follow-up than in the original submission. The larger safety database allows for characterization of risks, which informs appropriate monitoring and management according to existing patient care standards and clinical practice guidelines.

The analysis included a robust evaluation of AESIs including hepatic and gallstone-related events (including pancreatitis), CV safety (including the impact of lipids and glycemic markers), renal events (including urolithiasis), and pruritus. Independent adjudication committees of experts evaluated the clinical narratives of every patient who experienced a clinical AE or a safety laboratory value that met the criteria agreed with the FDA.

Specialized physicians, including gastroenterologists, hepatologists, and healthcare providers working with them, are well-qualified to identify and manage appropriate candidates for treatment with OCA using the standard of clinical care and a combination of NITs, as recommended by the AASLD practice guidance for the clinical assessment and management of NAFLD (Rinella 2023). Management of potential safety issues is also within the scope of daily practice, given these specialists' advanced training and expertise managing patients with chronic liver disease. Many of these hepatologists, gastroenterologists, and their APPs have experience treating patients with OCA (i.e., Ocaliva) for PBC.

8.1. Risks

- No increased risk was observed for hyperglycemia, urolithiasis, or pancreatitis.
- Pruritus and dyslipidemia were the most common AEs. Pruritus, dyslipidemia, and gallstone-related events were more likely to occur in the OCA treatment groups compared to placebo.
- Rates of adjudicated CV, hepatic, and AKI events were low overall, but higher in the OCA 25 mg group compared to placebo.
- Overall, key safety events include hepatic safety, gallstones, CV, and renal safety.
- Pruritus, the most common TEAE, remains a well characterized ADR of OCA.

8.2. Risk Management

8.2.1. Serious Liver-Related Adverse Events and Hepatic Impairment

The 2017 safety amendment in Study 303 provides reassurance that the risk for clinically significant hepatic safety events can be managed with standard of clinical care monitoring and drug interruption in cases where liver injury is suspected. This safety amendment, along with published guidance, informs management recommendations in the proposed label.

The proposed labeling states that efficacy in patients with cirrhosis has not been established, and further, excludes patients with decompensated cirrhosis (i.e., Child-Pugh Class B or C), any history of a prior decompensation event, compensated cirrhosis with evidence of portal hypertension (i.e., ascites, gastroesophageal varices, persistent thrombocytopenia), or evidence of complete biliary obstruction.

To further manage hepatic safety risk with OCA, routine liver-related biochemistries should be monitored and treatment with OCA should be supervised by a hepatologist or gastroenterologist, as these specialists are well versed in the monitoring and management of patients with chronic liver disease.

Proposed labelling recommends obtaining liver tests (including ALT, AST, ALP, and total and direct bilirubin) before initiating treatment with OCA, early after initiation of treatment, and as clinically indicated thereafter, which is consistent with recent published guidance (Fontana 2022). In Study 303, patients had safety labs (including liver biochemistries) collected at each study visit including baseline, Month 1, Month 3, Month 6, and every 6 months thereafter.

Treatment with OCA should be promptly interrupted in patients with suspected liver injury or cirrhosis/hepatic impairment based on:

- Signs or symptoms such as anorexia, right upper abdominal discomfort, dark urine, jaundice, or new onset or worsening of fatigue.
- Any of the following biochemical criteria:
  - Total bilirubin ≥2x ULN [or direct bilirubin ≥2x ULN in patients with Gilbert syndrome or predominately indirect hyperbilirubinemia]

- ALT >5x ULN (in patients with normal ALT prior to treatment), ≥3x baseline (in patients with abnormal ALT prior to treatment), or ≥300 U/L
- ALP >2x ULN
- Albumin <Lower limit of normal (LLN)
- Persistent thrombocytopenia
- INR >1.5 (except for patients on warfarin)

Patients with suspected liver injury or hepatic impairment should continue to be monitored after OCA treatment interruption as clinically indicated and treatment with OCA resumed only if an alternative cause has been identified and resolution of the event has occurred. Treatment with OCA should be permanently discontinued in patients with established hepatic impairment and/or progression to cirrhosis.

8.2.2. Gallstone-Related Events

Proposed labeling excludes patients with complete biliary obstruction, as OCA undergoes biliary elimination, and is consistent with existing labelling for OCLAVIA in PBC. A proportionate risk for OCA 25 mg relative to placebo was observed in gallstone-related events, regardless of gallstone status; hence, proposed labeling does not require baseline imaging to document gallstone status but recommends interruption of OCA for symptomatic gallstone-related events. Clinical management should be consistent with existing standards of clinical practice. If symptomatic cholelithiasis is suspected, gallbladder studies and appropriate clinical management and follow-up are indicated. After complete evaluation, treatment, and resolution of the event, patients may resume OCA treatment, provided there are no signs or symptoms suggestive of an ongoing biliary obstruction (e.g., retained bile duct stones).

These recommendations for expectant management of asymptomatic cholelithiasis and intervention for symptomatic gallstone disease are consistent with bariatric surgery practice (Leyva-Alvizo 2020) and labeling for GLP-1 receptor agonists.

8.2.3. Cardiovascular

Proposed labeling excludes patients with a major CV ischemic event in the preceding 12 months, as these patients were excluded from Study 303.

Given the background risk for CV disease in the NASH population, lipids and glycemic markers should be managed per existing clinical guidelines.

8.2.4. Renal Safety

Proposed labelling recommends monitoring renal function parameters, including blood creatinine, as clinically appropriate.

8.2.5. Pruritus

Pruritus, the most common TEAE, remains a well characterized ADR of OCA. Proposed labeling recommends that for patients with intolerable or severe pruritus, temporary interruption should be considered, along with other treatments for pruritus as clinically appropriate (e.g., bile acid binding resin, antihistamine, or other antipruritic treatment). Discontinuation should be

considered in patients who continue to experience persistent intolerable or severe pruritus despite management strategies.

9. BENEFIT-RISK CONCLUSIONS

9.1. Therapeutic Context

NASH is a serious and slowly progressive liver disease that is increasing in prevalence with increasing rates of obesity and type 2 diabetes in the US. The CRN defines the stages of fibrosis from F0 to F4. Patients progress from steatohepatitis through varying stages of fibrosis (F1 to F3) before reaching cirrhosis (F4). This final stage is life-threatening, with an increased risk of liver cancer, liver transplantation, hepatic decompensation and death. NASH is now the second most common indication for adults on the liver transplant waitlist and is the leading indication for liver transplantation for women in the US (Noureddin 2018). It is estimated that 26 million persons in the US are living with NASH, of which ~15 million have F0 or F1, ~8.3 million have pre-cirrhotic fibrosis (4.9 million F2, 3.4 million F3), and ~2.5 million have F4 (cirrhosis) (Razavi 2022). On the basis of these estimates and the mortality observed in the NASH CRN study (0.89 and 1.76 deaths per 100 person-years for F3 and F4, respectively). The annual number of deaths that can be expected among persons who currently have F3 disease is 17,800 and that the number among persons with F4 disease is 22,880 (Sanyal 2021a).

The only effective therapy to date is a sustained >10% weight loss, which may be achieved with bariatric surgery. An agreed goal of pharmacologic therapy for NASH is to slow the progress of, halt, or reverse fibrosis while patients are still pre-cirrhotic. However, there is currently no approved pharmacologic therapy, creating an urgent need for a safe and effective treatment.

Fibrosis stage is the single, strongest predictor of the risk of both liver-specific outcomes and all-cause mortality (Sanyal 2021a, Hagström 2017), and emerging evidence suggests that improvement in fibrosis is associated with reduction in these risks (Sanyal 2021b, Aminian 2021). Therefore, patients with pre-cirrhotic fibrosis represent the greatest opportunity for intervention. To date, there is no definitive evidence that pharmacologic antifibrotic intervention reduces risk. Based on the available evidence, antifibrotic effect is reasonably likely to predict clinical benefit.

9.2. Benefits

The statistically significant effect of OCA 25 mg observed in the original analysis on the fibrosis primary endpoint (improvement of fibrosis by ≥1 stage with no worsening of NASH) was confirmed using the Consensus Method, with a doubling of the responder rate compared to placebo. Intra- and inter-reader variability of liver histopathology introduces uncertainty. In Study 303, demonstration of antifibrotic effect of OCA has now been replicated in analyses of 2 independent Month 18 biopsy reading methodologies. The consistent, dose-related response observed across this and other fibrosis histologic endpoints, including reversal of fibrosis and with fewer patients experiencing worsening of fibrosis resolves this uncertainty. Liver biochemistries and other noninvasive biomarkers, with persistent patterns observed at Month 48, further support the antifibrotic effect of OCA 25 mg.

The totality of efficacy data across multiple fibrosis endpoints supports OCA 25 mg as an important antifibrotic advancement for the treatment of NASH.

It is reasonably likely that the treatment effect demonstrated will predict positive clinical benefit in patients who remain on OCA 25 mg therapy. Clinical benefit is expected to be confirmed during the outcomes portion of Study 303, which is fully enrolled, with 2,477 patients with fibrosis due to NASH. Intercept is currently updating the forecast of when the total number of outcomes will be reached based on adjudicated blinded outcome data.

9.3. Risks

With the larger safety database (40,000 PYs of data, including studies in patients with NASH and 30,000 post-marketing safety data from the PBC indication) and longer-term exposure (~700 patients with ≥4 years of exposure across OCA treatment groups), the safety and tolerability of OCA 25 mg are well-characterized and support anticipated chronic dosing, with monitoring that is consistent with the current standard of care.

Pruritus and dyslipidemia were the most common AEs. Pruritus, dyslipidemia, and gallstone-related events were more likely to occur in the OCA treatment groups compared to placebo. Rates of adjudicated CV, hepatic, and AKI events were low overall, but higher in the OCA 25 mg group compared to placebo. Overall, key safety events include hepatic safety, gallstones, CV, and renal safety. Pruritus, the most common TEAE, remains a well characterized ADR of OCA.

The fact that the events occurring more frequently on OCA than on placebo overlap with known co-morbidities and ADRs of concomitant treatments used in patients with NASH combined with the low event rates introduces uncertainty. Even in the substantial safety database, it is impossible to definitively rule in or rule out OCA relatedness for several of these safety events. Intercept addresses this uncertainty by including these safety events in our proposed risk management plan. An unblinded data monitoring committee (DMC) continues to review safety data.

Proposed labeling includes that treatment should be supervised and managed by hepatologists and gastroenterologists and describes how to monitor and manage the safety profile. Risk management is discussed in detail in Section 8.

9.4. Benefit-Risk Conclusions

The totality of evidence supports a favorable benefit-risk profile for OCA 25 mg that meets the criteria for accelerated approval (FDA 2014).

OCA fulfills an urgent unmet medical need for a safe and effective antifibrotic NASH therapy with the ability to slow the progress of, halt, or reverse disease progression and improve clinical outcomes. The totality of evidence supports a favorable benefit-risk profile for OCA 25 mg that meets the criteria for accelerated approval.

- NASH is a serious, slowly progressive, and life-threatening disease with no approved therapies.

- Fibrosis stage is the single strongest predictor of liver-specific and all-cause mortality in individuals with NASH.
- OCA has demonstrated a clear antifibrotic effect across preclinical and clinical studies that is reasonably likely to predict a positive clinical benefit.
- Clinical benefit is expected to be confirmed during the outcomes portion of Study 303, which is fully enrolled.
- OCA 25 mg has a well-characterized safety profile supportive of anticipated chronic dosing based on exposure and long-term follow-up, including a rigorous, comprehensive assessment of key safety risks via 3 independent hepatic, CV, and renal adjudication committees.
    - The majority of hepatic and renal events were mild and can be managed with standard of clinical practice monitoring.
    - No difference was observed for adjudicated MACE.
    - Proposed labelling recommends interruption of OCA in symptomatic gallstone-related events until resolution, consistent with existing clinical practice. OCA can be safety resumed after cholecystectomy.
- The safety profile is consistent with the background comorbidities of patients with pre-cirrhotic fibrosis due to NASH and OCA's known MOA, and these observed safety events are known and commonly managed by gastroenterologists and hepatologists.

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APPENDIX A. HISTOLOGICAL SECONDARY AND OTHER ENDPOINTS AT MONTH 18 BY CONSENSUS METHOD (ITT_OLD POPULATION [N=931])

	Placebo (N=311)	OCA 10 mg (N=312)	OCA 25 mg (N=308)
Improvement of Fibrosis by ≥2 Stage			
Number (%) of Responders	8 (2.6%)	17 (5.4%)	19 (6.2%)
Treatment Difference[a] (95% CI)	-	2.9% (-0.2%, 5.9%)	3.6% (0.4%, 6.8%)
OCA:Placebo Odds Ratio[b] (95% CI)	-	2.11 (0.93, 4.79)	2.40 (1.07, 5.37)
p-value Versus Placebo[c]	-	0.0685	0.0281
Improvement of Fibrosis by ≥1 Stage and Resolution of NASH (Composite)[d]			
Number (%) of Responders	2 (0.6%)	11 (3.5%)	12 (3.9%)
Treatment Difference[a] (95% CI)	-	2.9% (0.6%, 5.1%)	3.3% (0.9%, 5.6%)
OCA:Placebo Odds Ratio[b] (95% CI)	-	5.46 (1.22, 24.51)	6.06 (1.37, 26.82)
p-value Versus Placebo[c]	-	0.0118	0.0066
No Worsening of Fibrosis and No Worsening of NASH (Composite)[d]			
Number (%) of Responders	101 (32.5%)	115 (36.9%)	135 (43.8%)
Treatment Difference[a] (95% CI)	-	4.4% (-3.1%, 11.9%)	11.4% (3.7%, 19.0%)
OCA:Placebo Odds Ratio[b] (95% CI)	-	1.13 (0.91, 1.41)	1.35 (1.10, 1.66)
p-value Versus Placebo[c]	-	0.2518	0.0036
Improvement of Fibrosis by ≥1 Stage			
Number (%) of Responders	49 (15.8%)	69 (22.1%)	91 (29.5%)
Treatment Difference[a] (95% CI)	-	6.3% (0.2%, 12.5%)	13.8% (7.3%, 20.3%)
OCA:Placebo Odds Ratio[b] (95% CI)	-	1.40 (1.01, 1.95)	1.88 (1.38, 2.55)
p-value Versus Placebo[c]	-	0.0435	<0.0001
Resolution of NASH by Pathologist's Overall Histopathologic Interpretation of the Presence or Absence of Definite NASH			
Number (%) of Responders	51 (16.4%)	60 (19.2%)	76 (24.7%)
Treatment Difference[a] (95% CI)	-	2.8% (-3.2%, 8.8%)	8.3% (1.9%, 14.6%)
OCA:Placebo Odds Ratio[b] (95% CI)	-	1.17 (0.83, 1.64)	1.50 (1.09, 2.07)
p-value Versus Placebo[c]	-	0.3591	0.0110

	Placebo (N=311)	OCA 10 mg (N=312)	OCA 25 mg (N=308)
Improvement of NASH Histological Features			
Steatosis			
Number (%) of Responders	68 (21.9%)	102 (32.7%)	135 (43.8%)
Treatment Difference[a] (95% CI)	-	10.8% (3.9%, 17.8%)	22.0% (14.7%, 29.2%)
OCA:Placebo Odds Ratio[b] (95% CI)	-	1.50 (1.15, 1.95)	2.00 (1.57, 2.56)
p-value Versus Placebo[c]	-	0.0024	<0.0001
Lobular Inflammation			
Number (%) of Responders	72 (23.2%)	78 (25.0%)	76 (24.7%)
Treatment Difference[a] (95% CI)	-	1.8% (-4.8%, 8.5%)	1.5% (-5.2%, 8.2%)
OCA:Placebo Odds Ratio[b] (95% CI)	-	1.08 (0.82, 1.43)	1.07 (0.81, 1.41)
p-value Versus Placebo[c]	-	0.5902	0.6557
Hepatocellular ballooning			
Number (%) of Responders	63 (20.3%)	58 (18.6%)	71 (23.1%)
Treatment Difference[a] (95% CI)	-	-1.7% (-7.8%, 4.5%)	2.8% (-3.7%, 9.3%)
OCA:Placebo Odds Ratio[b] (95% CI)	-	0.92 (0.67, 1.26)	1.14 (0.84, 1.54)
p-value Versus Placebo[c]	-	0.5982	0.4010

CRN=Clinical Research Network; ITT=intent-to-treat; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid; TZD=thiazolidinedione

Notes: Fibrosis stage was defined using the NASH CRN criteria. Study eligibility was based on the original baseline fibrosis stage defined using the centrally read biopsy slide (i.e., the unpaired screening read).

Steatosis, lobular inflammation, and hepatocellular ballooning were defined using the NASH CRN criteria.

Baseline and post-baseline NASH CRN steatosis, lobular inflammation, and hepatocellular ballooning were based on the reading of biopsy slides using the Consensus Method.

"No worsening of NASH" was defined as no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis.

Any patient with a missing Month 18 biopsy was considered as a nonresponder.

[a] Common Treatment Risk Difference=Percentage of responders in active treatment group - Percentage of responders in placebo, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no); the Mantel-Haenszel method was used to construct the CIs.

[b] Common Treatment / Placebo Odds Ratio=Percentage of Responders in Active Treatment Arm/Percentage of Responders in Placebo, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no); the Mantel-Haenszel estimate of the common odds ratio and the associated asymptotic CIs are reported.

[c] Using the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).

[d] Composite endpoints were defined as both endpoints being met in the same patient.

APPENDIX B. LIVER BIOCHEMISTRY AND LIVER FUNCTION AT MONTH 18 AND MONTH 48 (ITT_ALL POPULATION [N=2187])

	Placebo (N=728)		OCA 10 mg (N=729)		OCA 25 mg (N=730)	
	Month 18	**Month 48**	**Month 18**	**Month 48**	**Month 18**	**Month 48**
ALT (U/L)	635	305	634	304	608	293
Baseline Mean (SD)[a]	77.3 (52.02)		71.1 (45.72)		71.9 (50.92)	
LS Mean Change from Baseline[b] (SE)	-12.1 (1.55)	-19.9 (1.94)	-25.2 (1.56)	-26.4 (1.95)	-30.1 (1.57)	-31.0 (1.97)
95% CI of LSM	-15.2, -9.1	-23.7, -16.1	-28.2, -22.1	-30.2, -22.6	-33.1, -27.0	-34.8, -27.1
AST (U/L)	634	303	631	307	605	287
Baseline Mean (SD)[a]	57.3 (37.42)		54.2 (32.49)		53.4 (32.38)	
LS Mean Change from Baseline[b] (SE)	-7.1 (1.15)	-11.2 (1.51)	-14.2 (1.16)	-14.9 (1.50)	-17.2 (1.17)	-17.0 (1.54)
95% CI of LSM	-9.4, -4.9	-14.1, -8.2	-16.4, -11.9	-17.9, -12.0	-19.5, -14.9	-20.0, -14.0
GGT (U/L)	636	306	636	309	609	293
Baseline Mean (SD)[a]	96.5 (116.59)		96.8 (113.09)		92.5 (111.31)	
LS Mean Change from Baseline[b] (SE)	-7.6 (3.12)	-6.7 (4.84)	-21.8 (3.14)	-20.2 (4.83)	-38.5 (3.16)	-35.0 (4.93)
95% CI of LSM	-13.7, -1.4	-16.2, 2.8	-27.9, -15.6	-29.7, -10.7	-44.7, -32.3	-44.7, -25.4
ALP (U/L)	636	306	636	309	609	293
Baseline Mean (SD)[a]	90.3 (34.21)		87.5 (30.35)		89.0 (33.16)	
LS Mean Change from Baseline[b] (SE)	-0.8 (1.12)	-0.8 (1.40)	7.0 (1.12)	6.8 (1.40)	15.9 (1.13)	14.5 (1.42)
95% CI of LSM	-3.0, 1.4	-3.5, 2.0	4.8, 9.2	4.0, 9.5	13.6, 18.1	11.7, 17.2

	Placebo (N=728)		OCA 10 mg (N=729)		OCA 25 mg (N=730)	
	Month 18	**Month 48**	**Month 18**	**Month 48**	**Month 18**	**Month 48**
Bilirubin (mg/dL)	635	305	634	304	608	293
Baseline Mean (SD)[a]	0.663 (0.316)		0.664 (0.300)		0.686 (0.352)	
LS Mean Change from Baseline[b] (SE)	0.012 (0.0096)	0.012 (0.0137)	0.009 (0.0096)	-0.001 (0.0137)	-0.012 (0.0097)	-0.039 (0.0139)
95% CI of LSM	-0.006, 0.031	-0.015, 0.038	-0.010, 0.028	-0.028, 0.026	-0.031, 0.007	-0.066, -0.011
Direct Bilirubin (mg/dL)	619	294	611	297	586	280
Baseline Mean (SD)[a]	0.253 (0.094)		0.257 (0.095)		0.262 (0.111)	
LS Mean Change from Baseline[b] (SE)	0.011 (0.0038)	0.018 (0.0049)	0.003 (0.0038)	0.015 (0.0049)	-0.002 (0.0039)	0.000 (0.0050)
95% CI of LSM	0.003, 0.018	0.008, 0.027	-0.004, 0.011	0.005, 0.024	-0.009, 0.006	-0.010, 0.010

ITT=intent-to-treat; LS=least squares; LSM=least squares mean; OCA=obeticholic acid

[a] Baseline was defined as the mean of all measurements prior to first dose of investigational product.

[b] LSM and 95% CI were calculated using a mixed effect repeated measures model with an unstructured covariance structure and treatment group, visit, visit by treatment interaction, and stratification factors as fixed effects and baseline as a covariate.