25 March 2021
EMA/CHMP/751783/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zektayos - Hepjuvo

International non-proprietary name: obeticholic acid

Procedure No. EMEA/H/C/005249/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

6-ECDCA or 6ECDCA	6a-ethyl-chenodeoxycholic acid
AASLD	American Association for the Study of Liver Diseases
ADMA	Asymmetric dimethy larginine
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
amu	atomic mass unit
APRI	aspartate aminotransferase-to-platelet ratio index
ASMF	Active substance master file
AST	aspartate aminotransferase
ATC	Anatomical/Therapeutic/Chemical
AUDIT	Alcohol Use Disorders Identification Test
AV	Acceptance value
BDL	Bile Duct Ligation
BMI	body mass index
CAD	Charged aerosol detection
CDCA	chenodeoxycholic acid
CEP	Certificate of Suitability (of a monograph of the Ph.Eur.)
cfu/CFU	Colony forming unit
CI	confidence interval
CKD	chronic kidney disease
CMH	Cochran-Mantel-Haenszel
CP	Child-Pugh
CP-A	Child-Pugh Class A cirrhosis
CRN	Clinical Research Network
CSR	clinical study report
CVD	cardiovascular disease
CYP1A2	Hydroperoxy Icosatetraenoate Dehydratase (cytochrome P450 1α2)
DB	double-blind
DBP	diastolic blood pressure
DCA	Deoxycholic acid
DCO	data cutoff
DDAH	Dimethylarginine Dimethylaminohydrolase
DILI	drug-induced liver injury
DIO	Diet Induced Obese
DMAP	Dimethylaminopyridine
DMC	Data Monitoring Committee
EAIR	exposure-adjusted incidence rate
EASL	European Association for the Study of the Liver
EC_{50}	Half maximal effective concentration
ECG	electrocardiogram

eDISH	drug-induced serious hepatotoxicity
EDQM	European Directorate for the Quality of Medicines
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
EMA	European Medicines Agency
eNOS	Endothelial nitric oxide synthase
EOS	end of study
EOT	end of treatment
ERA	Environmental Risk Assessment
EU	European Union
F1, F2, F3, F4	NASH fibrosis stage; F4 = cirrhotic
FCC	Food chemicals codex
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor 19
FIB-4	fibrosis-4
FLINT	Farnesoid X Receptor (FXR) Ligand Obeticholic Acid in NASH Treatment
FRS	Framingham Risk Score
FTIR	Fourier transform infrared spectrophotometry
FXR	farnesoid X receptor
GC	Gas chromatography
GGT	gamma-glutamyltransferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good manufacturing practices
HbA1c	hemoglobin A1c
HCC	hepatocellular carcinoma
HDL	high-density lipoprotein
hERG	human ether-à-go-go-related gene
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HPBL	Human peripheral blood lymphocytes
HPLC	High performance liquid chromatography
HR	hazard ratio
ICH	International Conference on Harmonisation
ICP	Inductively coupled plasma
INN	International Nonproprietary name
INR	international normalized ratio
INT-747	Obeticholic acid (OCA)
IP	investigational product
IR	Infrared spectrophotometry
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
JECFA	Joint Evaluation Committee on Food Additives
KLCA	7-Ketolithocholic acid

LCA	Lithocholic Acid
LDA	Lithium diisopropylamine
LDL	low-density lipoprotein
LDPE	Low-density polyethylene
LoQ	Limit of quantification
LPS	Lipopolysaccharide
LS	least-square
LTSE	long-term safety extension
MAA	Marketing Authorisation Applications
MACE	major adverse cardiovascular event
MAP	Mean arterial pressure
MCC	Microcrystalline cellulose
MCP-1	Monocyte Chemoattractant Protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MHE	Maximum Human Exposure
mITT	modified Intent-to-Treat
mRNA	Messenger ribonucleic acid
MS	Mass spectrometry
MTD	Maximum Tolerated Dose.
MW	Molecular weight
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
n-BuOAc	n-Butyl acetate
NDA	New Drug Application
NF	National Formulary
NFS	NAFLD fibrosis score
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NLT	Not less than
NMT	Not more than
NOAEL	No Observable Adverse Effect Level
OCA	obeticholic acid
OL	open-label
PBC	primary biliary cirrhosis or primary biliary cholangitis
PCTFE	Poly-chloro-tri-fluoro-ethylene
PD	pharmacodynamic(s)
PDGF	Platelet-Derived Growth Factor
PEC	Predicted Environmental Concentration
PEG	polyethylene glycol
PET	Polyethylene terephthalate
Ph.Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PND	Postnatal Day

PPAR	Peroxisome Proliferator-Activated Receptor:PPARα, PPARβ/δ, PPARγ
ppm	Parts per million
PSC	primary sclerosing cholangitis
PT	preferred term
PTP	primary treatment phase
PVC	Polyvinyl chloride
QD	once daily
QP	Qualified person
QTc	corrected QT interval
RH	Relative humidity
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	standard deviation
SEY	subject exposure years
SI	International System of Units
SmPC	Summary of Product Characteristic
SMQ	standardized MedDRA query
SOC	system organ class
TAA	Thioacetamide
TAMC	Total aerobic microbial count
TE	transient elastography
TEAE(s)	treatment-emergent adverse event(s)
TGF-β	Transforming Growth Factor beta
TSE	Transmissible spongiform encephalopathy
TTC	Threshold of toxicological concern (*for genotoxic impurities*)
TYMC	Total combined yeasts and molds count
TZD	thiazolidinedione
UDCA	ursodeoxycholic acid
UIP	University of Iowa Pharmaceuticals
ULN	upper limit of normal
US	United States
USP	United States Pharmacopoeia
UV	Ultraviolet
w/w	Weight to weight ratio
WD	Western diet
XRPD	X-ray powder diffraction

1. CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Zektayos-Hepjuvo for improvement of liver fibrosis and resolution of steatohepatitis in adult patients with significant liver fibrosis due to nonalcoholic steatohepatitis (NASH), without clinical signs or symptoms of cirrhosis:

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

Inspection issues

GMP inspection(s)

Not required.

GCP inspection(s)

Not required.

New active substance status

Not applicable.

Additional data exclusivity /Marketing protection

Taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, itis not considered that the new therapeutic indication brings significant clinical benefit.

Similarity with authorised orphan medicinal products

Not applicable.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome, a cluster of closely related clinical features linked to visceral obesity and characterized by insulin resistance, dyslipidemia, and hypertension (Marra 2013, NIDDK 2018). NAFLD encompasses a spectrum of histologic changes that begin with accumulation of excess fat in the liver (simple steatosis), which, over time, can progress to chronic inflammation, fibrosis, and ultimately cirrhosis (Marra 2013, NIDDK 2018). While simple steatosis itself is considered a relatively benign condition, up to one-third of patients in the spectrum of steatosis develop NASH, a chronic, progressive, and ultimately life-threatening liver disease that is characterized by hepatocellular injury, inflammation, and progressive fibrosis.

2.1.2. Epidemiology

The prevalence of NASH is large 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. Precise estimates of the prevalence of NASH are precluded by significant cultural, geographical, and socioeconomic differences related to obesity, as well as patient reluctance for undergoing biopsies. Global prevalence estimates of NASH are limited, but based on the available data, range from 1.5% to 6.5% of the population (Younossi 2019). It is likely that NASH is underdiagnosed because affected patients are generally symptom free and often have minimal biochemical abnormalities.

The prevalence of NASH in the EU is projected to increase by ~30% between 2016 and 2030 (from ~13 million to ~18 million), with increases in fibrosis stages 2 and 3 of 60% and 88%, respectively (stage 2: from ~2.5 million to ~4.0 million and stage 3: from ~1.6 million to ~3.0 million) (Estes 2018a, Estes 2018b). The prevalence of decompensated cirrhosis and hepatocellular carcinoma (HCC) in the EU is also expected to increase (Estes 2018b). Even greater prevalence trends are also predicted for the US (Figure 2).

2.1.3. Clinical presentation, diagnosis and stage/prognosis

NAFLD is typically suspected based on elevated ALT levels in combination with other clinical and biochemical features, such as high body mass index (BMI) and elevated levels of triglycerides, low-density lipoprotein (LDL) cholesterol, and hemoglobin A1c (HbA1c) (Chalasani 2018), or incidental findings during noninvasive abdominal scans (Sattar 2014). In the early stages of NAFLD, ALT is typically higher than AST levels. As inflammation and fibrosis progress, AST and the AST:ALT ratio typically increase in addition to continued elevations in ALT; GGT may also be elevated.

Many patients with NASH may not be diagnosed until fibrosis has developed because of the lack of specific symptoms related to NASH. When physical symptoms do appear, they can include upper abdominal pain and fatigue (NIDDK 2018). Pruritus is frequently reported in patients with liver conditions, but the occurrence varies widely by condition and the pathogenesis remains unclear (Kremer 2011). Although pruritus data in NAFLD are sparse, in a 2016 study that interviewed patients with liver conditions over a 6-month time frame, approximately 45% of 358 NAFLD patients had pruritus (Oeda 2018).

Conventional biochemical tests (eg, ALT and AST) can provide insight for diagnosing NASH and measuring disease severity. Noninvasive markers have not yet been validated (Spengler 2015, Sayiner 2016, Younossi 2016), largely driven by the lack of available therapies or large clinical trial data that would form the basis of validation. However, substantial progress has been made in the last decade to develop diagnostic technologies that are able to noninvasively quantify disease severity and features of NASH (Machado 2013, Papagianni 2015) and are increasingly implemented in clinical practice for identifying patients and monitoring disease severity.

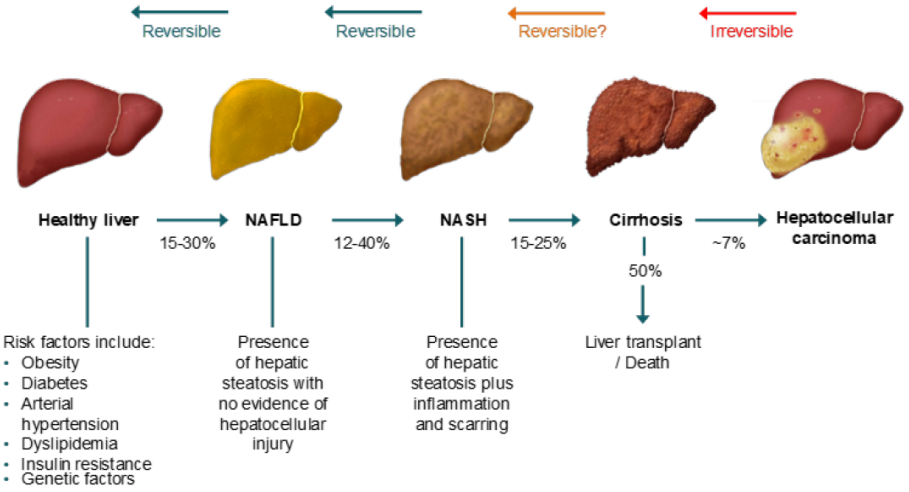
Currently, liver biopsy is the only method that can provide a definitive diagnosis for patients with NASH and determine fibrosis stage, which has been associated with an increased risk of all-cause and liver-related mortality (Dulai 2017).

Rate of Progression

Fibrosis stages in NASH are based on descriptive histology, with the rate of change between stages likely being nonlinear (Figure 3). The average time to progression to the next fibrosis stage has been estimated around 12.5 years (0.08 to 0.09 between stages annually [McPherson 2015, Younossi 2016]). In a retrospective study of 60 patients with NAFLD/NASH, the average annual progression rate was 0.15 (range: 0.03 to 0.78) (Hagström 2018). Annual transition probabilities of patients from fibrosis stage 2 to fibrosis stage 3, as well as from fibrosis stage 3 to fibrosis stage 4, are estimated to be higher than other fibrosis stage transitions (Younossi 2018). The incidence of progression to advanced fibrosis (stages 3 and 4) in the NASH population is estimated to be 67.95 per 1000 person-

years (Younossi 2016). Although fibrosis can spontaneously reverse, this reversal is less likely to occur in patients with fibrosis stage 3 and above (Schuppan 2018). In a meta-analysis of 10 studies (4 of which evaluated patients with biopsy-proven NASH), one in every five patients were identified as rapid progressors (Bertot 2016). Furthermore, type 2 diabetes and obesity are among the factors associated with a more rapid fibrosis progression (Angulo 2015, McPherson 2015, Singh 2015, Schuppan 2018).

Figure 1 NASH Is a Progressive Disease Associated with the Development of Fibrosisand Cirrhosis



NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis
Source: Adapted from Texas Liver Institute 2018.

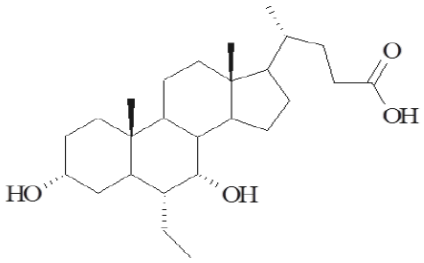
2.1.4. Management

NASH currently has no approved pharmacologic therapies and, as such a serious condition with high unmet medical need. Therapeutic options for NASH are largely limited to lifestyle modifications and therapies for the treatment of comorbidities (such as diabetes) (Ratziu 2016).

2.2. About the product

Obeticholic acid (OCA) is a farnesoid X receptor (FXR) agonist and a modified bile acid derived from the primary bile acid chenodeoxycholic acid (CDCA), the natural human FXR ligand. FXR is expressed at high levels in the liver and intestine, and OCA activation of FXR leads to effects for the treatment of NASH (Adorini 2012, Mudaliar 2013).

The chemical name of OCA is 3α,7α-dihydroxy-6α-ethyl-5β-cholan-24-oic acid. It is also referred to as 6α-ethyl-chenodeoxycholic acid or 6-ECDCA. The molecular formula is $C_{26}H_{44}O_4$ and the molecular weight is 420.64 g/mol.



OCA is an agonist for FXR, a nuclear receptor expressed at high levels in the liver and intestine that regulates liver fibrosis, inflammation, and metabolic and bile acid pathways. OCA decreases the expression of profibrotic genes in hepatic stellate cells, the major source of extracellular matrix in liver injury, and exhibits antifibrotic effects in rodent models of fibrosis. Activation of FXR by OCA inhibits the nuclear factor κB (NF-κB)-mediated induction of inflammatory mediators in both human HepG2 cells and mouse primary hepatocytes cultured in vitro. Consistent with these nonclinical findings, clinical studies have shown that OCA reverses liver fibrosis and improves hepatic inflammation in patients with liver fibrosis due to NASH.

Proposed Indication

The proposed indication is based on the surrogate endpoint outcomes on liver histology:

INVENTED NAME is indicated for improvement of liver fibrosis and resolution of steatohepatitis in adult patients with significant liver fibrosis due to nonalcoholic steatohepatitis (NASH), without clinical signs or symptoms of cirrhosis.

Proposed Dosing Recommendation

The recommended dosage regimen of OCA is 25 mg once daily. OCA may be taken with or without food. For patients taking a bile acid-binding resin, take OCA at least 4 to 6 hours before or4 to 6 hours after taking the bile acid-binding resin, or at as great an interval as possible.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The Applicant has requested Scientific Advice three times from the CHMP concerning OCA for the treatment of NASH with fibrosis. The initial request was in January 2015 (EMA/CHMP/SAWP/238095/2015), the second (a parallel EMA/FDA procedure on exclusively paediatric aspects) in 2016 (EMA/CHMP/SAWP/802015/2016), and the third in September 2018 (EMA/CHMP/SAWP/775188/2018). The 2015 and 2018 procedures focused primarily on the clinical development strategy in the adult NASH population

In the initial Scientific Advice interaction (2015), a co-primary endpoint comprising measures of the effects of OCA on improvement of fibrosis and on the resolution of NASH was considered acceptable:

- Improvement of 1 stage of fibrosis and no worsening of steatohepatitis (as defined by no increase in ballooning or inflammation); AND
- "Resolution of NASH" as defined by the overall histopathological interpretation (ie, subjects would have a biopsy interpretation of "not NAFLD" or "simple steatosis" or "NAFLD without steatohepatitis") and no worsening of fibrosis.

This approach required that both endpoints achieve statistical significance for the primary efficacy analysis to be considered successful.

Following the initial Scientific Advice, the Applicant revisited the topic at the subsequent 2018 follow up procedure and requested to change the co-primary endpoint analysis to an analysis that requires either of the two components of the initial co-primary to be met for statistical success. This position was adopted by the FDA in the granting of either of the two endpoints sufficient for the pivotal measure of efficacy as is now reflected in the draft FDA guidance.

The CHMP declined to endorse this view in the written advice to the Applicant and their position was consolidated by the publication following the November CHMP meeting (at exactly the same time as

the advice was provided) of a CHMP draft Reflection Paper specifying the coprimary endpoint requirement, for consultation.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

All manufacturers involved are appropriately authorised. For the European manufacturing sites involved in the manufacture, testing and release of the drug product, valid GMP certificates are provided and/or available via Eudra GMPD. Two sites located in the UK and responsible for batch release testing need to be withdrawon from the dossier. For the two sites located in the US (that are responsible only for the stability testing) proof of GMP compliance is available in the "Inspection Classification Database" in FDA website.

A single QP declaration covering the two sites involved in the manufacture of the active substance and the additional site responsible for the milling is provided. It is signed by the QP at the manufacturer of the dosage form and applicable also to the batch release site, it states that the active substance is manufactured in compliance with the detailed guidelines on Good Manufacturing Practice for active substances used as starting materials and is based on on-site audits conducted within the last three years at the manufacturing sites of the active substance.

GCP

Clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

PRIME

Not applicable.

Accelerated assessment

Not applicable.

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.
- Unmet medical needs will be addressed
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Biosimilarity

Not applicable.

Additional data exclusivity/ marketing protection

The applicant requested consideration of one year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

New active substance status

Not applicable.

Orphan designation

Not Applicable.

Similarity with orphan medicinal products

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0104/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0104/2018 was not yet completed as some measures were deferred.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as immediate release coated tablets containing 25 mg of the active substance obeticholic acid.

Other ingredients are: microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, colloidal silicon dioxide and a non-functional coating containing Poly(vinyl alcohol) partially hydrolysed, titanium dioxide, macrogol/PEG 3350 and talc.

The product is available in polyvinyl chloride/poly-chloro-tri-fluoro-ethylene/polyvinyl chloride (PVC/PCTFE/PVC) thermoform blister strips sealed with an aluminium foil layer. Pack size: 28, 30, 90 and 100 film-coated tablets.

3.1.2. Active Substance

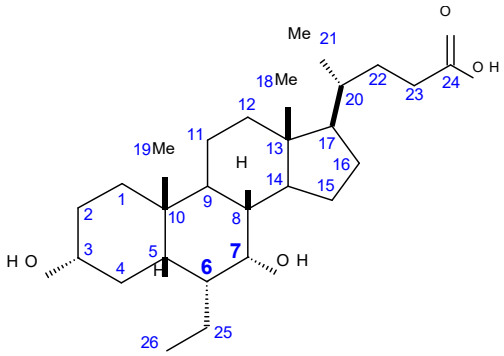
The applicant proposes two providers of the active substance and the dossier includes a complete separate module 3.2.S for each of them. The manufacturing process development was completed by one of the proposed providers and later on transferred to the second manufacturer. During the transference of the process, the second manufacturer introduced some changes as a consequence of

adaptation to the new site and also of further optimisation. Notwithstanding the changes introduced, the manufacture of the active substance is essentially the same in both sites (the same starting material, the same route of synthesis, the same critical steps, similar in-process controls, the same intermediates with the same specifications, comparable impurities profile and, of course the same specifications). Considering the close similarity in the quality profile of the active substance sourced from both providers, a single section 3.1.2 on the drug substance is included in this Overview.

The ASMF procedure is NOT used in the procedure. Full information on the quality of the active substance is included in the dossier.

General Information

The structure of obeticholic acid (INN) is:



$C_{26}H_{44}O_4$ MW: 420.63

Obeticholic acid is not described in the Ph.Eur. and other pharmacopoeias. It is a modified bile acid, structurally derived from chenodeoxicholic acid (CDCA), the principal human bile acid. It contains 11 stereocenters and 9 of them are present in cholic acid, the raw material of bovine origin used in the synthesis of the starting material KLCA. The remaining 2 stereocenters (at C6 and C7) are formed during the last manufacturing steps of manufacturing process of obeticholic acid.

Obeticholic acid is a white to off-white powder, moderately hygroscopic, with pH dependent solubility in aqueous media (from insoluble or slightly soluble at pH≤6 to freely soluble at pH≥7). Discussion on polymorphism and particle size is provided in section 3.2.S.3 Characterisation.

Manufacture, process controls and characterisation

Two sites are proposed for the manufacture and control of the active substance

An additional site is responsible for the milling of the substance manufactured at one of the sites. Four additional control sites for specific tests and/or for stability testing are proposed.

Description of manufacturing process and process controls, control of critical steps and intermediates

The process includes 6 synthetic steps using a commercially available well-defined starting material with acceptable specifications

The proposed specifications for the all the reagents, solvents and processing aids are deemed satisfactory.

A justification of the steps considered critical for the quality of active substance is presented as well as of the control processes. The justification of the proposed critical steps, control processes and

intermediate specifications is based in the experience acquired during development and takes into consideration the analysis of the effect of these parameters in the impurity profile of the active substance.

The account of process development history is detailed and summarises the main changes during the process development.

Changes and further optimization of the process during transference to the second manufacturer are described. This section includes tables comparing the differences in the manufacturing process and in the control of critical process steps. The differences can be qualified as minor and the lack of impact on the quality of the active substance is justified.

Characterisation and Impurities

The characterisation of the active substance includes the analysis by ^{1}H and ^{13}C Nuclear Magnetic Resonance, Fourier Transformed Infrared Spectrometry, UV Absorption, Mass Spectrum and Single Crystal X-ray Powder Diffraction. In addition, extensive information on the solid state properties and on the control of the amorphous form, as well as studies on thermal properties and on particle size are provided.

The discussions on potential and actual impurities provided by both OCA manufactures are exhaustive. The origin of present and potential related substances is based on the chemistry processes used and, where necessary, in additional experimental studies, including purge studies and exhaustive discussion on the origin and fate of impurities all along the process from the synthesis of the starting material to the end of the manufacturing process of the active substance. The justification of the limits is satisfactory and according to the batch results and in line with thresholds set in guideline ICH Q3A except the limits for two impurities that are considered qualified at higher levels.

The discussion on residual solvents is in general satisfactory.

The-specification includes tests for appearance, identity by IR (Ph.Eur. 2.2.24) and by HPLC, water content (Ph.Eur. 2.5.32), sulphated ash (Ph.Eur. 2.4.14), palladium (ICP-MS), related substances (HPLC), residual solvents (GC), particle size (laser diffraction), solid state form (XRPD) and microbial limits, TAMC and TYMC (Ph.Eur. 2.6.12). The selection of tests follows the general principles of guideline ICH Q6A as it includes typical tests for appearance, identity, assay and purity. The proposed test methods are common for the intended purposes. The analytical procedures are described with detail and have been validated according to the relevant ICH guideline. Detailed reports are included.

The justification of the proposed specification is in general endorsed as follow the requirements of relevant guidelines and compendial requirements. In most cases the proposed limits are also based on batch results. The limit for several related impurities complies with qualification threshold stated in guideline ICH Q3A for a maximum daily dose of 25 mg of obeticholic acid. The limit for other impurities is higher than the qualification threshold but these impurities have been qualified and the limits are lower than the qualified level, in line with batch results and considering the decision trees of guidelines ICH Q3A and ICH Q6A.

Residual solvents are controlled according to relevant guidelines.

Regarding the control of elemental impurities, the justification includes the results of the content of elements of groups 1 and 2A, as required by the guideline ICH Q3D for oral administration and of Pd used as catalyst during the manufacturing process in six representative batches of the active substance. All the results are below the respective LOQ (that are reported) and well below the corresponding PDEs calculated according to ICH Q3D Option 2a using two tablet weights = 2 x 208 mg.

Results of all the batches manufactured for use during the non-clinical, clinical and stability studies are submitted. A total of 32 batches are included and for them, the manufacturer, batch size and use are stated.

As there are not official compendial standards, well characterized in-house substances are used except for one impurity that is commercially available.

Obeticholic acid is packed in a double LDPE bag, a secondary PET/Al bag with desiccant and a fibreboard drum. The bags are sealed with cable strips.

Stability

The applicant proposes a re-test period of 36 months for the substance stored in the proposed package in a refrigerator (2ºC - 8ºC).

Formal stability studies have been conducted on 10 batches of at least pilot size and for 5 commercial size batches. For six of the pilot size batches and for the 5 commercial size batches, the studies were conducted at both long term (5ºC ± 3ºC) and accelerated condition (25ºC/60%RH) and the available results cover the scheduled 6 months under accelerated condition for all the batches and between 12 and 48 months under long term condition. For the remaining 4 pilot size batches only long term studies have been conducted and cover between 12 and 24 months. The stability indicating tests are appearance, water content, assay, related substances and for particular time points microbiological control test and solid-state form. The design of the stability studies is according to the relevant stability guidelines and the results show that all results are well within the specifications and that significant trends are not seen except for the content of one impurity that grows in a consistent manner but always well below the proposed limit. The results support the proposed re-test period and storage conditions.

Stress studies (including a photostability study conducted in line with the guideline on photostability studies) showed that the substance is not sensitive to the exposition to light and that undergoes significant degradation under acid, base, oxidative, oxidative/alkaline and thermal stress.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Obeticholic acid (OCA) film coated tablets are formulated as an immediate release solid dosage form containing 25 mg of OCA drug substance per tablet. The tablets are white to off white, oval-shaped and debossed with RGN on one side and 25 on the other side.

The tablets are packaged in PVC/PCTFE/PVC thermoformed blister strips sealed with an aluminium foil layer.

Pharmaceutical development

Pharmaceutical development addresses all the items relevant for the dosage form. Pharmaceutical development uses a traditional approach and does not use enhanced quality by design tools. Design space is not claimed in the manufacturing process.

The company identified the physico-chemical properties of the drug substance that are clinically relevant for the patient. These properties have been adequately specified and are they adequately controlled. OCA is a Biopharmaceutical Class System (BCS) Class II compound (poorly soluble and highly permeable). The PSD of the obeticholic acid active substance has an important and critical role in the content uniformity and dissolution of the tablets. It has been observed that the larger particle

size of drug substance can create less homogeneous blends and have also impact on the dissolution rate. As consequence, a particle size control step using a jet mill was implemented into the obeticholic drug substance manufacturing process. The obeticholic acid active substance is a stable amorphous solid. This state is confirmed by X-ray Powder Diffraction (XRPD).

The selection of the excipients is justified. They all are well known and widely used for this dosage form. Compatibility studies demonstrated there aren't relevant interactions with the active substance.

The main formulation development was conducted at three manufacturing sites and the dossier provides a good summary of the (small) changes introduced during development. The excipients and their amounts were set almost from the beginning and the only changes done were introduced in the colour of coating used and, in the shape, and debossing as required during clinical studies.

The physico-chemical properties of the drug product have been also discussed. Solid state form of the drug substance (amorphous form) is conserved in the dosage form. The particle size of the final blend before compression has been set and it is attained by the use of appropriate grade of excipients and by applying suitable controls during the milling of the blend.

Information on the solubility of the drug substance and its impact on the dissolution of the tablets is also provided. Obethicholic acid is a weak acid and then its solubility is poor al low pH (below pH=6). This has conditioned the development of procedure of the dissolution test. The pH of the dissolution media was set at 6.8 and the need to use a small amount of surfactant is justified to guarantee the accuracy of the dissolution method during its validation. The discriminatory power of the dissolution test can be considered relatively poor as it was able to distinguish only batches manufactured with milled and unmilled drug substance and a batch without disintegrant. Nevertheless, this is not considered critical because the tablets have shown a rapid dissolution, >85% dissolved at 15 minutes and the dissolution specification is set accordingly (Q=80% in 15 minutes).

The account of the manufacturing process development is deemed satisfactory. The process has undergone few changes during development. The dosage form used in initial clinical studies were capsules filled with a granulate containing the same excipients used in the 5 mg and 10 mg tablets and almost the same used in the 25 mg tablets. The tablets were selected soon during development as the final dosage form and the manufacturing process suffered a number of (minor) changes during development. The process includes dry granulation of the active substance with the total amount of the filler MCC and portions of the remaining excipients to get an intragranular pre-blend that is dry granulated in a roller compacter and the granulate is later blended with the remaining amounts of the other excipients to get the extragranular blend that is later compressed and finally coated with Opadry.

Comparability studies (in-vivo and mainly in vitro) of the different dosage forms/strengths used during clinical development and the proposed commercial tablets have been conducted and confirm the equivalence among the clinical capsules and the different tablets used during development and the proposed commercial tablets.

The selection of the blister proposed as commercial package is justified and the microbiological attributes of the dosage form are discussed.

Manufacture of the product and process controls

GMP status of all the sites involved in the manufacture and release of the finished product is demonstrated according to regulatory requirements.

The manufacturing process consists of five main steps: pre-blending, dry granulation, final blending, compression and coating. The process is considered to be a standard manufacturing process.

The in-process controls and control of critical parameters conducted at each manufacturing steps are described and briefly justified.

All the excipients included in the batch formula of the uncoated tablets and the purified water used to prepare the coating solution are described in the Ph.Eur. and are controlled according to the relevant monographs. For the coating Opadry II White, suitable specifications are proposed.

Product specification, analytical procedures, batch analysis

The release and shelf-life specifications of the finished product are provided.

Proposed specifications are according to the minimum requirements of the Ph.Eur. for the dosage form and with the general principles of guideline ICH Q6A. Nevertheless, the proposed periodicity of the test microbiological control should be stated in the proposed specifications.

The test procedures are described with the required level of detail. Quantification of obeticholic acid in the dissolution test is done by HPLC-CAD (charged aerosol detection) and uniformity of dosage units is determined by content uniformity. The test procedures have been validated according to guideline ICH Q2. The design of the validation experiments is described, and complete results are provided and show the suitability of the test procedures for the intended use.

Results are provided for all the batches used during clinical and pharmaceutical development. The batches are representative of the proposed commercial process. All the results comply with the proposed specifications at the time of manufacture. Batches representative of the proposed commercial tablets are included.

The justification of the specifications is in general endorsed

Reference standards are those used in the control of the active substance. The components of the blister are described, and suitable specifications are provided, as well as declarations of compliance with Ph.Eur. and European regulations on food contact materials for the materials in contact with the product.

The commercial container closure system for obeticholic acid 25 mg tablets is polyvinyl chloride (PVC)/poly-chloro-tri-fluoro-ethylene (PCTFE)/polyvinyl chloride thermoform blisters sealed with aluminum foil layer blisters. The choice of the container/closure is justified for the physical/chemical properties of the pharmaceutical oral dosage form and adequate to protect the finished product from microbial contamination. The container closure system proposed for marketing is the same that have been used to perform the stability data provided.

Stability of the product

Formal stability studies (long term, accelerated and, if accelerated results fail, intermediate conditions) on drug product manufactured at the proposed manufacturing site have been conducted on six commercial size batches called registration stability batches (three of 10 mg and three of 25 mg). Results of 10 mg batches are considered only as supportive data as this strength is not applied for.

The results under accelerated condition for the 10 mg tablets cover 6 months for two batches and 0 months for the third batch. Under long term conditions, the results for 10 mg tablets has reached 18 months for one batch, 9 months for other and 0 months for the third one.

The results under accelerated condition for the 25 mg tablets cover 6 months for two batches and 0 months for the third batch. Under long term conditions the data for 25 mg batches cover 18 months for two of the batches and 0 months for the third batch. This exceeds the minimum data requirement

at time of submission in the guideline 'Stability testing of existing active ingredients and related finished products': 6 months under both accelerated and long term condition on at least two pilot scale batches (option a, conventional dosage form and active substance known to be stable). All the results under both long term and accelerated conditions comply with the shelf life specifications. Nevertheless, statistically significant linear trends can be seen for the parameters assay, two individual impurities, total impurities and water content (more intense under accelerated condition). The projected shelf lives considering the trends under long term conditions of these parameters have been calculated and the shortest one is 50 months. Considering the whole stability data available the proposed shelf life of 30 months (up to two times the available time point but not exceeding this time point plus 12 months) is according to the referred stability guideline.

The storage condition in the proposed SmPC is «This medicinal product does not require any special storage conditions» and this is supported by stability results but such proposal should be explicitly declared in section 3.2.P.8.1 (See LoQ).

The results of stress studies conducted on the finished product are overall consistent with the results obtained in the active substance. The results of the photostability study confirm that the drug product is not sensitive to light exposure.

The holding time for the bulk tablets (12 months) is based on stability studies conducted during development.

Biosimilarity

N/A

Post approval change management protocol(s)

N/A

Adventitious agents

The only material of animal or human origin is cholic acid, is a bile acid derivative and is of ovine or bovine origin. The provider of cholic acid holds a valid TSE-CEP issued by the EDQM. A copy of the CEP that includes the relevant declaration of access is included in the dossier.

GMO

N/A

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Overall, the information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

There are a number of other concerns that need to be addressed before the quality part of the dossier can be considered satisfactory.

3.2. Non clinical aspects

3.2.1. Pharmacology

Obeticholic acid (OCA) is a selective and potent farnesoid X receptor (FXR) agonist, structurally derived from the principal human bile acid chenodeoxicholic acid (CDCA), which is the natural human FXR ligand. The pharmacological properties of bile acids including that of OCA are well documented in the scientific literature.

OCA received marketing authorisation in EU for the treatment of primary biliary cirrhosis (PBC). The applicant showed, direct anti-inflammatory, anti-fibrotic and gene modulatory effects of OCA in test systems such as cultured HSCs, mouse primary hepatocytes, and human liver cell lines. *In vivo*, hepatoprotective effects of OCA were demonstrated in rat models of cholestasis, acute liver injury, liver fibrosis, cirrhosis, and portal hypertension induced by chemical injury (lithocholic acid and thioacetamide) or bile duct ligation. Reduced hepatic fibrosis by OCA was associated with decreased hepatic NF-κB pathway activity through up-regulated IκBα.

The present application is submitted in support of a new indication, treatment of nonalcoholic steatohepatitis (NASH) fibrosis in adult patients. NASH is characterized by steatosis, lobular inflammation, hepatocyte ballooning and degeneration progressing to liver fibrosis, which develops in a subset of patients with NAFLD.

The effects of OCA have been evaluated in *in vivo* disease models of NASH including melanocortin 4 receptor-deficient (MC4R-KO), leptin deficient (ob/ob), or low density lipoprotein receptor-deficient (Ldlr-/-) Leiden mice fed high-fat diets, among others. However, it is recognized that there is no animal model that fully resembles the human condition. Currently, human-based *in vitro* models for NASH provide a valuable tool to study this disease. A review existing models and the literature supporting their use for NASH has been provided by the applicant.

The Applicant reported that OCA prevents the development and progression of NASH in a MC4R-KO mice model of disease,as it ameliorated liver fibrosis and decreased serum concentrations of non-invasive markers of NASH and NASH-related fibrosis (collagen type IV and VCAM-1).It was noted that among various cell types expressing FXR, OCA acts mainly on hepatocytes, where it inhibits metabolic stress-induced p53 activation and hepatocyte death, thereby suppressing hCLS formation and interstitial fibrosis.

In a series of experiments carried out in DIO-NASH and ob/ob-NASH mouse models, the applicant reported that OCA reduced hepatomegaly and NAS scores in both type of mouse. OCA therapy (low and high dose) improved markers of NASH as compared to NASH vehicle controls. In addition, OCA-treated mice showed improvements in hepatic steatosis and inflammation. These effects were supported by global gene expression (RNA sequencing) and liver lipid biochemistry.

It was also shown that the intervention with OCA in developing fibrosis in (Ldlr-/-) Leiden mice NASH model, reduces collagen deposition and de novo synthesis and modulates metabolic and inflammatory gene expression.

OCA effects in combination with different therapies in NASH models have been also evaluated. These studies showed clear improvements on NASH endpoints when OCA was co-administered with the GLP-1R agonist IP118, the dual PPAR α/δ agonist elafibranor, or the pan-PPAR agonist bezafibrate.

Regarding secondary pharmacodynamic studies, OCA did not bind to the other receptors (in particular with nuclear receptors involved in metabolic pathways), channels or transporters that were tested, with the exception of weakly activating the bile acid-activated G protein-coupled receptor TGR5 (EC_{50} = 20

μM). The glyco- and tauro-conjugated derivatives of OCA do not show any activity for 14 different nuclear receptors tested.

As for safety pharmacology assessment, results from the safety neurological, respiratory and GI studies did not reveal any apparent effect. Regarding the cardiovascular system, *in vitro* studies showed that OCA at concentrations up to 82.8μM had no clear effect on cloned hERG channel currents in HEK293 cells. This result was consistent with the dog cardiovascular safety study, in which the NOEL occurred at the highest dose tested (20 mg/kg).

3.2.2. Pharmacokinetics

Absorption of OCA was evaluated in a single-dose radiolabel study in rats and in repeat-dose toxicity studies in mice, rats, rabbits and dogs. Absorption and systemic exposure were also evaluated in juvenile rats.

The pharmacokinetic studies employed validated methods for quantitative determination of OCA and its metabolites in plasma of all animal species. Acceptable linearity, precision, accuracy and specificity of test items were observed over different concentration ranges.

In oral administration studies was found that absorption of OCA was rapid, with a Tmax ranging from 0.25 hour in rodents to 4 hours in dogs. Formation of conjugates of OCA, tauro-OCA and glyco-OCA, was observed in all studies. The Tmax for these conjugates was longer, approximately 2 hours to 24 hours across species.

Studies in mice revealed that, for both sexes, exposure to OCA and tauro-OCA generally increased proportionally or more than proportionally with increasing dosage. OCA exposure was higher in females than in males while exposure to tauro-OCA was similar. AUC ranged from less than 2-fold to approximately 6-fold. Cmax tended to be approximately 2-fold higher for females than males. Exposure to tauro-OCA was much greater than exposure to OCA for both sexes. Exposure to the glyco-conjugate was minimal and detected only at the high dose.

The oral administration of OCA in rats resulted in systemic exposure to the parent and tauro-OCA and glyco-OCA. Exposures to each analyte generally increased in proportion to increasing dose, with a low accumulation of OCA (<6-fold) and higher accumulation of tauro-OCA (5.9-10-fold). Exposure to glyco-OCA was negligible compared to OCA exposure. No conclusive data were obtained regarding the exposure in male and female rats, since in some studies no difference in exposure in both sex were observed while in other differences were seen.

In juvenile rats, OCA exposure was higher than in adult animals on PND 6 and 21, and was similar to adult animals by PND 28 and 56. The majority of total drug was in the tauro-OCA form on PND 6; OCA and tauro-OCA were at similar levels on PND 21; and tauro-OCA was lower than parent (similar to adult ratios) on PND 28 and 56.

The pharmacokinetics of obeticholic acid was also studied in 3 embryo/fetal development studies in the rabbit. In these studies, exposure generally increased proportionately with increasing dose, with systemic exposure to OCA and glyco-OCA in roughly equivalent amounts and with negligible exposure to tauro-OCA.

Systemic exposure of dogs to OCA was found to increase roughly proportionately with dose and there was no evidence of accumulation of OCA with multiple doses. Also, in dog, there was a little to no exposure to glyco-OCA, and there were no consistent exposure differences between sexes.

Accumulation of OCA and OCA conjugates was observed in all species after repeat dosing, with a slightly greater accumulation of OCA in rats, relative to the mouse and dog, and this is consistent with a much lower metabolite/parent ratio (tauro-OCA/OCA) in the rat.

Regarding the distribution, the mass-balance study (6-ECDCA) determined that OCA-related material is generally confined to the hepatobiliary system. The radiolabel study in rats also demonstrated a pattern of distribution indicative of enterohepatic circulation with relatively little distribution to, or accumulation in, peripheral tissues.

[^{14}C]-OCA at 10 µM was moderately metabolized in liver S9 fractions from mice, rats, rabbits, dogs, monkeys and humans. Nine metabolites were tentatively identified by LC/MS in S9 incubation samples.

In vivo in mice, OCA is metabolized primarily to tauro-OCA. No other major metabolites resulting from a 7-dehydroxylation process, glucuronides, or other polar metabolites were identified.

In rats, OCA and tauro-OCA were 84.5% and 11.4%, respectively, of radioactivity recovered in the 1 hour post-dose plasma sample. At 24 hours, tauro-OCA increased to 50% and OCA decreased to 37.7%, and an epimer of OCA was also observed in plasma (7.3%) which could be 6-EUDCA. No other metabolites were identified in plasma. In feces, there were more metabolites, suggesting that they may be formed by bacteria in the GI tract.

These studies *in vitro* and *in vivo* in rats confirmed the predominant metabolism of OCA to the tauro-conjugate as well as the presence of 6-EUDCA and OCA 3-glucuronide. This latter is found in female rats but not in males. Conversely, OCA 24-glucuronide was observed in male rats but not females.

In the rabbits, equivalent concentrations of OCA and glyco-OCA in plasma were found. Only glyco-OCA was tested in bile and liver.

OCA and its conjugates undergo a high degree of entero-hepatic recirculation and are eliminated exclusively in feces via biliary excretion. Tauro-OCA was secreted in milk in lactating female rats following oral administration of OCA at 5, 25 and 40 mg/kg.

No information for pharmacokinetic drug interactions has been shown in the non-clinical part.

3.2.3. Toxicology

No deaths were reported in the acute toxicity studies performed in rats and dogs. In dogs, some findings were considered OCA-related, such as decrease in body weight and decrease in serum liver function enzymes. The single dose of OCA that resulted in no adverse effects was the highest dose levels tested for rats (300 mg/kg), while the MTD in dogs was 750 mg/kg.

Two preliminary repeat dose toxicity studies were conducted with mice and dogs. In both studies, animals were dosed with OCA for 7 consecutive days. In the case of mice, NOEL was established at 50 mg/Kg/day. Upper dose levels (175 and 300 mg/Kg/day) showed liver toxicity and mortality, especially in males rather than in females. For dogs, NOAEL was reported at 20 mg/Kg/day, given that ≥50 mg/Kg/day exhibited alteration of serum enzymes and effects on liver.

As for the repeat dose toxicity pivotal studies, they were conducted in mouse, rat and dog species. Starting with mice studies, a 13-week repeat dose toxicity study was performed with OCA. The three dose levels tested were 4, 12, 40, and 120/80 mg/kg/day in males and in females administered 12, 40, and 120/80 mg/kg/day. The NOAEL could not be established for males, given the hepatocellular necrosis reported at the lowest dose level. Contrarily, NOAEL for females was 4 mg/Kg/day.

In the case of rats, the first study (28-day repeat dose toxicity) showed an increase in liver enzymes at 75 mg/Kg/day. In a second repeat dose toxicity study (13 weeks), the NOAEL was established at 6 mg/Kg/day. The dose level of 15 mg/Kg/day revealed increased liver weights and albumin levels.

Repeat dose toxicity studies with OCA were also conducted in dogs (4- and 39-week). In the 4-week study, the applicant considered NOAEL to be 15 mg/Kg/day, given that 50 mg/Kg/day produced microscopic findings of cystic hyperplasia, atrophy, and centrilobular degeneration in the liver, and increased liver enzymes (AST, ALT, ALP, GGT), albumin, and total protein increases. A similar value for NOAEL was reported by the applicant in the 39-week repeat dose toxicity study.

Unscheduled deaths were reported at high doses (≥120/80 mg/kg/day in mice and 150 mg/kg/day in rats) in these studies. Most of them were attributed to liver injury in both species, and additionally GI injury in the case of rats. No deaths have been reported in dogs treated with OCA doses up to 50mg/kg/day.

It is noted that in the study 019958, performed in rat for 13 or 26 week, one male treated at the dose level of 6 mg/kg/day of OCA, was sacrificed for humane reasons at Day 47. Necropsy findings were malocclusion, red cervical lymph nodes, black cecum contents, sections of small intestine distended with gas and black material surrounding the eyes and nose. Although the cause of the death was not considered to be test-article related, this finding should have been mentioned in the toxicology written summary.

Taken together, the results of the repeat dose toxicity studies indicated that the major site of target organ toxicity was the hepatobiliary system (liver, bile duct and gall bladder), in the nonclinical species (mice, rats, and dogs), which is in line with the reported toxicity of other bile acids as CDCA and DCA. Findings included increased liver weights, alterations in serum chemistry parameters indicative of hepatic (ALT, AST, LDH) and biliary (ALP, GGT, and/or bilirubin) toxicity.

Histopathological lesions were also reported in these studies. The most relevant were cholangiohepatitis, bile duct hyperplasia and individual hepatocyte degeneration/necrosis at 60 mg/kg/day in the case of rats, and cystic hyperplasia and/or secretion in the gallbladder, hepatocellular atrophy, and centrilobular hepatocellular degeneration occurred at 50 mg/kg/day for dogs. However, the applicant noted that a full recovery for histopathologic changes and partial recovery of serum chemistry were reported after the 14-day recovery period.

The applicant provided a table with the calculation of the exposure ratios based on the total OCA equivalents measured in humans at 10 mg (2972 ng*h/mL) and 25 mg (9165 ng*h/mL) and plasma levels obtained in the toxicokinetics. In this sense, the applicant refers to the intended human dose and maximum human exposure in the case of 10 mg and 25 mg, respectively. However, the recommended dosage regimen is 25 mg once daily. Dose of 10 mg should be deleted. The Applicant was asked for an estimate of safety margins for the proposed marketed dose of 25 mg. The applicant has provided this request but has also included the safety margins for a 10 mg dose. Since only Zektayos 25 mg film-coated tablets authorization is requested, the applicant is asked to remove both the 10 mg doses and the safety margins for the 10 mg dose from the dossier and future documentation sending.

OCA and its conjugates, tauro-OCA and glyco-OCA, resulted to be non-mutagenic after testing in a bacterial reverse mutation assay. Similarly, no clastogenic result was found in mammalian chromosome aberration assay in human peripheral blood lymphocytes. In addition, OCA was not genotoxic in an *in vivo* mammalian erythrocyte micronucleus assay.

OCA and its conjugates were tested for carcinogenic potential in 2-year assays performed in rats and mice. In these studies, OCA was not carcinogenic at doses of up to 20 mg/kg/day and 25 mg/kg/day in rats and mice, respectively.

The potential reproductive toxicity of OCA was evaluated in rats and rabbits on the classical battery of studies. Additionally, a juvenile rat study was carried out in rats.

The only adverse treatment-related effects on development (reduced fetal body weights and increased post-implantation loss) have been found in rat embryo-fetal development study at 75 mg/kg/day. These effects were observed in five females and as no other effects on reproductive or developmental was reported, these effects were considered the result of marked maternal toxicity rather than a specific developmental effect. At dose of 25 mg/kg/day no maternal toxicity or developmental effects were found.

There were no teratogenic effects of OCA at doses up to 75 mg/kg/day in rats and 20 mg/kg/day in rabbits.

No specific studies were done to assess the presence of OCA or conjugates in breast milk, but tauro-OCA exposure was measured in nursing rat pups on postnatal Day 10. These results suggest the transfer of OCA or tauro-OCA during lactation.

Two juvenile animal studies were carried out with OCA, covered from PND4 to PND56. In these studies, treatment-related mortality was reported at doses of 15 mg/kg/day on PND 4, which was attributed to hepatic bile duct hyperplasia. This finding is limited to the pre-weaning or early post-weaning period (i.e, PND 12 to 25), and corresponding to a time when AUC exposure is similar to exposure associated with lethal doses in adults (60 mg/kg/day). In post-weaning period (PND 28 to 56), exposures and histopathological changes at necropsy are similar to those seen in adults. Systemic exposures to OCA and tauro-OCA were greater during pre-weaning period (PND 1 to 21) compared with adult exposures at the same doses. These data could also support the hypothesis that OCA or tauro-OCA is transferred into breast milk.

The absence of local tolerance, antigenicity and immunotoxicity studies, and studies in dependence, is considered acceptable.

No studies on metabolites have been submitted. A disproportionate human 3 ether-glucuronide of OCA was identified. However, it was considered to have been adequately qualified for safety issues.

As stated by the Applicant in the Toxicology Written Summary, six impurities have been identified (Impurities 1 to 6) in OCA batches. Impurities 1 through 5 are process impurities and Impurity 6 (OCA dimer) is a degradation product. These were shown to have no structural alert for mutagenicity, when evaluated using DEREK and MultiCASE software. Moreover, structural alerts for mutagenicity were revealed for acetaldehyde (raw material used in the Step 3 of the Manufacturing process of I18-5) and for the synthetic intermediate, I18-5. A Risk Assessment with a detailed description of the in silico assays performed was provided by the Applicant.

3.2.4. Ecotoxicity/environmental risk assessment

The Applicant presented the ERA for OCA in line with guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CPMP/SWP/4447/00 corr2).

The conclusion about the screening of OCA for persistence, bioaccumulation and toxicity is not supported, since the $\log D_{OW}$ is higher than 3 at pH 5 and 7 and consequently, bioaccumulation should be assessed in Tier B. Hence, the applicant is asked to provide a study on bioaccumulation in fish according to OECD TG 305**.** The study can be provided post-approval with an updated ERA

On the other hand, the result of PECSW calculation (0.175 µg/L), made by the sum of PEC for each indication, is above the action limit of 0.01 µg/L. Thus, a recalculated PECSW using Fpen refined value for each indication has been also provided. Since this PECSW value is also above the action limit of 0.01 µg/L, the applicant has supplied same Phase II studies in compliance with ERA Guideline, as other studies

are in progress. Solely study summaries in the ERA are not sufficient for the evaluation. Therefore, the applicant is requested to provide all available study reports, apart from those being in progress, i.e. Adsorption/Desorption (OECD 106), Aerobic Transformation In Aquatic Sediment (OECD 308), Fish Early Life Stage Test (OECD 210). Otherwise, the fourth study in progress, Sediment-Water *Chironomus* Toxicity Test (OECD 218), is not requested by ERA Guideline in Phase II Tier A

If once Phase II Tier A is finished a potential risk for Zektayos to the environment is identified, then a Tier B assessment in compliance with ERA Guideline (EMEA/CPMP/SWP/4447/00 corr2) should be conducted.

3.2.5. Discussion on non-clinical aspects

Most of the information supporting OCA for the indication of NASH fibrosis was submitted and reviewed in the previously approved marketing application for the PBC indication. For this authorisation, the Applicant showed, direct anti-inflammatory, anti-fibrotic and gene modulatory effects of OCA in different test systems *in vitro*. *In vivo*, hepatoprotective effects of OCA were demonstrated in rat models of cholestasis, acute liver injury, liver fibrosis, cirrhosis, and portal hypertension induced by chemical injury or bile duct ligation. Reduced hepatic fibrosis by OCA was associated with decreased hepatic NF-κB pathway activity through up-regulated IκBα.

In the present application, the effects of OCA have been evaluated in *in vivo* disease mice models of NASH. However, it is recognized that there is no animal model that fully resembles the human condition. Since human-based *in vitro* models for NASH provide a valuable tool to study the disease, the Applicant elaborated on these models and their applicability in OCA efficacy testing.

OCA combination with different therapies in NASH models was also presented. Clear improvements on NASH endpoints were observed when OCA was co-administered with the GLP-1R agonist IP118, the dual PPAR α/δ agonist elafibranor, or the pan-PPAR agonist bezafibrate.

Regarding pharmacokinetics, absorption of OCA is high, and distribution is primarily within the enterohepatic circulation. Circulating forms of OCA are primarily the pharmacologically active glyco- or tauro-OCA conjugates and, to a lesser extent, the active parent compound. OCA and its conjugates are eliminated exclusively in feces via biliary excretion. OCA and/or its metabolites are excreted in milk.

Oral administration of OCA above the NOAEL to mice, rats, and dogs in pivotal, repeat dose toxicity studies resulted primarily in effects on the hepatobiliary system. The target organs of toxicity in the juvenile studies were the same as those in adults, namely the liver and bile duct. Increased toxicity at a given dose was attributed to higher systemic exposure in the pre-weaning period and not to increased risk in juvenile animals.

In the toxicology section, the applicant refers to the intended human dose and maximum human exposure in the case of 10 mg and 25 mg, respectively. However, the dose of 10 mg will not be used for the NASH indication. The Applicant has provided an estimate of safety margins for the proposed marketed dose of 25 mg and for a 10 mg dose. Since only Zektayos 25 mg film-coated tablets authorization is requested, the applicant is asked to remove both the 10 mg doses and the safety margins for the 10 mg dose from the dossier and future documentation sending.

Impurities were shown to have no structural alert for mutagenicity, when evaluated using DEREK and MultiCASE software. Moreover, structural alerts for mutagenicity were revealed for acetaldehyde and for the synthetic intermediate, I18-5. The Applicant has provided a Risk Assessment with a detailed description of the in silico assays performed.

Regarding ERA, some concerns have been raised that have to be resolved by the Applicant. Provide a study on bioaccumulation in fish according to OECD TG 305**,** and all Phase II Tier A study reports are

requested to be provided, and, if once Phase II Tier A is finished a potential risk for Zektayos to the environment is identified, then a Tier B assessment in compliance with ERA Guideline (EMEA/CPMP/SWP/4447/00 corr2) should be conducted.

3.2.6. Conclusion on non-clinical aspects

The non-clinical aspects of obeticholic acid have been assessed, comprising pharmacodynamics, pharmacokinetic and toxicological aspects. Under a non-clinical point of view no major objections were found, however, some concerns require clarification from the applicant.

3.3. Clinical aspects

Tabular overview of clinical studies

Table 1 Overview of Clinical Pharmacology Studies

Study No.	Objective(s)
Bioavailability (BA) Study Reports	
747-104	To assess the effect of fed conditions (high fat, high calorie) on the PK of OCA
D8601002	To evaluate safety and PK of OCA after single and multiple oral administration of OCA in Japanese healthy adult male volunteers
747-113	1) Determine the absolute BA of OCA in healthy male subjects 2) Assess the mass balance recovery from excreta for carbon-14 [^{14}C]-OCA (administered in a capsule) in healthy male subjects after an oral dose 3) Assess the metabolite profile of [^{14}C]-OCA in plasma, urine, andfecal samples after an oral dose
Bioequivalence (BE) Study Reports	
747-115	To evaluate the biocomparability of 2 tablet formulations (commercial image and clinical development) of OCA in healthy subjects
747-116	To evaluate the biocomparability of a capsule formulation compared to a commercial image tablet formulation of OCA in healthy subjects: a 10-mg tablet intended for commercial use was compared to a 10-mg capsule used in Phase 2 studies in the OCA clinical development program
PK/tolerability study reports on Healthy Subject	
747-101	To assess the safety and tolerability of single escalating oral doses of OCA in healthy male Subjects
747-102	To assess the safety and tolerability of daily doses (12 days) of OCA in healthy subjects
747-105	To evaluate the PK of OCA and its conjugates (G-OCA and T-OCA) following single and multiple doses of OCA 5 mg, 10 mg, and 25 mg in healthy subjects
747-107	To identify an appropriate OCA dosing regimen that achieves target supratherapeutic plasma OCA and conjugates (G-OCA and T-OCA) concentrations in healthy subjects in preparation for a thorough QT study
DDI study reports on Healthy Subject	
747-109	To assess DDI of OCA on the single dose PK of CYP3A4 [sensitive substrate: midazolam] andCYP1A2 [sensitive substrate: caffeine]
747-110	1) To assess the effect of steady-state OCA on the PK of R-warfarin and S-warfarin after administration of a single racemic warfarin dose in healthy adult subjects 2) To examine the effect of OCA on the single-dose PD of racemic warfarin, through assessment of coagulation parameters PT, aPTT, and INR, in healthy adult subjects 3) Examine the safety and tolerability of OCA and racemic warfarin co-administration in healthy adult subjects
747-111	To assess the effect of steady-state OCA on the plasma PK of rosuvastatin after administration of a single rosuvastatin dose in healthy adult subjects
747-112	1) Assess the effect of steady-state OCA on the single-dose plasma PK of dextromethorphan(CYP2D6 substrate) in healthy adult subjects 2) Assess the effect of steady-state OCA on the single-dose plasma PK of omeprazole (a CYP2C19 substrate) in healthy adult subjects 3) Assess the effect of omeprazole on the steady-state plasma PK of OCA in healthy adult subjects
747-114	To assess the effect of steady-state OCA on the single-dose plasma PK of digoxin in healthy adult subjects
QT study reports	
747-108	To determine, in healthy subjects, that OCA, G-OCA, and T-OCA at therapeutic and supratherapeutic concentrations do not differ from placebo in the largest time matched mean change from baseline in 12-lead ECG corrected QT interval

PK on special populations study reports	
747-103	To assess the PK of OCA and its conjugates (G-OCA and T-OCA) in subjects with mild to severe hepatic impairment compared with healthy volunteers with normal hepatic function
747-120	To investigate the effect of renal impairment on the single dose PK of OCA
Patients PD and PK/PD study reports	
747-117	To evaluate safety, PK and PD of OCA in subjects with NASH with fibrosis
747-118	To evaluate safety, PK and PD of OCA in subjects with cirrhosis due to NASH
747-209	To investigate the effects of OCA and Atorvastatin treatment on Lipoprotein Metabolism in subjects with NASH
747-303	To evaluate safety and efficacy of OCA in subjects with NASH

DG = digoxin; DSP-1747 = OCA; FA = fatty acid; G-OCA = glycine conjugate of OCA; h = hour; IIT = investigator-initiated trial; MOA = mechanism of action; NAS = NAFLD activity score; OL = open label; POC = Proof of concept; PT = prothrombin time; QT = corrected measure between Q wave and T wave (in heart's electrical cycle);T-OCA = taurine conjugate of OCA; TG = hepatic triglycerid

3.3.1. Pharmacokinetics

OCA is a FXR agonist structurally similar to the primary bile acid chenodeoxycholic acid (CDCA) and consequently, its PK properties are similar to that of CDCA. Much of the PK information supporting OCA for the indication of liver fibrosis due to NASH was submitted and reviewed in the previously approved application for the PBC indication (EMEA/H/C/004093). OCA clinical pharmacology program included: characterization of the PK through single- and multiple-dose studies, bridging bioequivalence studies, ADME study, investigation of extrinsic (DDI and food effect studies) and intrinsic factors (hepatic and renal impairment) in HS and a thorough QT study. New submitted PK studies were related to renal impaired subjects and target population (NASH patients).

- **Analytical methods**

To determine OCA and its main conjugates' (G- and T-OCA) PK parameters the Applicant used LC MS/MS methods, which were fully validated for plasma (VAL-RPT-633, RPT-01947, RPT-02968, PRD11-209 and RPT-03718) and urine (VAL-RPT-560, RPT-03237 and PRD11-210) and qualified for liver tissue (RPT-04977). The minor metabolite (3-O-glucuronide-OCA) was investigated only in plasma using a validated LC MS/MS method (RPT-04304). FGF-19, C4, bile acids and related G- and T-conjugates were used as PD biomarkers. FGF-19 was determined in plasma using an enzyme-linked immunosorbent assay (ELISA) method, which was qualified (RPT-03172) and thereafter validated (RPT-03476). C4 was determined in plasma using a validated LC-MS/MS method (RPT-03767). Bile acids and related glycine and taurine conjugates' levels were investigated in plasma using a qualified LC-MS/MS method in plasma (RPT-04786) and a commercially available colorimetric assay based on an enzymatic cycling method in the presence of NADH and a chromophore in liver tissue (RPT-04964).

- **Bioavailability**

As observed for healthy subjects, absorption of unconjugated OCA was rapid with tmax between 1 and 1.5 hours following QD doses of OCA 10 mg and 25 mg. These results show that no disease state effects are expected with NASH and the absorption of OCA.

Absolute bioavailability was determined by the ratio of dose normalized AUC for oral dose/dose normalized AUC for IV dose. As shown below, the mean absolute bioavailability (F) of OCA was approximately 17%. This relatively low value for bioavailability is consistent with the efficient uptake typical of bile acids into the liver, the primary site of action of OCA.

- **Bioequivalence**

Two biocomparability studies were performed during the PBC development program of OCA. NASH Studies 747-117, 747-118, 747-209, and 747-303 all used the same tablet formulation of OCA.

- Study 747-115 was conducted to assess the biocomparability of the OCA 10 mg clinical tablet relative to the OCA 10-mg commercial image tablet.

Table 2

Table 15: Statistical Comparisons of Plasma Exposure PK Parameters Following a Single Dose of OCA 10-mg Commercial Image Tablet and OCA 10-mg Clinical Development Tablet

Statistical Comparison PK Parameter	Geometric LSM Ratio (90% CI of the Ratio) N = 157	
	OCA	Total OCA[a]
Commercial Image Tablet Versus Clinical Development Tablet		
$AUC_{0\text{-}72}$ (h·ng/mL)	106 (102 - 110)	101 (97.2 - 104)
$AUC_{0\text{-}168}$ (h·ng/mL)	104 (99.7 - 109)	102 (98.6 - 105)
AUC_{∞} (h·ng/mL)	101 (95.0 - 107)	103 (99.6 - 106)
C_{max} (ng/mL)	118 (108 - 129)	112 (107 - 118)

ANOVA = analysis of variance; $AUC_{0\text{-}72}$ = area under the concentration-time curve from time 0 to 72 hours postadministration; $AUC_{0\text{-}168}$ = area under the concentration-time curve from time 0 to 168 hours postadministration; AUC_{∞} = area under the concentration-time curve from time 0 to infinity; CI = confidence interval; C_{max} = peak (maximum) plasma concentration; LSM = least-squares mean; ng-eq = nanogram equivalents; OCA = obeticholic acid; PK = pharmacokinetic
Note: The natural log-transformed OCA and total OCA PK parameters were assessed with an ANOVA model, including treatment, period, and sequence as fixed effects, and subject nested within sequence as a random effect. Geometric LSM, geometric LSM ratio (commercial image tablet/clinical development tablet), and associated 90% CIs were exponentiated to the original scale. The geometric LSM ratios and associated 90% CIs were multiplied by 100.
[a] ng-eq
Source: CSR 747-115, Section 14, Table 14.2.1 and Table 14.2.2

- Study 747-116 was conducted to assess the biocomparability of the OCA 10 mg capsule relative to the OCA 10-mg commercial image tablet.

Table 3

Table 16: Statistical Comparisons of Plasma Exposure PK Parameters Following a Single Dose of OCA 10-mg Capsule and OCA 10-mg Commercial Image Tablet

Statistical Comparison PK Parameter	Geometric LSM Ratio (90% CI of the Ratio) N = 152	
	OCA	Total OCA[a]
Capsule Versus Commercial Image Tablet		
$AUC_{0\text{-}72}$ (h·ng/mL)	102 (97.2 - 107)	104 (101 - 107)
$AUC_{0\text{-}168}$ (h·ng/mL)	101 (95.5 - 108)	104 (101 - 107)
AUC_{∞} (h·ng/mL)	105 (98.6 - 113)	103 (99.9 - 106)
C_{max} (ng/mL)	92.3 (84.8 - 100)	98.3 (93.9 - 103)

ANOVA = analysis of variance; $AUC_{0\text{-}72}$ = area under the concentration-time curve from time 0 to 72 hours postadministration; $AUC_{0\text{-}168}$ = area under the concentration-time curve from time 0 to 168 hours postadministration; AUC_{∞} = area under the concentration-time curve from time 0 to infinity; CI = confidence interval; C_{max} = peak (maximum) plasma concentration; LSM = least-squares mean; ng-eq = nanogram equivalents; OCA = obeticholic acid; PK = pharmacokinetic
Note: The natural log-transformed OCA and total OCA PK parameters were assessed with an ANOVA model, including treatment, period, and sequence as fixed effects, and subject nested within sequence as a random effect. Geometric LSM, geometric LSM ratio (commercial image tablet/clinical development tablet), and associated 90% CIs were exponentiated to the original scale. The geometric LSM ratios and associated 90% CIs were multiplied by 100.
[a] ng-eq
Source: 747-116, Section 14, Table 14.2.1 and Table 14.2.2

- **Influence of food**

Study 747-104 investigated the PK of OCA in a total of 31 healthy subjects following a single dose of 10 mg or 25 mg OCA under fed and fasted conditions. Overall, a high-fat, high-calorie meal did not appear to have a clinically meaningful effect on the absorption of OCA following a 10-mg or 25-mg OCA dose. Although the mean Cmax and overall (area under the concentration-time curve calculated to the last observable concentration at time t [AUCt]) plasma OCA and glyco-OCA exposures were marginally higher under fed conditions relative to fasted conditions, the small magnitude of difference based on the geometric mean ratios and observed variability based on the associated 90% confidence intervals (CIs) suggest that the observed differences are not expected to be clinically meaningful. Based on the results of this study, OCA may be administered without regard to meals.

- **Distribution**

Table 4

Table 11: Mean (SD) of IV Plasma Pharmacokinetic Parameters: Regimen B, Study Part 1: PK Population (N = 5)

	OCA Part 1	
Parameter	**IV [^{14}C]-OCA** N = 5	**Total Radioactivity** N = 5
C_{max} (ng/mL)	9.71 (0.3279)	9.13 (0.5512)
AUC_{0-t} (hours*ng/mL)	3.86 (0.1738)	18.5 (4.234)
CL (L/hours)	25.0 (1.052)	N/A
V_z (L)	618 (341.9)	N/A
V_{ss} (L)	210 (62.14)	N/A

AUC_{0-t} = Area under the concentration versus time curve from time zero to the last sampling time with quantifiable analyte; CL = total plasma clearance; C_{max} = Maximum observed analyte concentration in plasma; IV= Intravenous; N/A= Not applicable; OCA = Obeticholic acid; V_{ss} = Volume of distribution at steady state; V_z = Volume of distribution; Regimen B = 15 minute IV infusion of 100 µg [^{14}C]-OCA
Source: Clinical Study Report 747-113, Section 14.2, Table 14.2.6 (Part 1)

- **Excretion**

The mean cumulative recovery (cumulative %Ae) of radioactivity in the urine and feces of subjects receiving oral [14C]-OCA is shown in Figure 8. Following a single oral dose of 25 mg [14C]-OCA a mean of 75.1% (range between 28.3% and 97.5%) of the total radioactivity administered was recovered from urine and feces by the end of the inpatient sampling period (504 hours postdose; Table 14.2.12). An average of 2.83% (range 1.57% to 4.00%) of the total radioactivity was recovered from the urine, and the majority of drug-related material in the urine was recovered within the first 312 hours after investigational product administration (Table 14.2.10).

An average of 72.3% (range 25.2% to 95.9%) was recovered from feces by 504 hours postdose (Table 14.2.11). However, because only 1 subject had achieved a cumulative recovery of greater than 90% at 504 hours, the other 7 subjects conducted additional home fecal collections beyond 504 hours postdose (7/8 subjects until 816 hours, 3/8 subjects until 888 hours postdose and 2/8 subjects until 1152 hours postdose). Total recovery (urine and feces combined, sampled up to 1152 hours) from each of the subjects ranged from 76.31% to 111.28% of the administered radioactivity). At 1152 hours, a mean of 87.0% of the total radioactivity administered (range 73.2 to 107%) was recovered from feces. The majority of drug-related material in the feces was recovered within 552 hours of dosing with investigational product.

- **Metabolism**

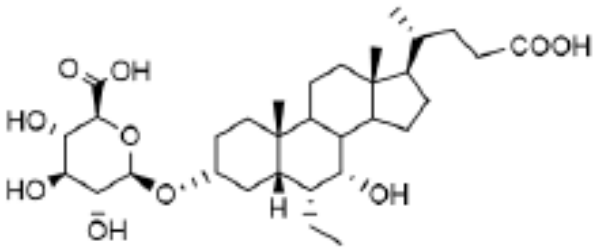
As was seen in healthy subjects, OCA was extensively conjugated to glycine and taurine with the mean steady-state plasma metabolic ratio of 4.49 and 4.50 for glyco-OCA and tauro-OCA, respectively, for subjects with liver fibrosis stages 2 and 3 due to NASH, and 4.34 and 2.90 for healthy subjects, respectively, receiving OCA 25 mg QD. There was minimal metabolism of OCA to glucuronide, which had a mean steady-state metabolic ratio of 1.55 in subjects with liver fibrosis stages 2 and 3 due to NASH. Glyco-OCA and tauro-OCA were the primary constituents of total OCA at 90% and 88% of the total OCA summation for subjects with liver fibrosis due to NASH and healthy subjects, respectively, with the remaining coming from unconjugated OCA. This would indicate that glyco-OCA and tauro-OCA are primarily responsible for the pharmacology of OCA. Mean overall plasma exposures (ie, AUC0-6h) of unconjugated OCA, glyco-OCA, tauro-OCA, and total OCA were 1.5-, 1.6-, 2.5-, and 1.9-fold higher, respectively, in subjects with liver fibrosis due to NASH relative to healthy subjects receiving OCA 25 mg QD. The increase in overall plasma OCA exposure in subjects with liver fibrosis due to NASH is due to a decrease in hepatic extraction that was characterized in the NASH physiologic PK model (see Section 3.8).

Two additional OCA metabolites were identified: OCA-3 glucuronide and OCA-24 glucuronide, based on the metabolite profiling of radioactivity, mass spectrometry, and authentic standards for the glucuronide metabolites. The structure of these metabolites is figure below.

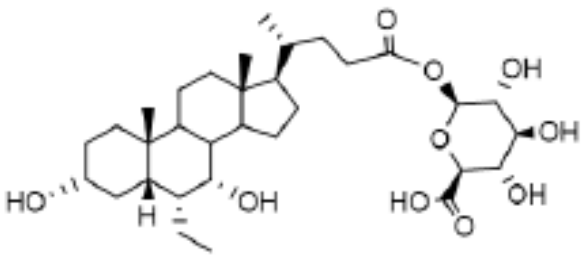
Figure 2

Figure 9: Structure of Glucuronide Metabolites

OCA-3 glucuronide



OCA-24 glucuronide



- **Dose proportionality**

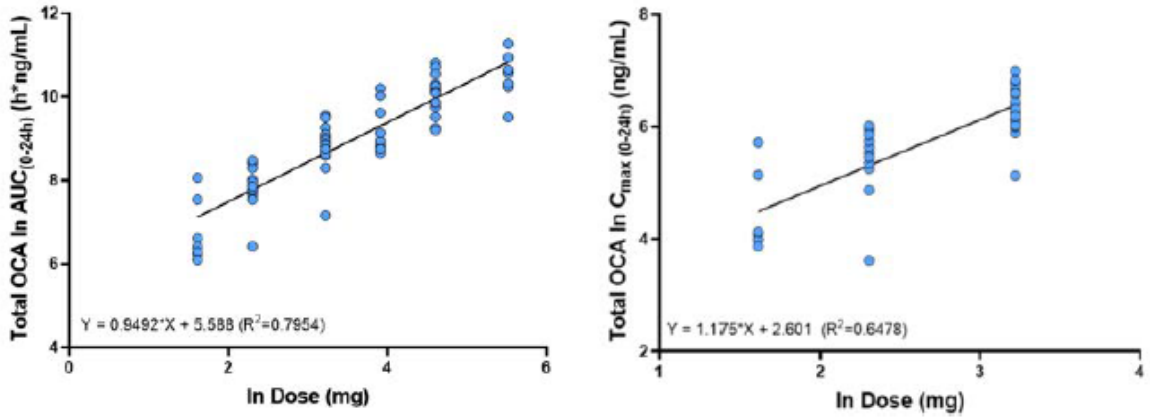
Table 5 and Figure 3

Table 2: Dose Proportionality Results for Unconjugated OCA, Glyco-OCA, Tauro-OCA, and Total OCA for Steady-State AUC0-24h and Cmax(0-24h) in Healthy Subjects

OCA Doses Assessed (mg)	Parameter	Analyte	Slope (90% CI)
5, 10, 25, 50, 100, and 250	AUC_{0-24h}	Total OCA	0.949 (0.850, 1.05)
		Unconjugated OCA	0.961 (0.873, 1.05)
		Glyco-OCA	0.988 (0.893, 1.08)
		Tauro-OCA	0.870 (0.733, 1.01)
5, 10, and 25	$C_{max(0-24h)}$	Total OCA	1.18 (0.928, 1.42)
		Unconjugated OCA	0.880 (0.690, 1.07)
		Glyco-OCA	1.12 (0.880, 1.35)
		Tauro-OCA	1.28 (0.955, 1.61)

AUC_{0-24h} = area under the concentration-time curve from time 0 to 24 hours postadministration; CI = confidence interval; $C_{max(0-24h)}$ = peak (maximum) plasma concentration from time 0 to 24 hours postadministration; glyco-OCA = glycine conjugate of obeticholic acid; OCA = obeticholic acid; tauro-OCA = taurine conjugate of obeticholic acid.
Dose proportionality was concluded if the 90% CI on the estimation of the power model slope included 1 and excluded 0.
Source: Module 5.3.5.3, PAR, Cross-Study OCA Pharmacokinetic Characterization for NASH Fibrosis, Table 25

Dose Proportionality Assessment of Steady-State Plasma AUC_{0-24h} and $C_{max(0-24h)}$ for Total OCA in Healthy Subjects (Studies 747-102/747-105/747-118)



AUC_{0-24h} = area under the concentration-time curve from time 0 to 24 hours postadministration; $C_{max(0-24h)}$ = peak (maximum) plasma concentration from time 0 to 24 hours postadministration; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid.
Symbols represent individual data points, and the line is the power model results for assessment of dose proportionality.
Source: Module 5.3.5.3, PAR, Cross-Study OCA Pharmacokinetic Characterization for NASH Fibrosis, Appendix Figure 13.1.1 (AUC_{0-24h}) and Appendix Figure 13.2.1 ($C_{max[0-24h]}$)

- **Time dependency**

Racs for unconjugated OCA, glyco-OCA, and total OCA were generally similar for subjects with liver fibrosis stages 2 and 3 due to NASH compared with healthy subjects; the Rac for tauro-OCA was approximately 2-fold higher in subjects with liver fibrosis due to NASH compared with healthy subjects.

The plasma PK parameters for total OCA, unconjugated OCA, glyco-OCA, and tauro-OCA following single doses and multiple doses over the dose range of 5 mg to 250 mg of OCA in healthy subjects is summarized as follows:

- Accumulation: At steady state, the Rac (AUC0-24h) of unconjugated OCA was approximately 2 across the 5- to 100-mg dose range, reflecting minimal accumulation. The conjugates showed significant accumulation at steady state; the Racs across the dose range were approximately 3 to 6 for glyco-OCA and 5 to 13 for tauro-OCA. Accumulation of total OCA (approximately 3.5 to 7) after multiple doses of OCA was similar to that of glyco-OCA, which is consistent with glyco-OCA being the predominant conjugate in healthy subjects. The effective half-life of total OCA was 3.4 to 4.8 days for OCA 25 mg.

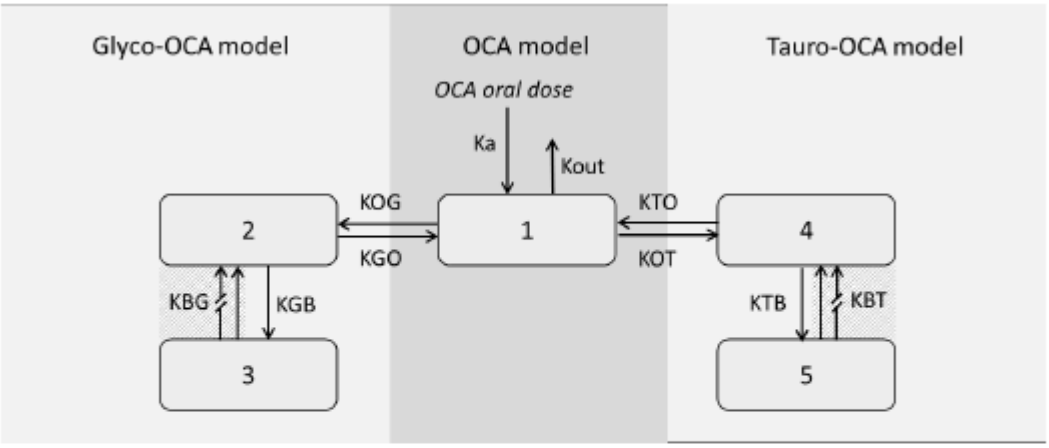
- **Pharmacokinetics in target population**

Base structural PK model

The selected structural population PK model for OCA and its conjugates had the same structure as presented in figure below. This model included a central compartment for OCA, tauro-OCA and glyco-OCA and an enterohepatic recirculation "gallbladder" compartment for glyco-OCA and tauro-OCA. BSVs were included in on all parameters except the rates from central compartment to gallbladder for glyco-OCA and tauro-OCA (KGB and KTB, respectively). A first-order rate constant of absorption adequately characterized drug absorption.

Figure 4

Figure 6.1 Schematic Representation of the Structural Population PK Model of OCA and its Conjugates



Compartments #1, 2, 4 represent the central compartment of OCA, glyco-OCA and tauro-OCA concentrations (ie, observed) in the plasma, respectively and compartments #3 and 5 represent the gallbladder compartments for glyco- and tauro-OCA, respectively; arrows with breaks correspond to intermittent gallbladder emptying

Ka = first-order rate of absorption; KBG = rate of gallbladder emptying into the central compartment for glyco-OCA during gallbladder contraction; KBT = rate of gallbladder emptying into the central compartment for tauro-OCA during gallbladder contraction; KGB = first-order rate for glyco-OCA accumulation in gallbladder; KGO = biotransformation rate of glyco-OCA into OCA; KOG = biotransformation rate of OCA into glyco-OCA; KOT= biotransformation rate of OCA into tauro-OCA; Kout= rate of fecal elimination of OCA; KTB = first-order rate for tauro-OCA accumulation in gallbladder; KTO = biotransformation rate of tauro-OCA into OCA; OCA = obeticholic acid

Table 6

2.2.2. Typical Values of the Structural Population PK Model of OCA, Glyco-OCA and Tauro-OCA

Parameter	Estimate
VOCA (L)	176
Vglyco (L)	195
Vtauro (L)	175
Ka (h^{-1})	0.817
Kout (h^{-1})	0.365
KOG (h^{-1})	0.585
KOT (h^{-1})	0.140
KGO (h^{-1})	0.0475
KTO (h^{-1})	0.0201
KGB (h^{-1})	0.112
KBG (h^{-1})	5.48
KTB (h^{-1})	0.142
KBT (h^{-1})	6.38
gbbl (fraction of tvKBG)	0.00896
Prop Error OCA (%)	74.4
Prop Error Glyco-OCA (%)	50.9
Prop Error Tauro-OCA (%)	52.4
Additional Error OCA (nM)	0.44777
Additional Error Glyco-OCA (nM)	0.337664
Additional Error Tauro-OCA (nM)	0.050235

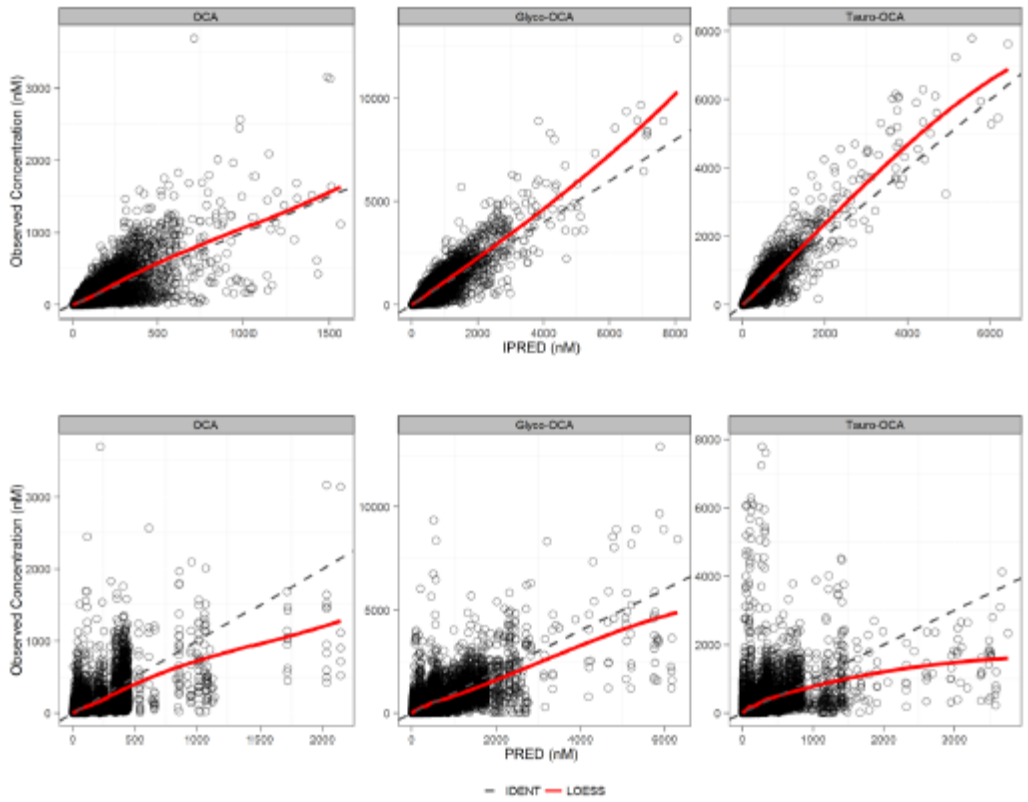
Parameter	Estimate	Shrinkage (%)
BSV Ka (%)	70.9	5.6
BSV VOCA (%)	53.9	10.7
Variance between BSV Vglyco and BDV VOCA	0.318	
BSV Vglyco (%)	67.7	7.4
Variance between BSV Vtauro and BDV VOCA	0.400	
Variance between BSV Vtauro and BDV Vglyco	0.547	
BSV Vtauro (%)	89.3	9.4
BSV Kout (%)	60.0	15.6
BSV KGO (%)	24.2	14.9
BSV KTO (%)	53.1	13.5
BSV KOG (%)	17.2	34.7
Variance between BSV KOG and BDV KOT	-0.00139	
BSV KOT (%)	23.3	45.9
BSV KBG (%)	129.5	8.5
Variance between BSV KBG and BDV KBT	1.66	
BSV KBT (%)	129.5	8.3

BSV = between subject variability; cpt = compartment; gbbl = constant rate of release from gall bladder emptying into the central compartment; Ka = first-order rate of absorption; KBG = rate of gall bladder emptying into the central compartment for glyco-OCA during gallbladder contraction; KBT = rate of gall bladder emptying into the central compartment for tauro-OCA during gallbladder contraction; KGB= first-order rate for glyco-OCA accumulation in gallbladder; KGO = biotransformation rate of glyco-OCA into OCA; KOG = biotransformation rate of OCA into glyco-OCA; KOT = biotransformation rate of OCA into tauro-OCA; Kout = rate of fecal elimination of OCA; KTB= first-order rate for tauro-OCA accumulation in gallbladder; KTO = biotransformation rate of tauro-OCA into OCA; MOF = minimum objective function; OCA = obeticholic acid; Prop. = proportional; Vglyco = volume if distribution for glyco-OCA; VOCA = volume if distribution for OCA; Vtauro = volume if distribution for tauro-OCA

Figure 5

2.2.3. Goodness-of-Fit for the Structural Population PK Model of OCA, Glyco-OCA and Tauro-OCA

Linear Scale



IDENT = identity line; IPRED = individual predicted data; LOESS = locally weighted scatter plot smoothing; PRED = population predicted data

Final model

Typical population PK values of OCA, glyco-OCA and tauro-OCA derived with the final model are presented in Appendix 2.4.1. OCA, glyco-OCA and tauro-OCA have volume of distribution of 195, 212 and 200 L respectively. The first order rate of absorption was 0.845 h-1. Residual error was high, with high proportional errors (72.6, 49.6 and 48.7% for OCA, glyco-OCA and tauro-OCA, respectively) but low additional error (0.374, 0.275 and 0.0801 nM for OCA, glyco-OCA and tauro-OCA, respectively).

The effect of hepatic impairment on rates of deconjugation of glyco-OCA and tauro-OCA (KGO and KTO, respectively) was negligible (KGO or KTO are 1% higher than the value in subjects with normal hepatic function). On the other hand, effects of hepatic impairment on VOCA, Vglyco, Vtauro KBG, KBT, KOG and KOT were stronger.

- Subjects with mild, moderate and severe hepatic impairment had lower VOCA (32.5%, 61% and 70%, respectively), Vglyco (30.9%, 77.9% and 81.8%, respectively) and Vtauro (24.5%, 64.5% and 75.2%, respectively) estimates than those in subjects with normal hepatic function.
- Subjects with mild, moderate and severe hepatic impairment had higher KBG (62%, 175% and 394%, respectively) and KBT (70%, 199% and 647%, respectively) estimates than those in subjects with normal hepatic function.

- Subjects with mild, moderate and severe hepatic impairment had lower KOG (5.0%, 52.6% and 72.5%, respectively) estimates than those in subjects with normal hepatic function.
- Subjects with mild, moderate and severe hepatic impairment had higher KOT (5.0%, 61% and 48%, respectively) estimates than those in subjects with normal hepatic function.

Table 7

2.4. Final Population PK Model of OCA, Glyco-OCA and Tauro-OCA

2.4.1. Typical values of Final Population PK Model of OCA, Glyco-OCA and Tauro-OCA

Structural Parameters

Parameter	Estimate
VOCA (L)	195
Vglyco (L)	212
Vtauro (L)	200
Ka (h^{-1})	0.845
Kout (h^{-1})	0.325
KOG (h^{-1})	0.555
KOT (h^{-1})	0.139
KGO (h^{-1})	0.0477
KTO (h^{-1})	0.0199
KGB (h^{-1})	0.0974
KBG (h^{-1})	7.52
KTB (h^{-1})	0.134
KBT (h^{-1})	10.4
gbbl (fraction of tvKBG)	0.00594
Prop Error OCA (%)	72.6
Prop Error Glyco-OCA (%)	49.6
Prop Error Tauro-OCA (%)	48.7
Additional Error OCA (nM)	0.374
Additional Error Glyco-OCA (nM)	0.275
Additional Error Tauro-OCA (nM)	0.0801

Parameter	Estimate	Shrinkage (%)
BSV Ka (%)	74.7	9.8
BSV VOCA (%)	31.3	10.7
Variance between BSV Vglyco and BDV VOCA	0.132	
BSV Vglyco (%)	54.2	8.6
Variance between BSV Vtauro and BDV VOCA	0.142	
Variance between BSV Vtauro and BDV Vglyco	0.276	
BSV Vtauro (%)	62.5	8.1
BSV Kout (%)	41.9	-1.1
BSV KGO (%)	26.3	11.8
BSV KTO (%)	53.9	10.8
BSV KOG (%)	11.3	43.9
Variance between BSV KOG and BDV KOT	-0.00451	
BSV KOT (%)	25.5	40.4
BSV KBG (%)	136.8	12.1
Variance between BSV KBG and BDV KBT	1.95	
BSV KBT (%)	144	11.9

BSV = between subject variability; cpt = compartment; gbbl = constant rate of release from gall bladder emptying into the central compartment; Ka = first-order rate of absorption; KBG = rate of gall bladder emptying into the central compartment for glyco-OCA during gallbladder contraction; KBT = rate of gall bladder emptying into the central compartment for tauro-OCA during gallbladder contraction; KGB= first-order rate for glyco-OCA accumulation in gallbladder; KGO = biotransformation rate of glyco-OCA into OCA; KOG = biotransformation rate of OCA into glyco-OCA; KOT = biotransformation rate of OCA into tauro-OCA; Kout = rate of fecal elimination of OCA; KTB= first-order rate for tauro-OCA accumulation in gallbladder; KTO = biotransformation rate of tauro-OCA into OCA; MOF = minimum objective function; OCA = obeticholic acid; Prop. = proportional; Vglyco = volume if distribution for glyco-OCA; VOCA = volume if distribution for OCA; Vtauro = volume if distribution for tauro-OCA

Table 8

Covariate Effect Parameters

Parameter	Description	Estimate	Value converted Into Multiplicative factor[a]
dVOdHEPIMP2	Effect of mild hepatic impairment on VOCA	-0.393	0.675
dVOdHEPIMP3	Effect of moderate hepatic impairment on VOCA	2.39	0.390
dVOdHEPIMP4	Effect of severe hepatic impairment on VOCA	3.10	0.295
dVGdHEPIMP2	Effect of mild hepatic impairment on Vglyco	-0.370	0.691
dVGdHEPIMP3	Effect of moderate hepatic impairment on Vglyco	4.08	0.221
dVGdHEPIMP4	Effect of severe hepatic impairment on Vglyco	4.60	0.182
dVTdHEPIMP2	Effect of mild hepatic impairment on Vtauro	-0.281	0.755
dVTdHEPIMP3	Effect of moderate hepatic impairment on Vtauro	3.69	0.355
dVTdHEPIMP4	Effect of severe hepatic impairment on Vtauro	4.97	0.248
dKOGdHEPIMP2	Effect of mild hepatic impairment on KOG	-0.0518	0.950
dKOGdHEPIMP3	Effect of moderate hepatic impairment on KOG	-0.746	0.474
dKOGdHEPIMP4	Effect of severe hepatic impairment on KOG	-1.29	0.275
dKOTdHEPIMP2	Effect of mild hepatic impairment on KOT	0.0507	1.05
dKOTdHEPIMP3	Effect of moderate hepatic impairment on KOT	0.475	1.61
dKOTdHEPIMP4	Effect of severe hepatic impairment on KOT	0.392	1.48
dKGOdHEPIMP2	Effect of mild hepatic impairment on KGO	0.0100	1.01
dKGOdHEPIMP3	Effect of moderate hepatic impairment on KGO	0.0103	1.01
dKGOdHEPIMP4	Effect of severe hepatic impairment on KGO	0.0101	1.01
dKTOdHEPIMP2	Effect of mild hepatic impairment on KTO	0.0101	1.01
dKTOdHEPIMP3	Effect of moderate hepatic impairment on KTO	0.0101	1.01
dKTOdHEPIMP4	Effect of severe hepatic impairment on KTO	0.0100	1.01
dKBGdHEPIMP2	Effect of mild hepatic impairment on KBG	0.480	1.62
dKBGdHEPIMP3	Effect of moderate hepatic impairment on KBG	1.01	2.75
dKBGdHEPIMP4	Effect of severe hepatic impairment on KBG	1.60	4.94
dKBTdHEPIMP2	Effect of mild hepatic impairment on KBT	0.528	1.70
dKBTdHEPIMP3	Effect of moderate hepatic impairment on KBT	1.10	2.99
dKBTdHEPIMP4	Effect of severe hepatic impairment on KBT	2.01	7.47
dVOdWT	Effect of baseline body weight on VOCA	1.01	NA
dVGdWT	Effect of baseline body weight on Vglyco	1.13	
dVTdWT	Effect of baseline body weight on Vtauro	1.07	
dKBGdWT	Effect of baseline body weight on KBG	0.764	
dKBTdWT	Effect of baseline body weight on KBT	0.679	

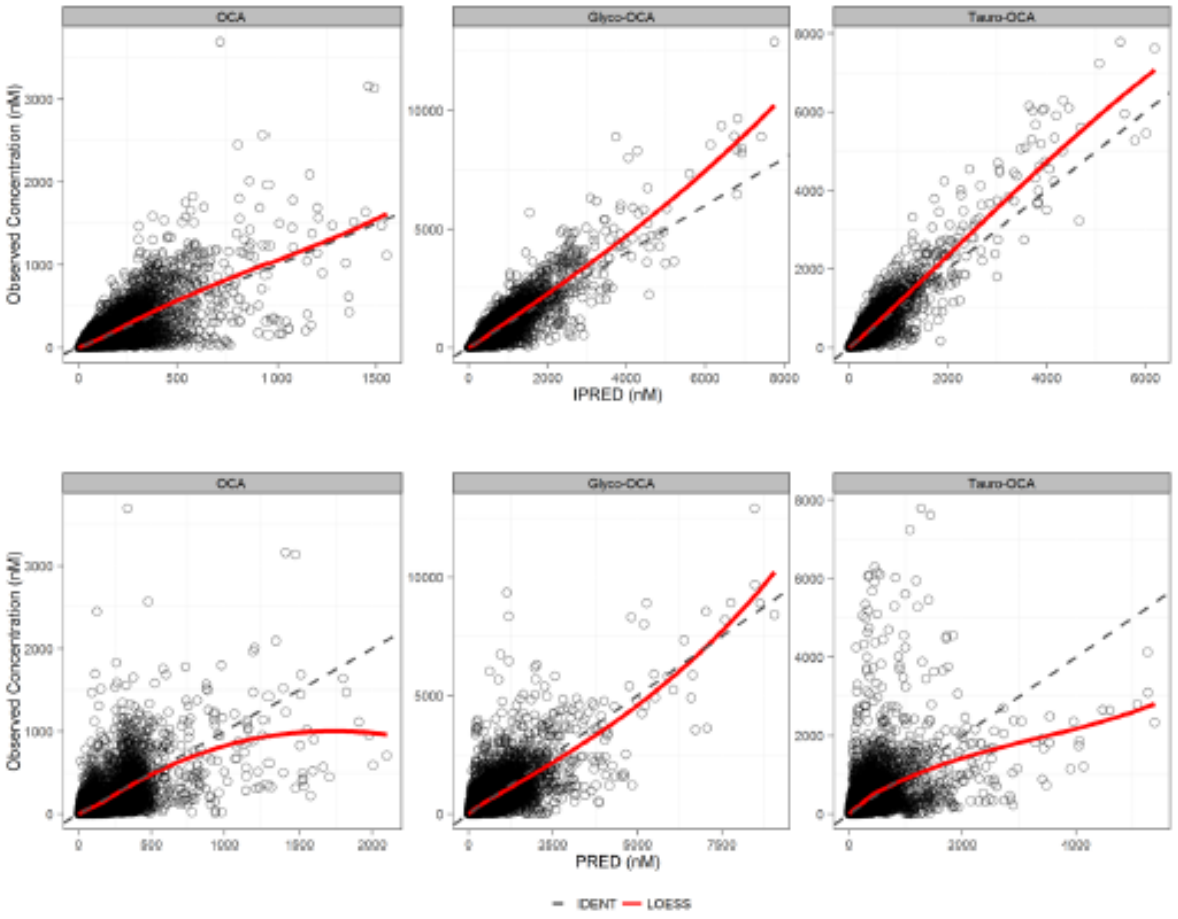
*: Multiplicative factor were calculated based on estimated values and model code (Refer to Section 2.5.3); for example for dVOdHEPIMP2, the multiplicative factor equals exp(dVOdHEPIMP2) and for dVOdHEPIMP3, the multiplicative factor equals exp(dVOdHEPIMP2*dVOdHEPIMP3)

KBG = rate of gall bladder emptying into the central compartment for glyco-OCA during gallbladder contraction; KBT = rate of gall bladder emptying into the central compartment for tauro-OCA during gallbladder contraction; KGO = biotransformation rate of glyco-OCA into OCA; KOG = biotransformation rate of OCA into glyco-OCA; KOT = biotransformation rate of OCA into tauro-OCA; NA = not applicable; Vglyco = volume if distribution for glyco-OCA; VOCA = volume if distribution for OCA; Vtauro = volume if distribution for tauro-OCA

Figure 6

2.4.2. Goodness-of-Fit for the Final Population PK Model of OCA, Glyco-OCA and Tauro-OCA

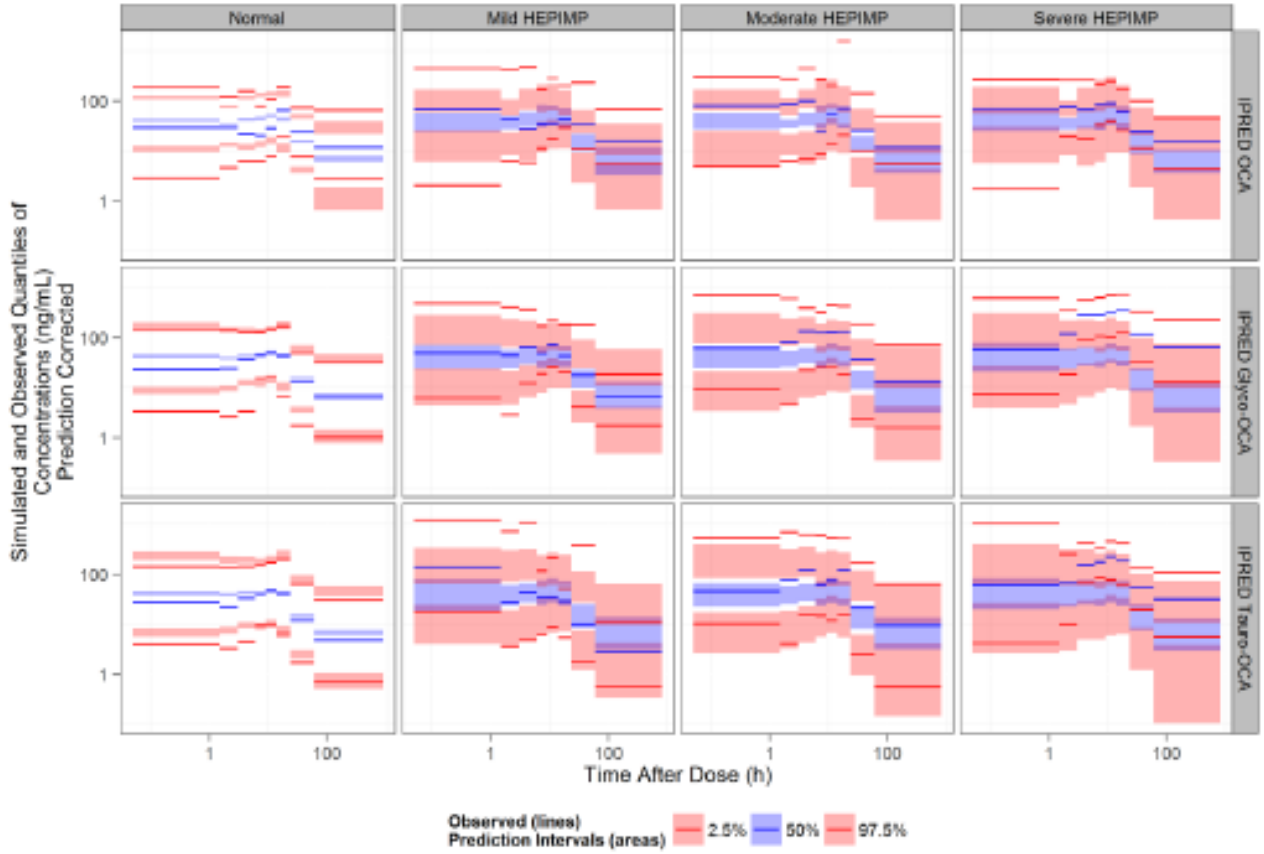
Linear Scale



IDENT = identity line; IPRED = individual predicted data; LOESS = locally weighted scatter plot smoothing; PRED = population predicted data

Figure 7

2.4.3. Prediction-Corrected VPC for the Final Population PK Model of OCA, Glyco-OCA and Tauro-OCA



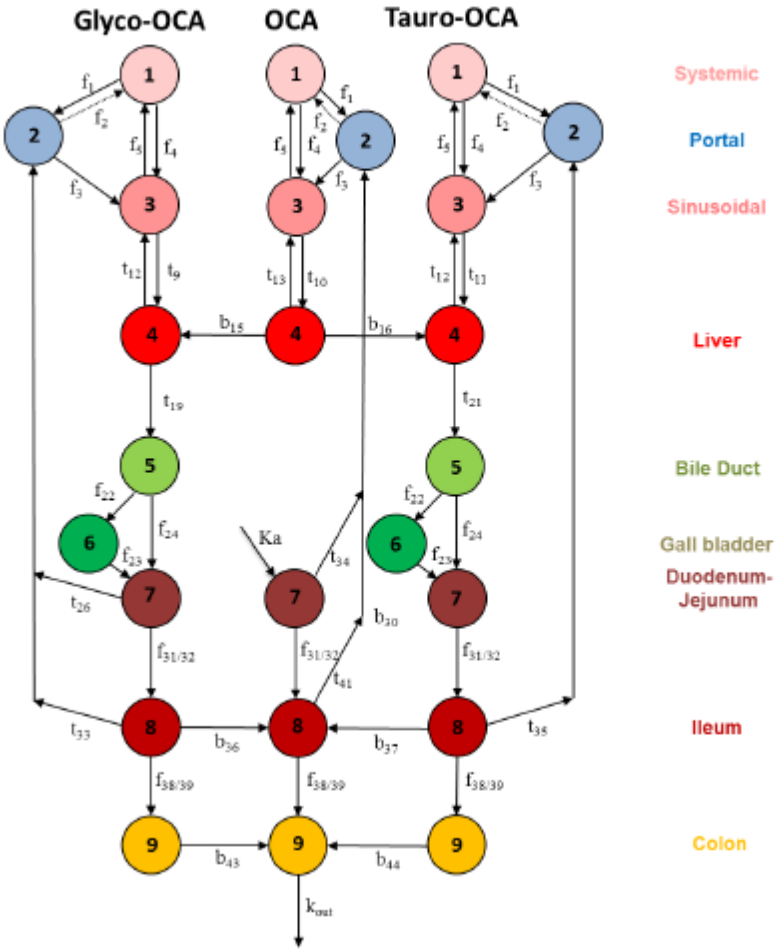
The solid blue line represents the median of the observed data. The solid red lines represent the upper and lower 2.5th and 97.5th percentiles of the observed data. The ribbons represent the upper and lower limits of the 95% percentile intervals (PI) of the median (blue ribbons) and 5th and 95th percentiles (pink ribbons) of the simulated IPRED.

HEPIMP = hepatic impairment; IPRED = individual predicted data

Physiological PK model in subjects with NASH fibrosis

Figure 8

Figure 18. Schematic Representation of Physiologic PK Model for Unconjugated OCA, Glyco-OCA and Tauro-OCA



The final model was therefore RUN007cov47 with allometric scaling with weight, fibrosis score on liver uptake changing after 10 months of treatment duration in F1/F2 and F3 subjects.

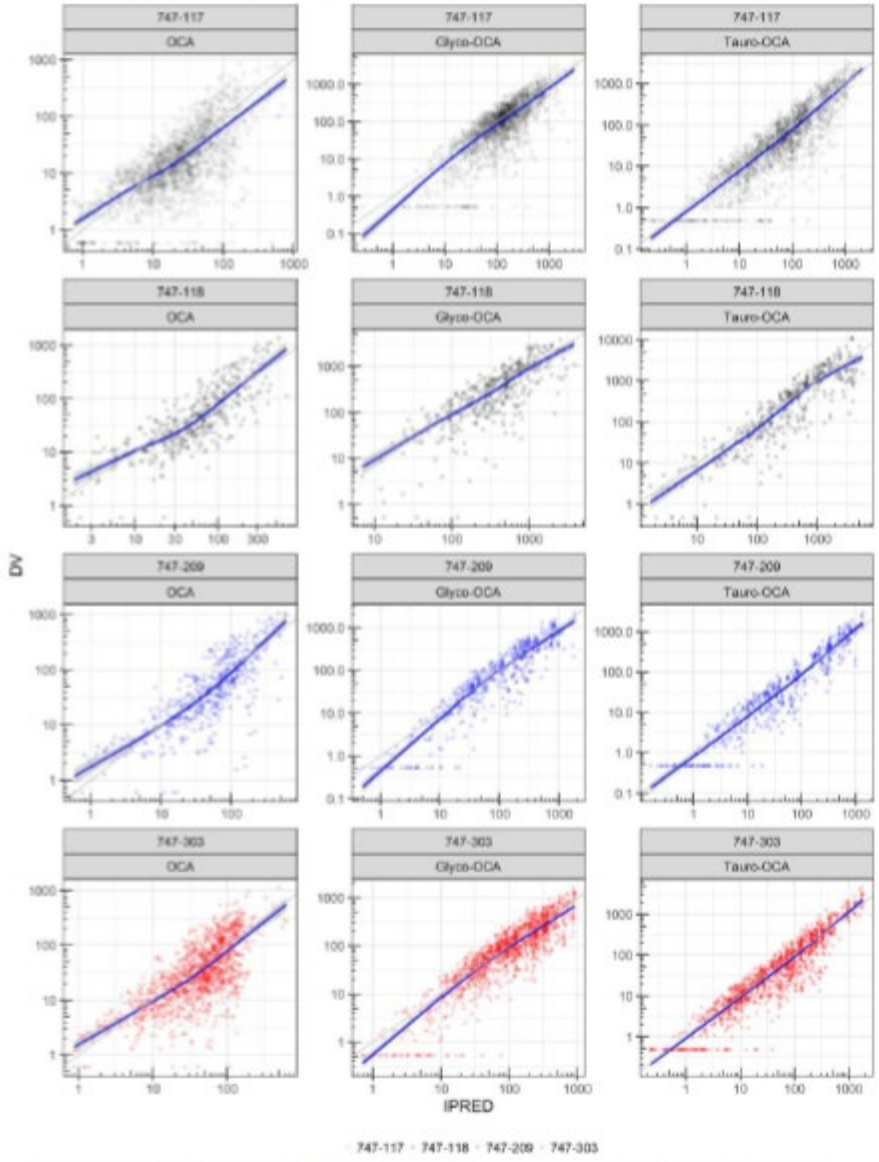
The estimated rate of tauro-conjugation in NASH subjects (112 L/h) was lower than estimated in healthy subjects (238 L/h). The glycine/taurine ratio of conjugation rates was also lower in NASH (3.07 L/h) relative to that derived in healthy subjects (3.91 L/h).

In NASH patients with fibrosis stage F4, the estimated conjugation rate with taurine was 5% higher than the one estimated in NASH patients with lower fibrosis stage. More precisely, without considering the hepatocyte loss effect, the change in the rate of conjugation with taurine was 18% higher than the reference rate in healthy subjects. However, after adding the effect of hepatocyte loss, the rate rate of conjugation with taurine is 1.18 * 0.891 = 1.05 time the reference rate in healthy subjects.

Residual variability (RV) in NASH subjects was modeled using a proportional error model for plasma and liver concentrations. The residual error in NASH subjects for plasma unconjugated OCA, glyco-OCA and tauro-OCA were 85.3%, 55.1%, and 57.9%, respectively. The residual error in NASH subjects for liver unconjugated OCA, glyco-OCA and tauro-OCA were 32.4%, 65.8%, and 62.5%, respectively.

Figure 9

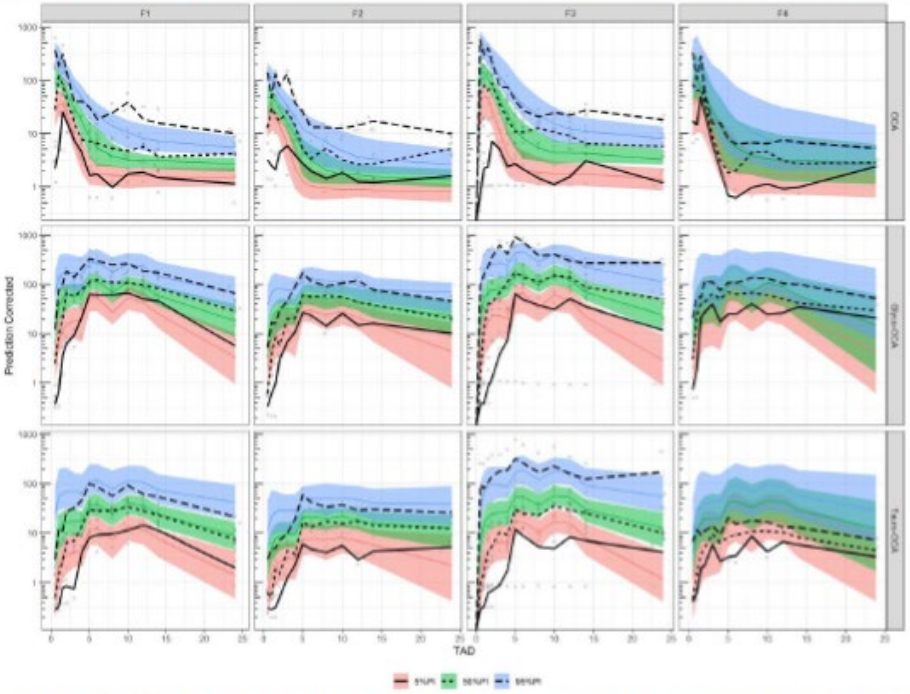
Figure 31. Goodness-of-Fit – Unconjugated OCA, Glyco-OCA and Tauro-OCA in NASH Subjects (RUN007cov47)



DV = observed; IPRED = individual prediction; LOESS = locally weighted scatterplot smoothing.
Note = blue line represents the LOESS

Figure 10

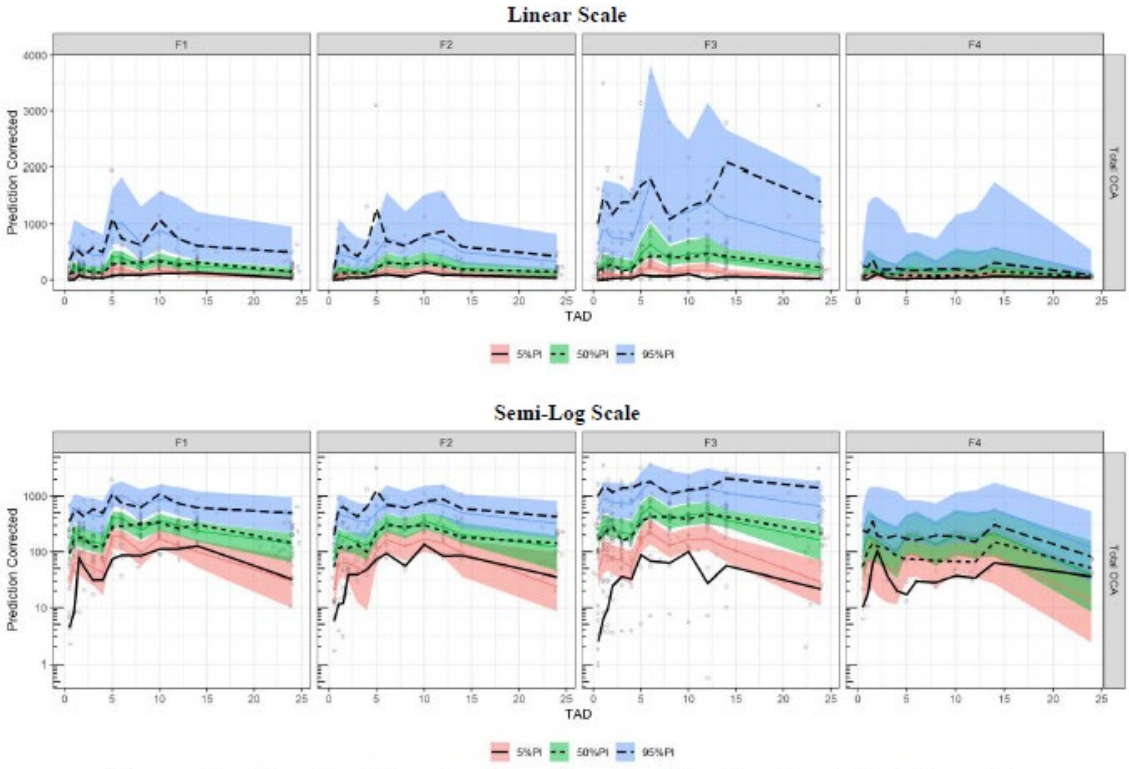
17.11 Physiologic PK Model of OCA – Model Including Fibrosis Stage on Uptake Parameter by Period (Model RUN007cov47) – Goodness-of-Fit – NASH Patients – Internal Visual Predictive Check – Study 747-117 – All visits - Semi-Log Scale



PI = percentile/confidence interval; lines = observed percentiles; areas = 90% confidence interval of simulated percentiles

Figure 11

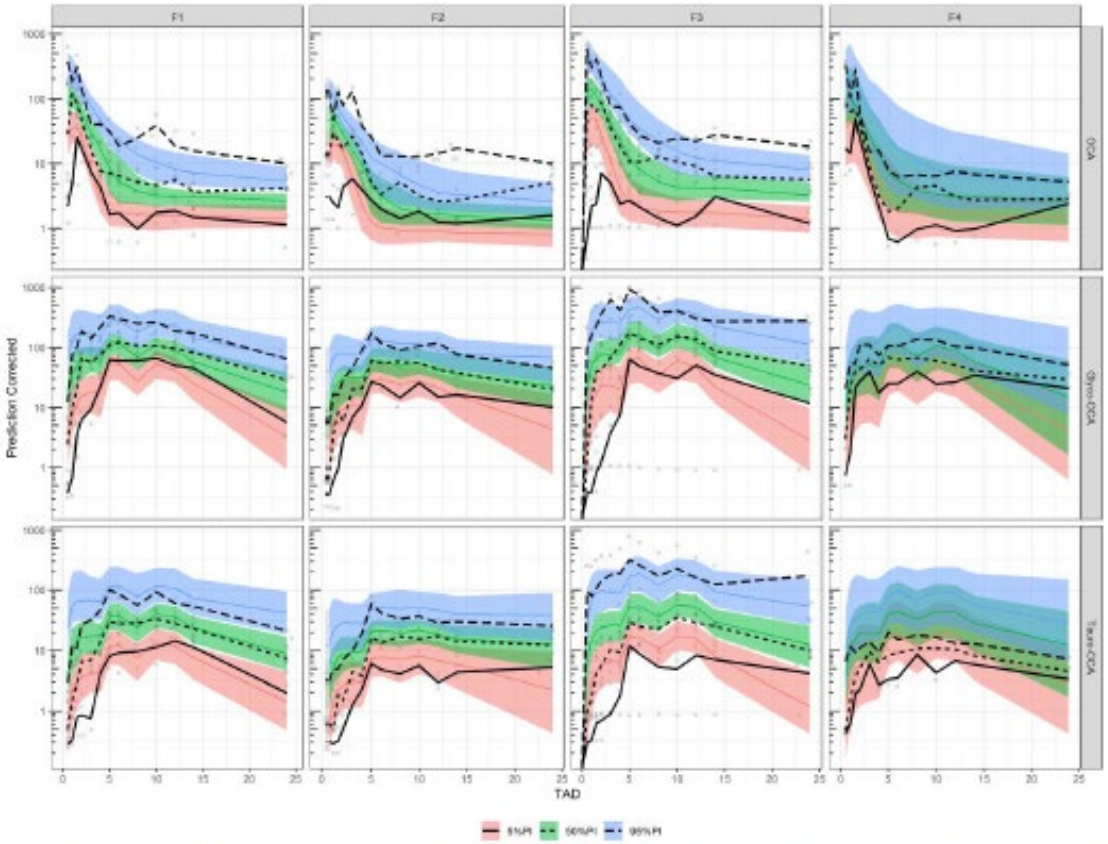
17.12 Physiologic PK Model of OCA – Model Including Fibrosis Stage on Uptake Parameter by Period (Model RUN007cov47) – Goodness-of-Fit – NASH Patients – Internal Visual Predictive Check – Study 747-117 – Total OCA – All visits



PI = percentile/confidence interval; lines = observed percentiles; areas = 90% confidence interval of simulated percentiles

Figure 12

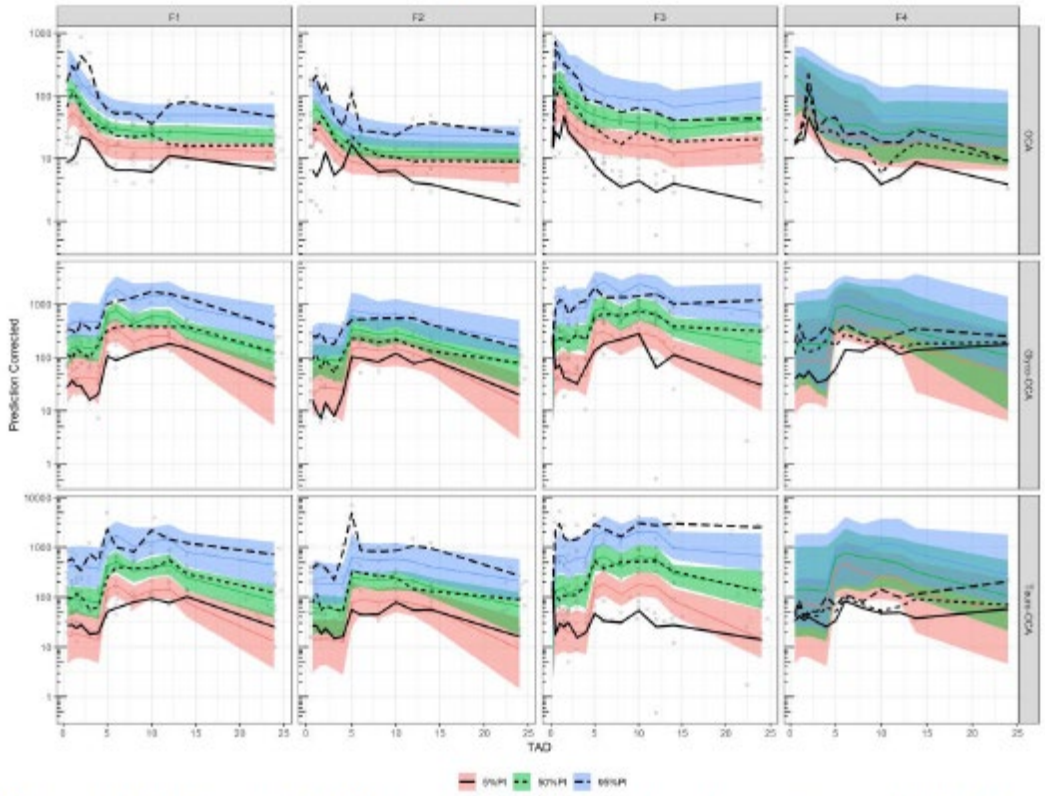
Figure 34. Visual Predictive Check – Internal – Unconjugated OCA, Glyco-OCA and Tauro-OCA in NASH Subjects – Study 747-117 – Day 1 (RUN007cov47)



PI = percentile/confidence interval; TAD = time after dose (h); lines = observed percentiles; areas = 90% confidence interval of simulated percentiles

Figure 13

Figure 35. Visual Predictive Check – Internal – Unconjugated OCA, Glyco-OCA and Tauro-OCA in NASH Subjects – Study 747-117 – Day 85 (RUN007cov47)



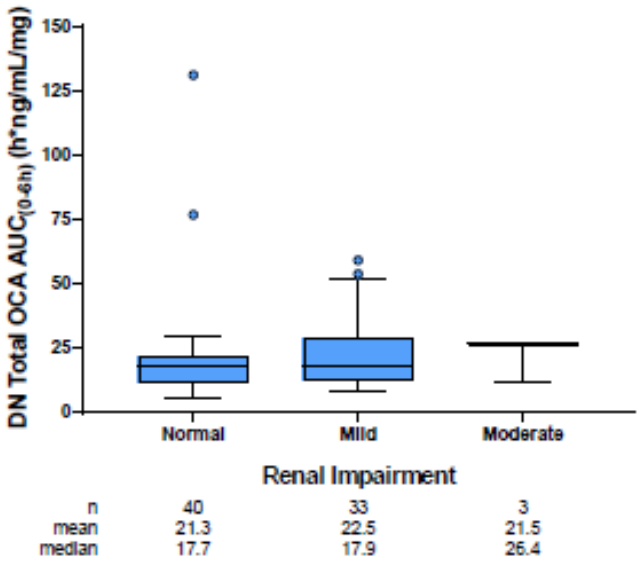
PI = percentile/confidence interval; TAD = time after dose (h); lines = observed percentiles; areas = 90% confidence interval of simulated percentiles

- **Impaired renal function**

OCA is only minimally eliminated by the kidneys. The effect of renal impairment on the PK was investigated and the results showed that such condition increases the exposure to OCA and its conjugates by about +50% with consistency across renal impairment categories. No meaningful differences in plasma exposure of total OCA were observed in subjects with liver fibrosis due to NASH who had mild or moderate renal impairment relative to subjects with normal renal function.

Figure 14

Figure 12: Effect of Renal Function on Total OCA Dose-Normalized Exposure Following a Single Dose of OCA in NASH Subjects (Studies 747-117, 747-209, and 747-303)

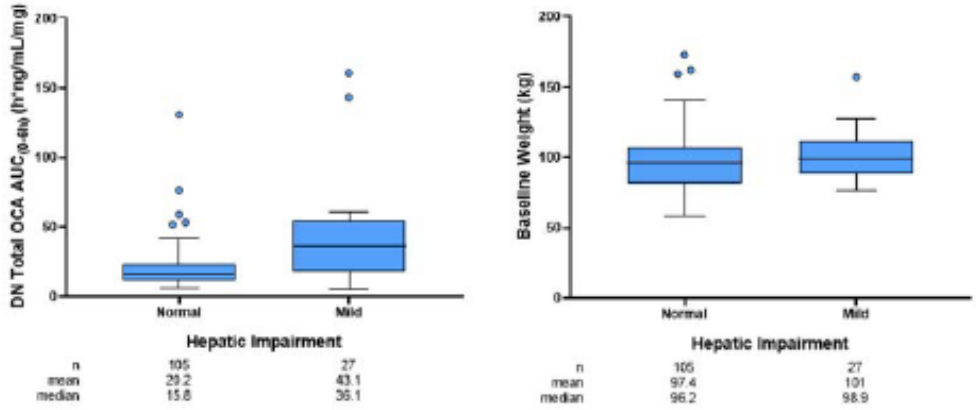


AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; DN = dose-normalized; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, Cross-Study OCA Pharmacokinetic Characterization for NASH Fibrosis, Appendix Figure 16.1.4

- **Impaired hepatic function**

Figure 15

Figure 8: Effect of Hepatic Impairment on Total OCA Dose-Normalized Exposure Following a Single Dose of OCA in NASH Subjects With and Without Cirrhosis (Studies 747-117, 747-118, 747-209, and 747-303)

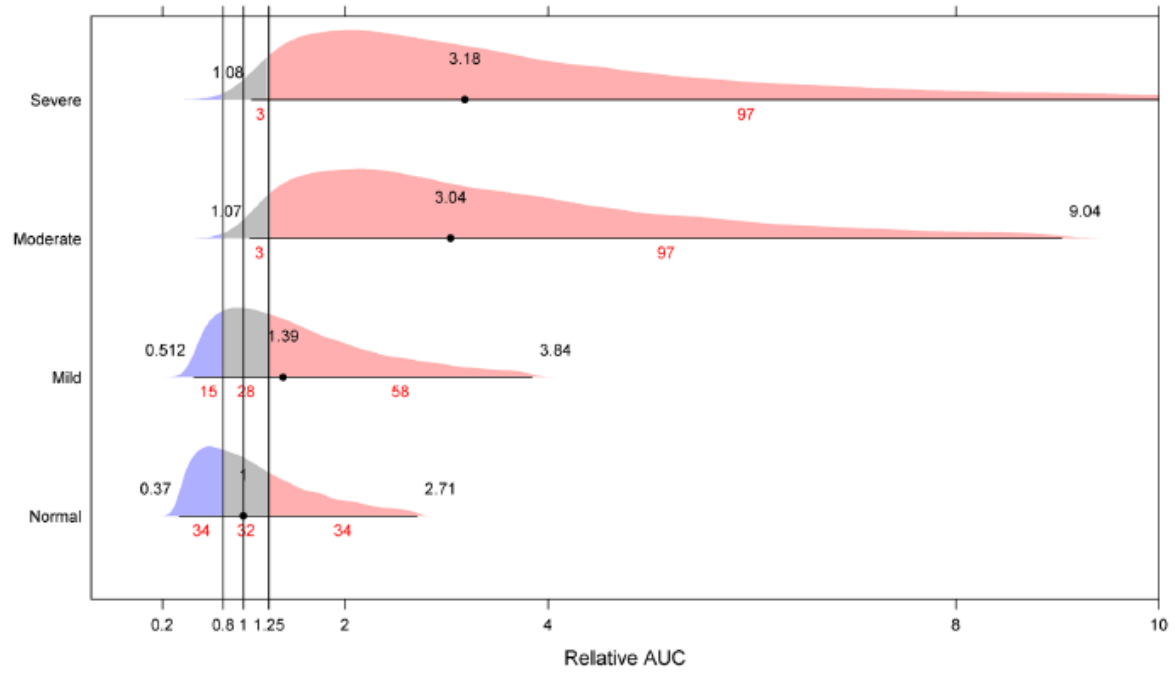


AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; DN = dose-normalized; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, Cross-Study OCA Pharmacokinetic Characterization for NASH Fibrosis, Appendix Figure 16.1.5 (Total OCA Dose) and Appendix Ad hoc Figure 1.1.5

A forest plot was generated to represent the effect of hepatic impairment on the exposure AUC (Figure below) The distribution of hepatic impairment was based on simulations of rich profiles under steady-state conditions (after 22 days) which take into account the variability of each parameter and then divided by the median of the exposure in healthy volunteers with median body weight.

Figure 16

Figure 8.4 Forest Plot: Relationship Between Degree of Liver Impairment and Exposure Metric (AUC of OCA, Glyco-OCA and Tauro-OCA)



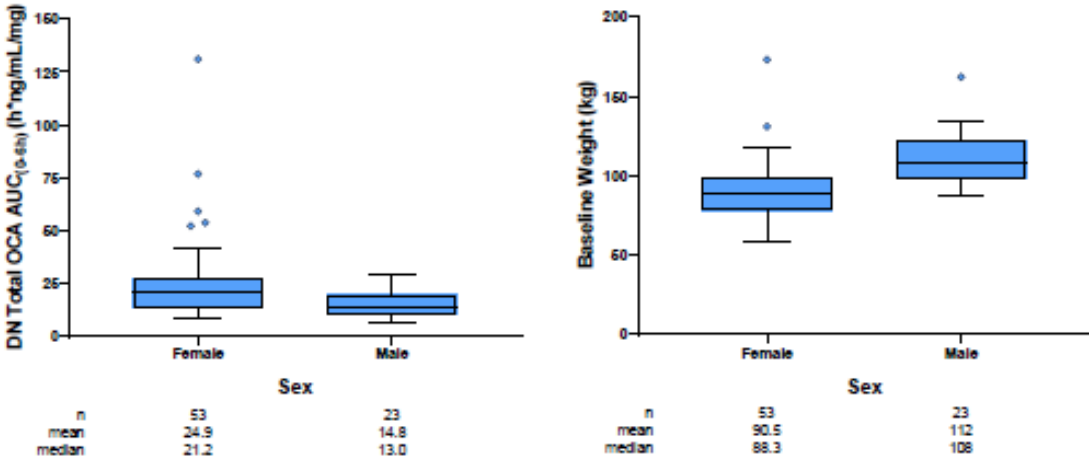
Note: The above figure assumed after daily dose of 10 mg of OCA at 8 AM and meals taken at 8AM, 12PM and 6PM with a dosing at 8AM; Black numbers represent the 5th, 50th and 95th percentiles of the relative AUC for each category; 95th percentile of the relative AUC in subjects with severe hepatic impairment was 10.6; red numbers represent the proportion below 0.8, within 0.8 and 1.25 and above 1.25 of the reference AUC value is 4174 mg×h/mL.
AUC= area under the curve

For a typical subject with severe, moderate, and mild hepatic impairment the median predicted 0-24 h AUC is expected to be 218%, 204% and 39% higher than those observed in a typical subject with normal liver function, respectively.

- **Gender**

Figure 17

Figure 10: Effect of Sex on Total OCA Dose-Normalized Exposure Following a Single Dose of OCA in NASH Subjects (Studies 747-117, 747-209, and 747-303)

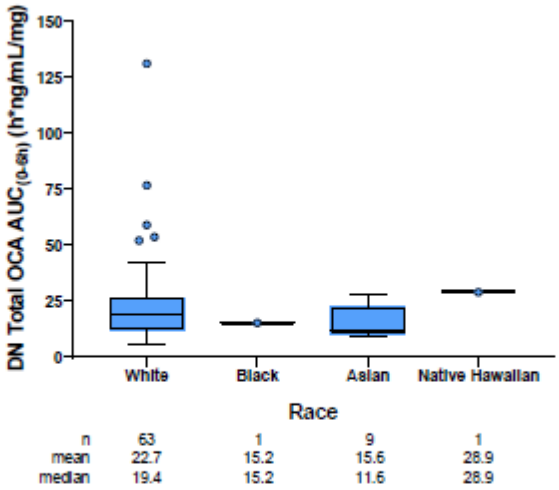


AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; DN = dose-normalized; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, Cross-Study OCA Pharmacokinetic Characterization for NASH Fibrosis, Appendix Figure 16.1.1 (Total OCA Dose) and Appendix Ad hoc Figure 1.1.1 (Baseline Weight)

- **Race**

Figure 18

Figure 11: Effect of Race on Total OCA Dose-Normalized Exposure Following a Single Dose of OCA in NASH Subjects (Studies 747-117, 747-209, and 747-303)

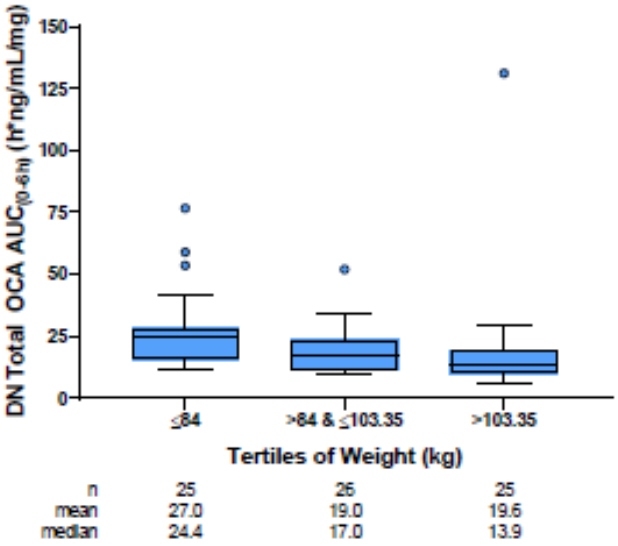


AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; DN = dose-normalized; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, Cross-Study OCA Pharmacokinetic Characterization for NASH Fibrosis, Appendix Figure 16.1.2

- **Weight**

Figure 19

Figure 5: Effect of Body Weight on Total OCA Dose-Normalized Plasma Exposure Following a Single Dose of OCA in NASH Subjects (Studies 747-117, 747-209, and 747-303; NASH Fibrosis Stages 2 and 3)

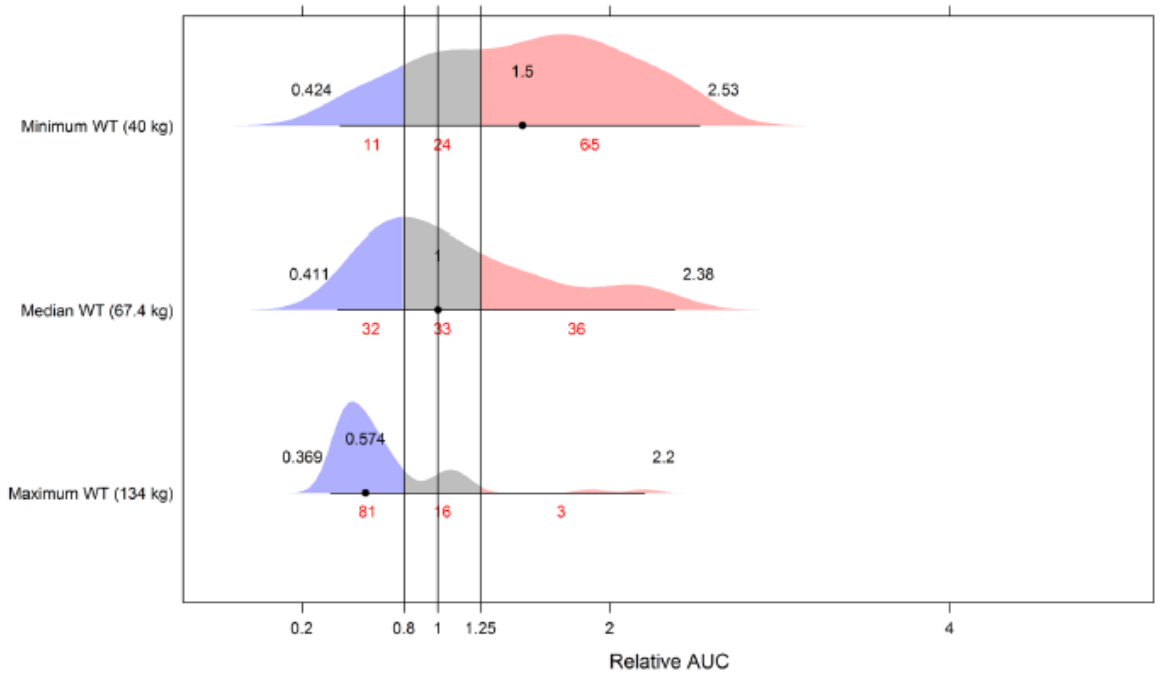


AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; DN = dose-normalized; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.

Source: Module 5.3.5.3, PAR, Cross-Study OCA Pharmacokinetic Characterization for NASH Fibrosis, Appendix Figure 15.3

Figure 20

Figure 8.5 Forest Plot: Relationship Between Body Weight and Exposure Metric (AUC of OCA, Glyco-OCA and Tauro-OCA)



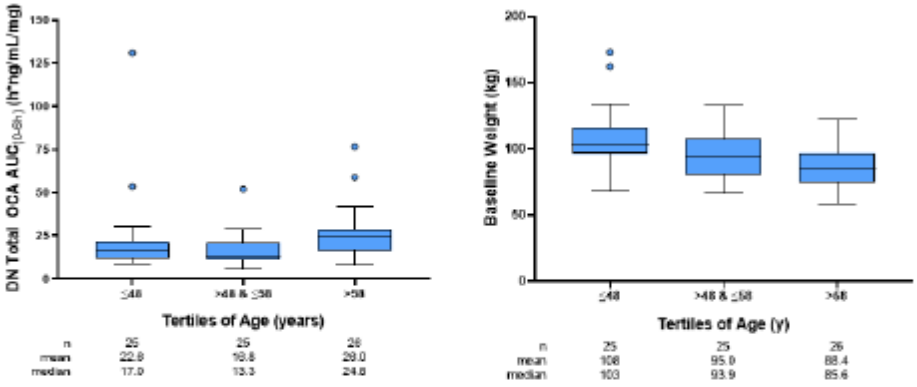
Note: The above figure assumed after daily dose of 10 mg of OCA at 8 AM and meals taken at 8AM, 12PM and 6PM with a dosing at 8AM; Black numbers represent the 5th, 50th and 95th percentiles of the relative AUC for each category, red numbers represent the proportion below 0.8, within 0.8 and 1.25 and above 1.25 of the reference AUC value in 4332 mg×h/mL.

The median AUC in a typical 40-kg subject is expected to be 50% higher than that of a typical 67.4-kg subject. Conversely, the median AUC in a typical 134-kg subject is expected to be 42.6% lower than that in a typical 67.4-kg subject.

- **Elderly**

Figure 21

Figure 9: Effect of Age on Total OCA Dose-Normalized Exposure Following a Single Dose of OCA in NASH Subjects (Studies 747-117, 747-209, and 747-303)



AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; DN = dose-normalized; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, Cross-Study OCA Pharmacokinetic Characterization for NASH Fibrosis, Appendix Figure 15.1 (Total OCA Dose) and Appendix Ad hoc Figure 1.1.6 (Baseline Weight)

Figure 22

Table 29: Age Distribution of Subjects with NASH F2/F3 Fibrosis (PK Population)

Statistic	<65 years	≥65 years & <75 years	≥75 years
Number of subjects	63	20	0
Percentage of subjects	75.9%	24.1%	0.0%

- **Children**

N/A

3.3.2. Pharmacodynamics

- **Primary pharmacology**

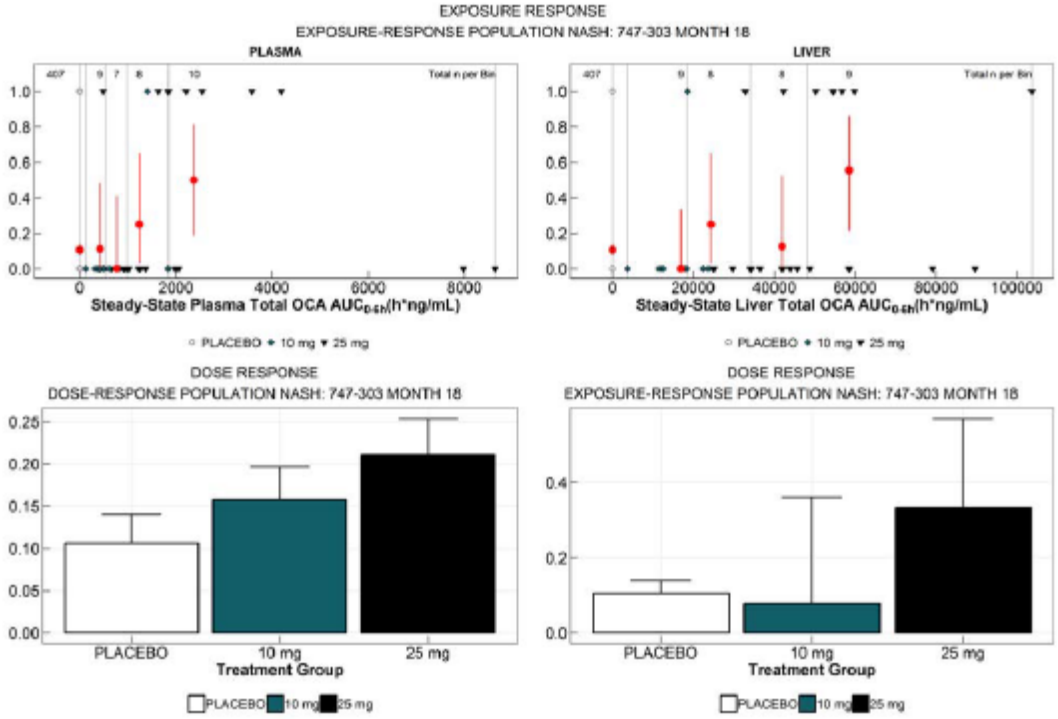
Exposure-efficacy relationship

Fibrosis Improvement by ≥1 Stage with No Worsening of NASH

Figure 23

Figure 19: OCA Dose- and Exposure-Response Relationships for Improvement of Fibrosis by ≥1 Stage with No Worsening of NASH - Study 747-303

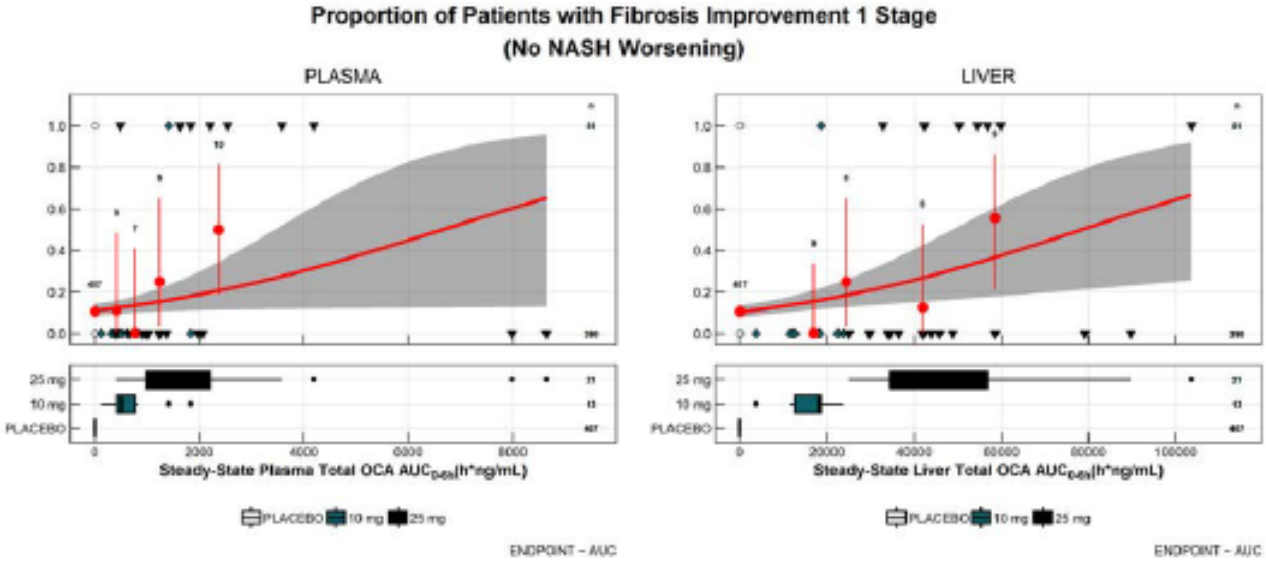
Proportion of Patients with Fibrosis Improvement 1 Stage (No NASH Worsening)



AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Dose-Response population: Placebo (N = 407); OCA 10 mg (N = 407); OCA 25 mg (N = 404);
Exposure-Response population: Placebo (N = 407); OCA 10 mg (N = 13); OCA 25 mg (N = 21).
Source: Module 5.3.5.3, PAR, OCA Exposure Response and Dose Response for NASH Fibrosis, Figure 2

Figure 24

Figure 20: Logistic Regression Analysis of Fibrosis Improvement ≥1 Stage with No Worsening of NASH Relative to Plasma or Post Hoc Liver Exposure

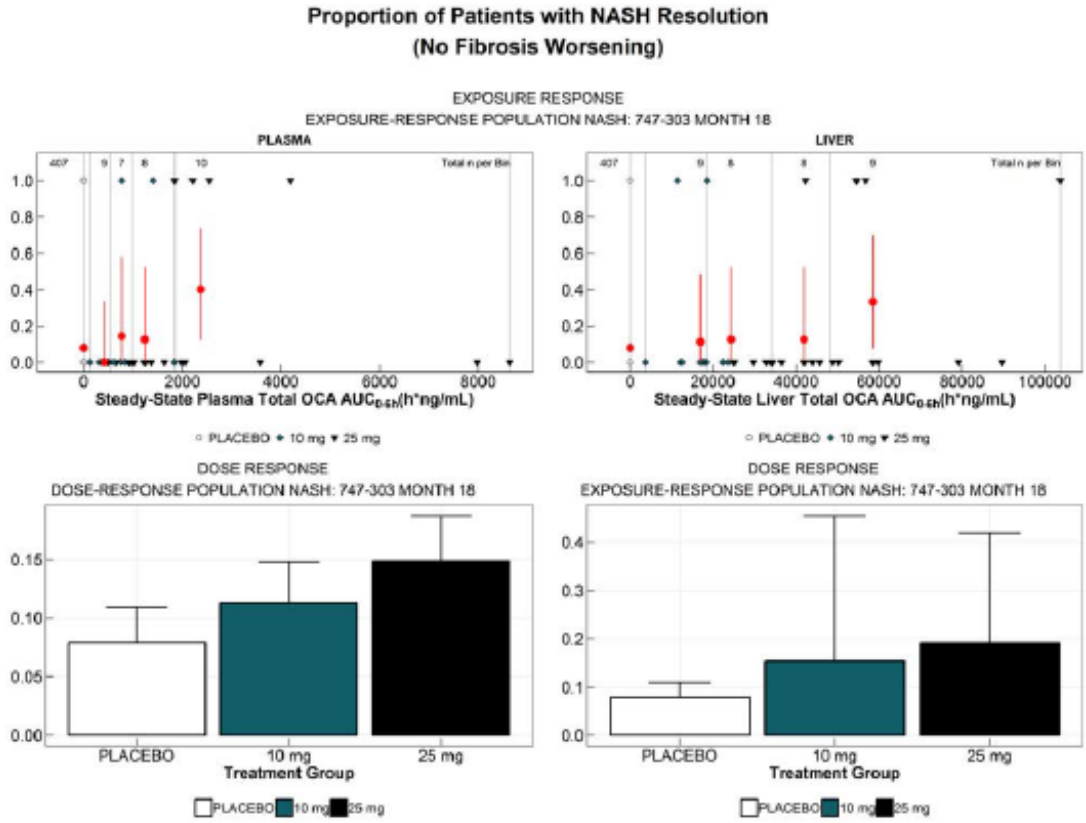


AUC = area under the plasma concentration-time curve; AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 4

Resolution of NASH with No Worsening of Fibrosis

Figure 25

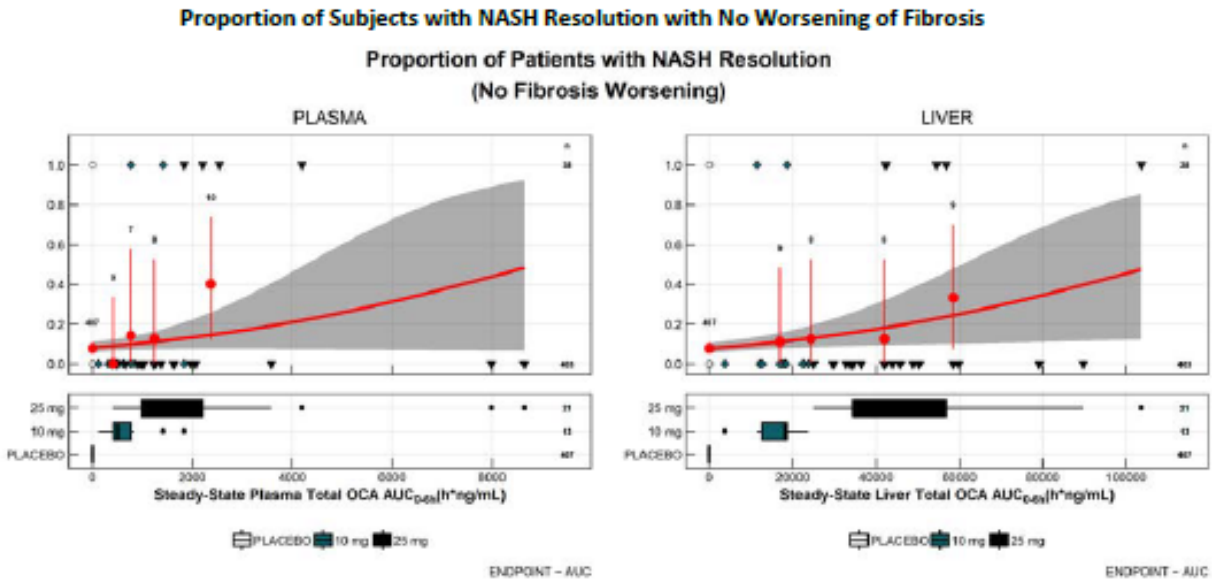
Figure 21: OCA Dose- and Exposure-Response Relationship for NASH Resolution with No Worsening of Fibrosis - Study 747-303



AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Dose-Response Population: Placebo (N = 407); OCA 10 mg (N = 407); OCA 25 mg (N = 404);
Exposure-Response Population: Placebo (N = 407); OCA 10 mg (N = 13); OCA 25 mg (N = 21).
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 5

Figure 26

Figure 22: Logistic Regression Analysis of NASH Resolution with No Worsening of Fibrosis Relative to Plasma or Liver Exposure

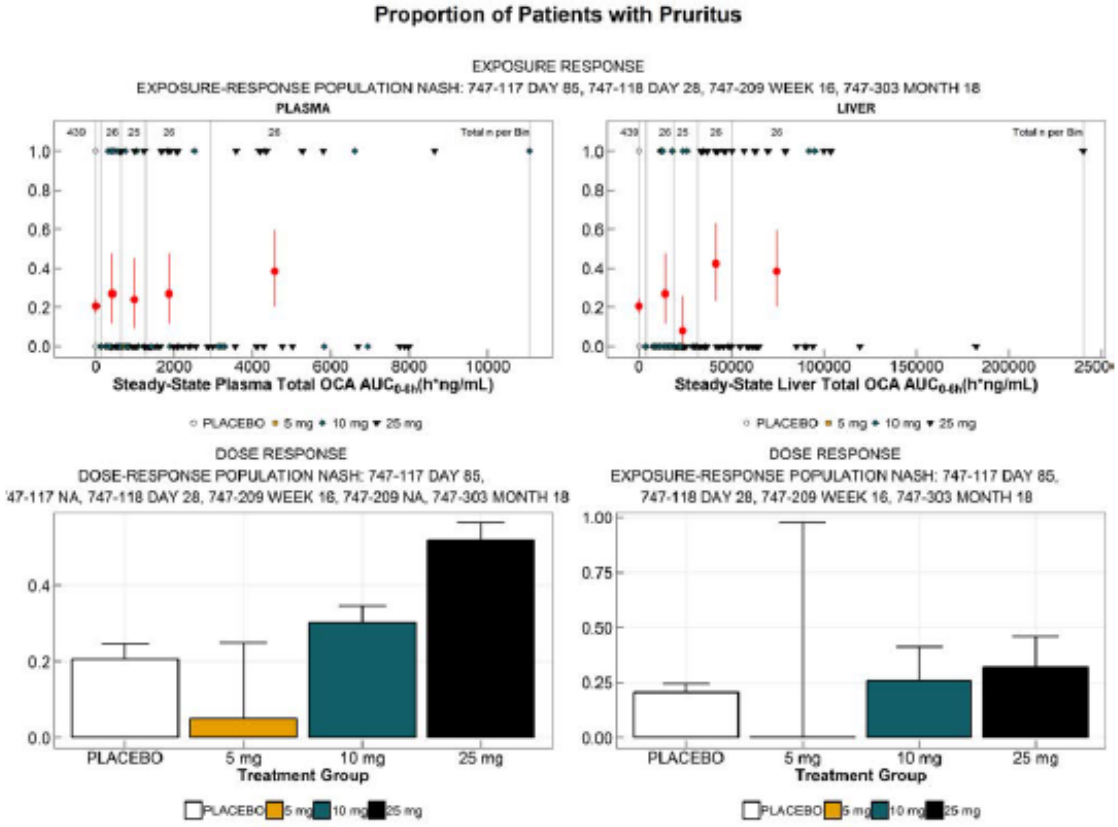


AUC = area under the concentration-time curve; AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 7

Tolerability (Pruritus)

Figure 27

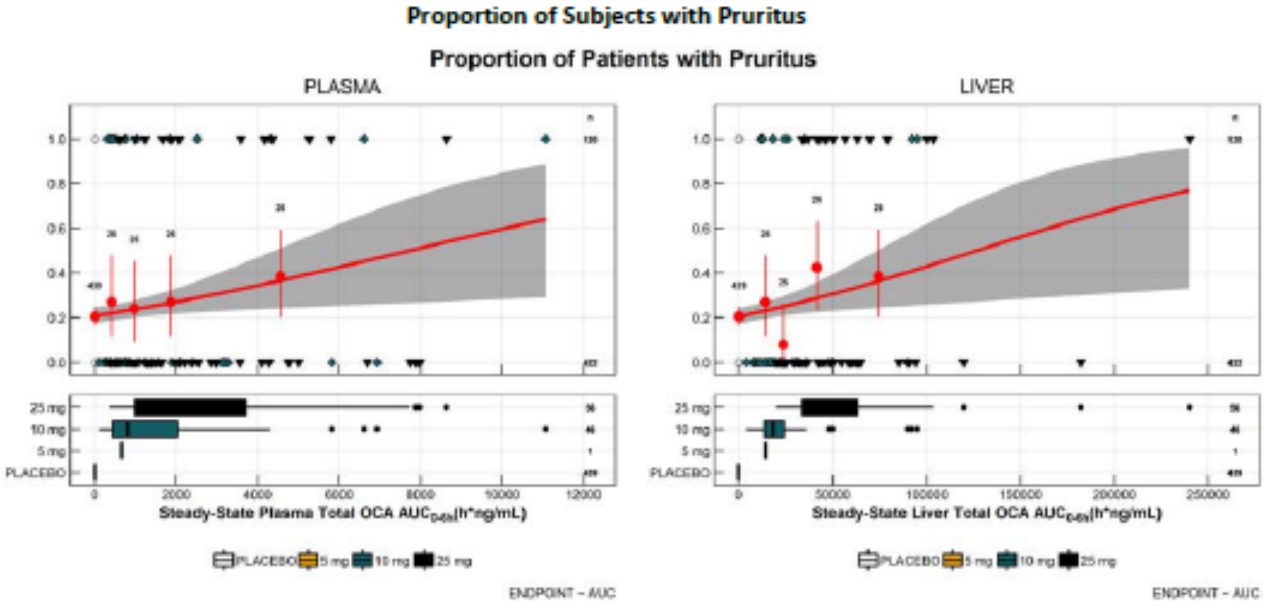
Figure 23: OCA Dose- and Post Hoc Exposure-Response Relationship for the Proportion of Subjects with Pruritus in Subjects with NASH Fibrosis Stages 1, 2, and 3 - Studies 747-117, 747-118, 747-209, and 747-303



AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 62

Figure 28

Figure 24: Logistic Regression Analysis of Pruritus Relative to Plasma or Liver Exposure

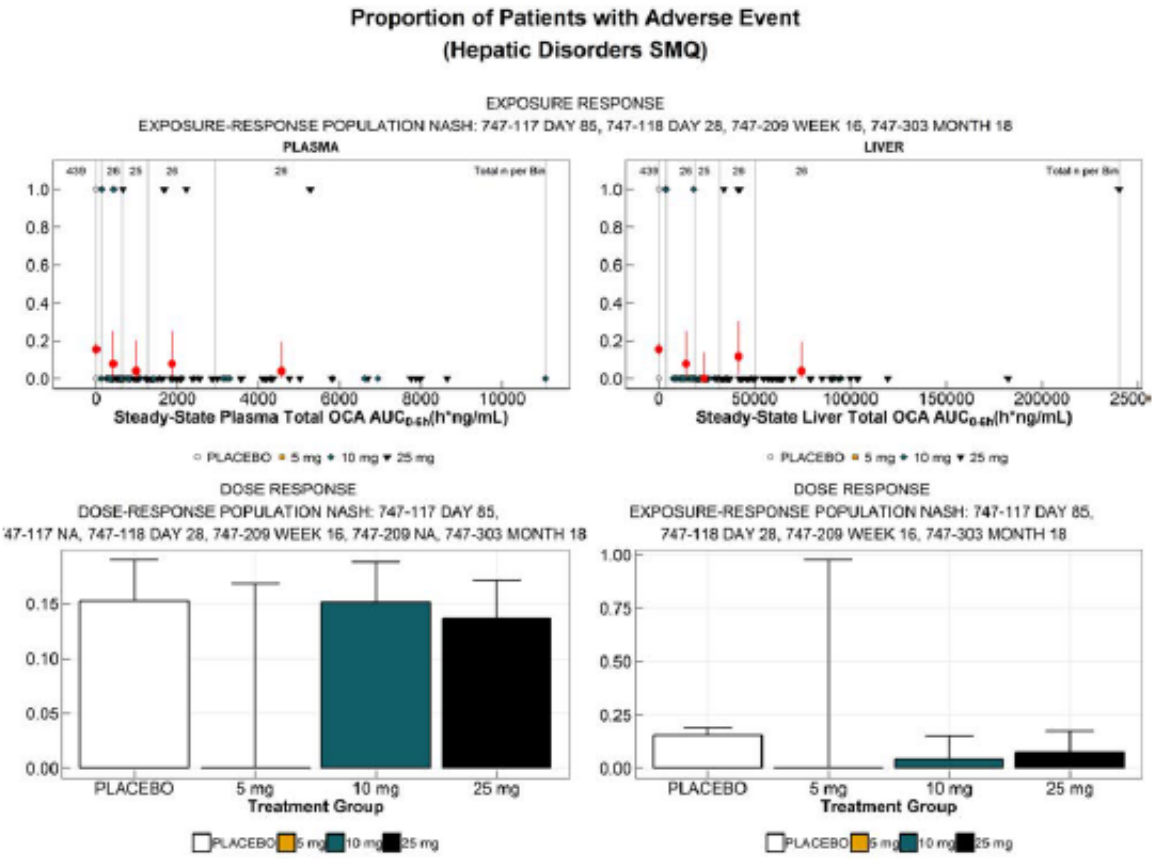


AUC = area under the concentration-time curve; $AUC_{0\text{-}6h}$ = area under the concentration-time curve from time 0 to 6 hours postadministration; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 64

Exposure-safety

Figure 29

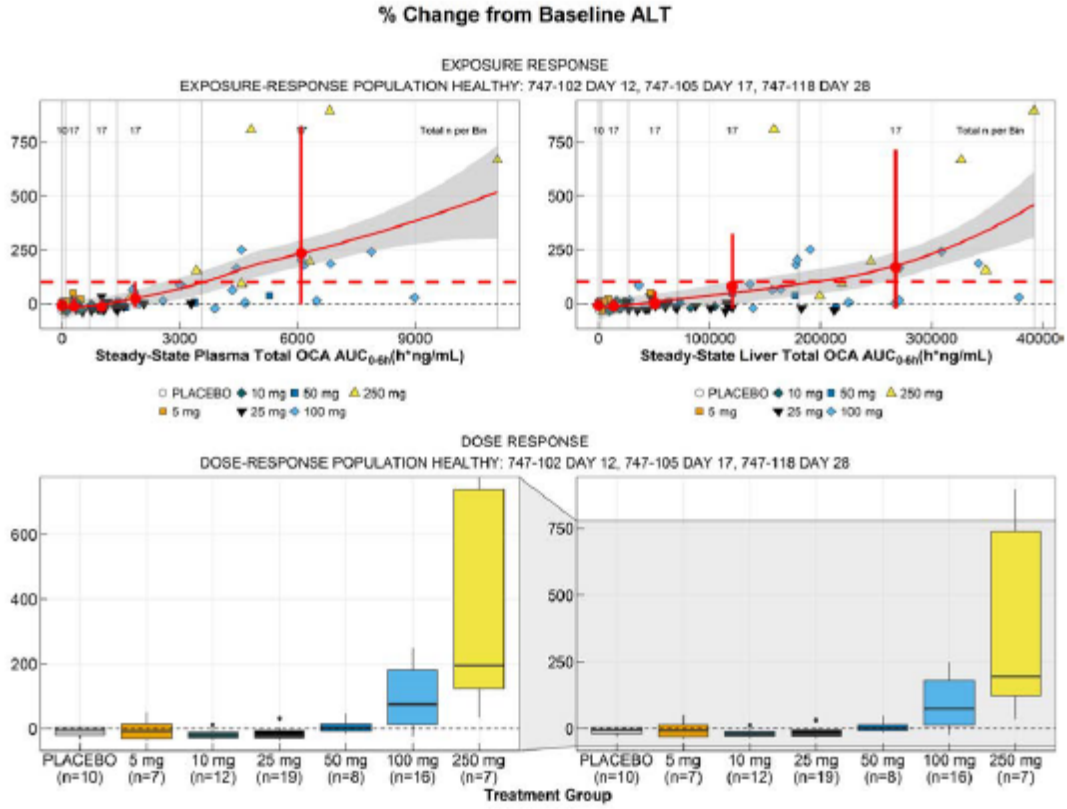
Figure 25: Proportion of Subjects with Hepatobiliary Disorder AEs in NASH Subjects with Fibrosis Stages 1 to 3 - Studies 747-117, 747-118, 747-209, and 747-303



AE = adverse event; $AUC_{0\text{-}6h}$ = area under the concentration-time curve from time 0 to 6 hours postadministration; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report; SMQ = Standardized MedDRA Query.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 65

Figure 30

Figure 26: Percent Change in ALT at End of Study Relative to Baseline for Placebo and OCA 5, 10, 25, 50, 100, and 250 mg in Healthy Subjects - Studies 747-102, 747-105, and 747-118



ALT = alanine aminotransferase; AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 67

- **Secondary pharmacology**

Table 9

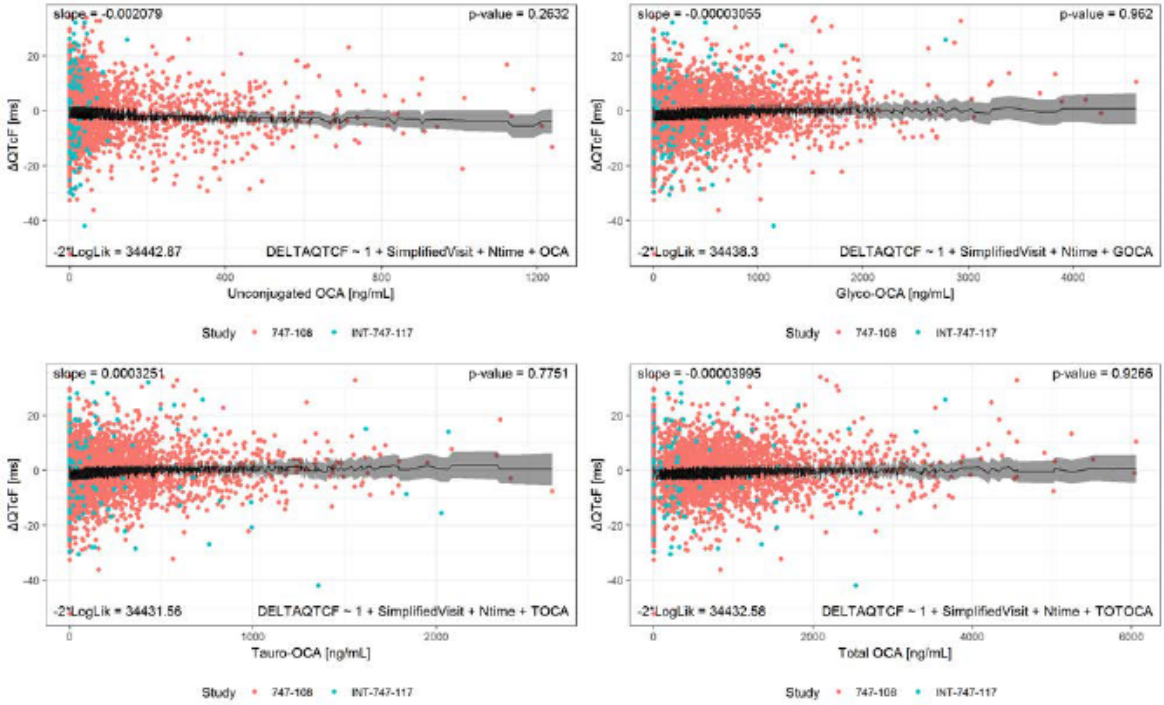
Table 11: Largest ΔΔQTcF Following Treatment with OCA 100 mg/day (Day 5): QT Evaluable Population (N = 125)

Timepoint (hours)	LS Mean (SE) ΔQTcF (msec)		Difference in LSM (SE) (ΔΔQTcF)	Adjusted Upper 95% CL
	Placebo (N = 63)	OCA (100 mg) (N = 62)		
3	-2.6 (1.17)	0.6 (1.18)	3.2[a] (1.66)	6.5

ΔQTcF = change in QTcF from baseline; CL = confidence limit; CSR = clinical study report; LSM = least squares mean; OCA = obeticholic acid; QTcF = QT interval corrected by the Fridericia's formula; SE = standard error.
[a] ΔQTcF at 3.0 hours was the primary endpoint. If the upper CL within the OCA treatment group was less than 10 msec, then the primary endpoint was met.
Source: 747-108, Section 14, Table 14.2.4.1

Figure 31

Figure 14: Plasma Exposure-Response Relationship for Unconjugated OCA, Glyco-OCA, Tauro-OCA, and Total OCA in Healthy Subjects and NASH Subjects with Fibrosis Stages 1 to 4 - Studies 747-108 and 747-117



Glyco-OCA = glycine conjugate of OCA; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; QTcF = QT interval corrected by the Fridericia's formula; tauro-OCA = taurine conjugate of OCA.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 69

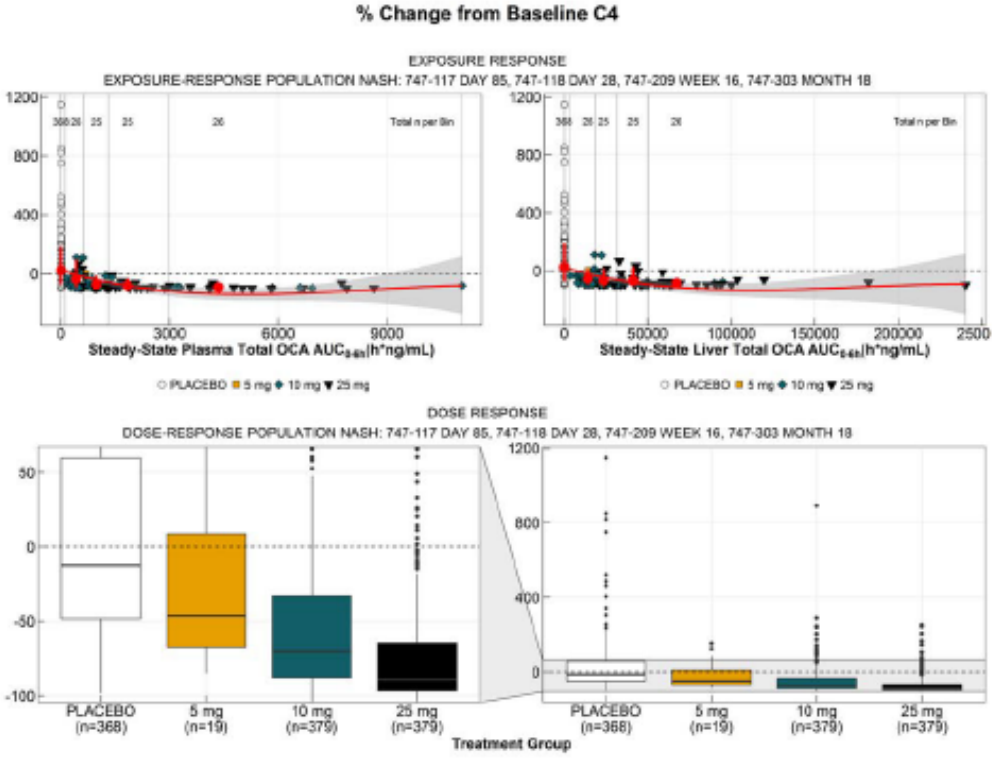
Relation between plasma concentration and effect

Biomarkers of FXR Activation

C4, FGF-19, and Bile Acids

Figure 32

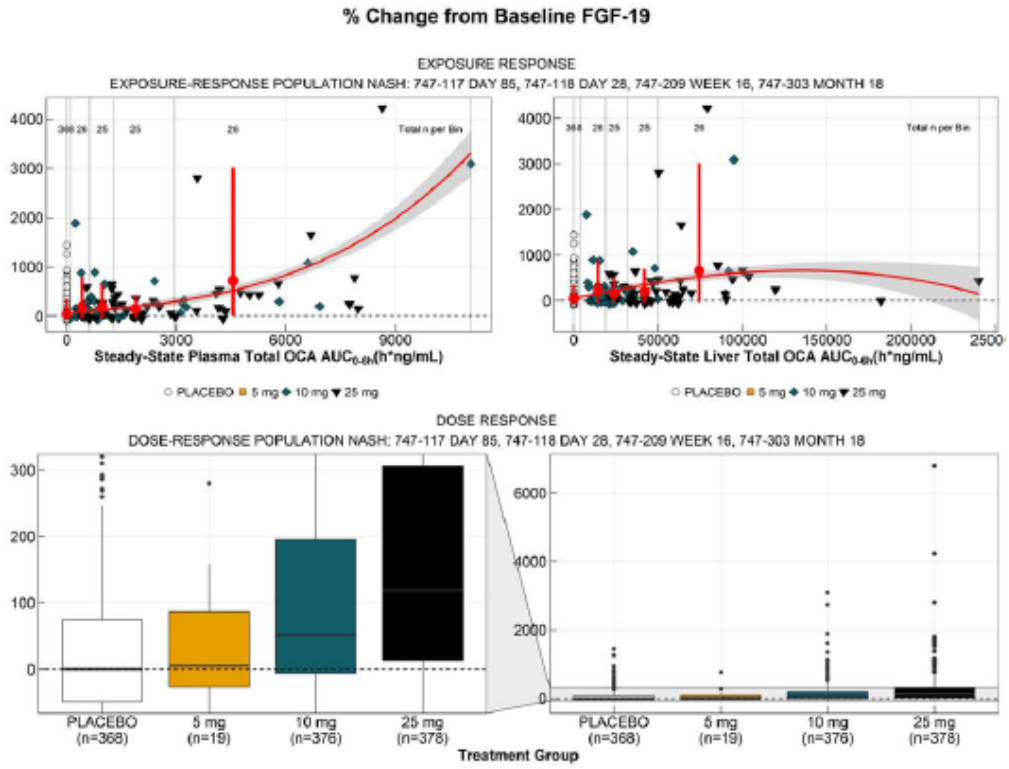
Figure 28: Percent Change in Plasma C4 at End-of-Study Relative to Baseline for Placebo and OCA 5 mg, 10 mg, and 25 mg in Subjects with NASH Fibrosis - Studies 747-117, 747-118, 747-209, and 747-303



AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; C4 = 7α-hydroxy-4-cholesten-3-one; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 23

Figure 33

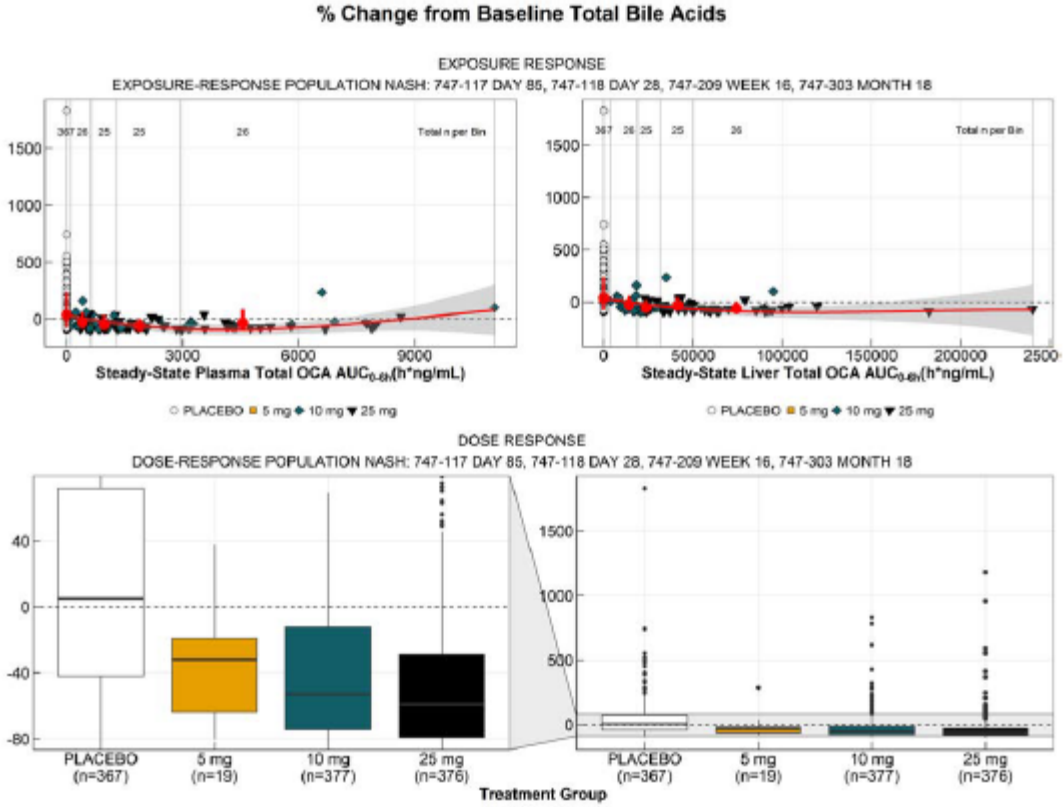
Figure 29: Percent Change in Plasma FGF-19 at End-of-Study Relative to Baseline for Placebo and OCA 5 mg, 10 mg, and 25 mg in Subjects with NASH Fibrosis - Studies 747-117, 747-118, 747-209, and 747-303



AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; FGF-19 = fibroblast growth factor-19; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 24

Figure 34

Figure 30: Percent Change of Plasma Endogenous Bile Acids at End-of-Study Relative to Baseline for Placebo and OCA 5 mg, 10 mg, and 25 mg in Subjects with NASH Fibrosis - Studies 747-117, 747-118, 747-209, and 747-303



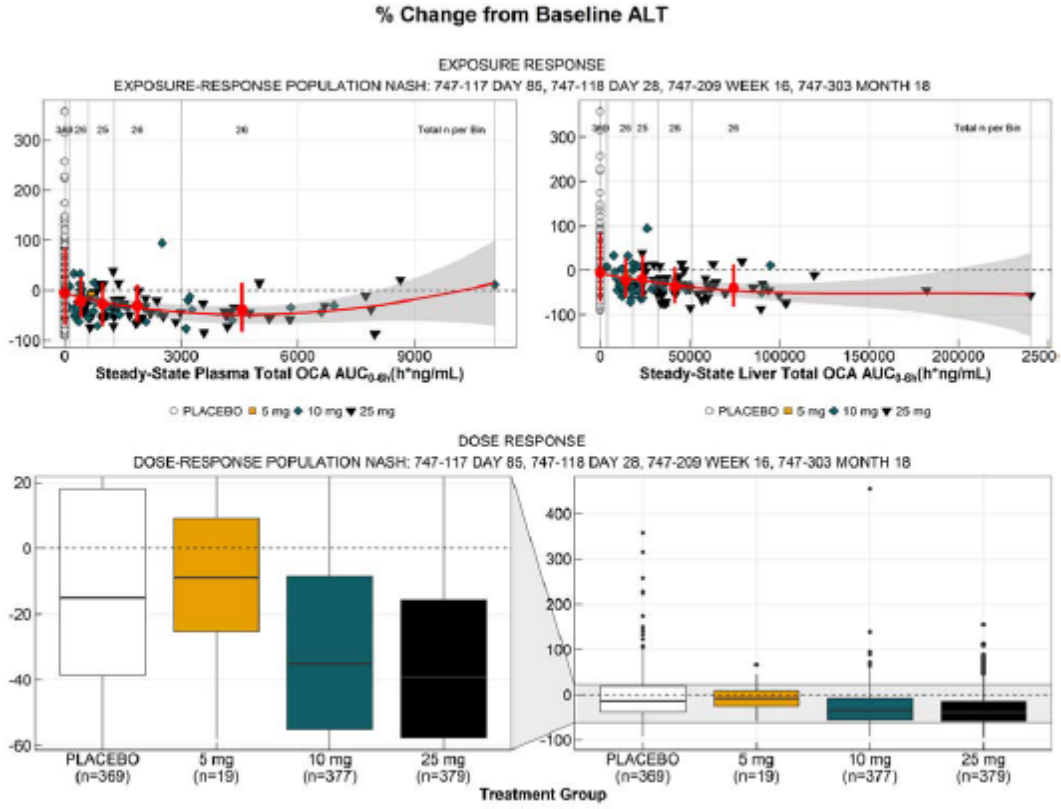
AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 25

Liver Biomarkers

ALT, AST, and GGT

Figure 35

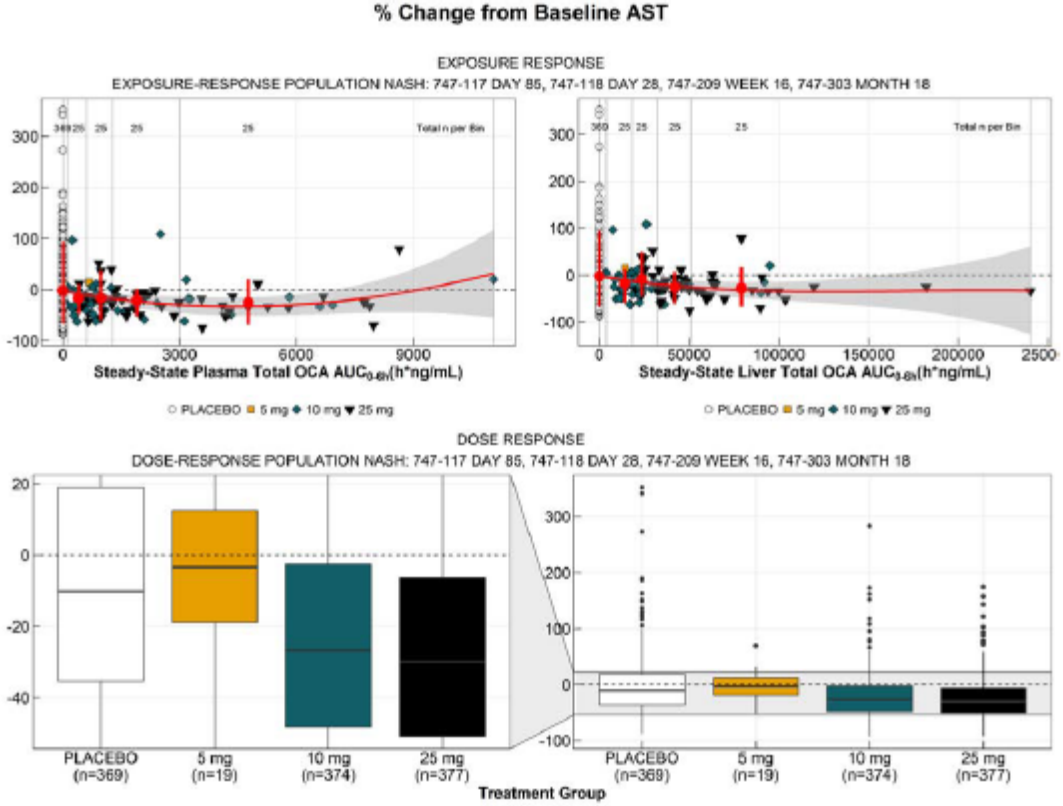
Figure 32: Percent Change in ALT at End-of-Study Relative to Baseline for Placebo and OCA 5 mg, 10 mg, and 25 mg in Subjects with NASH Fibrosis - Studies 747-117, 747-118, 747-209, and 747-303



ALT = alanine aminotransferase; $AUC_{0\text{-}6h}$ = area under the concentration-time curve from time 0 to 6 hours postadministration; n = specific number of subjects within the group; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 45

Figure 36

Figure 34: Percent Change in AST at End-of-Study Relative to Baseline for Placebo and OCA 5 mg, 10 mg, and 25 mg in Subjects with NASH Fibrosis - Studies 747-117, 747-118, 747-209, and 747-303

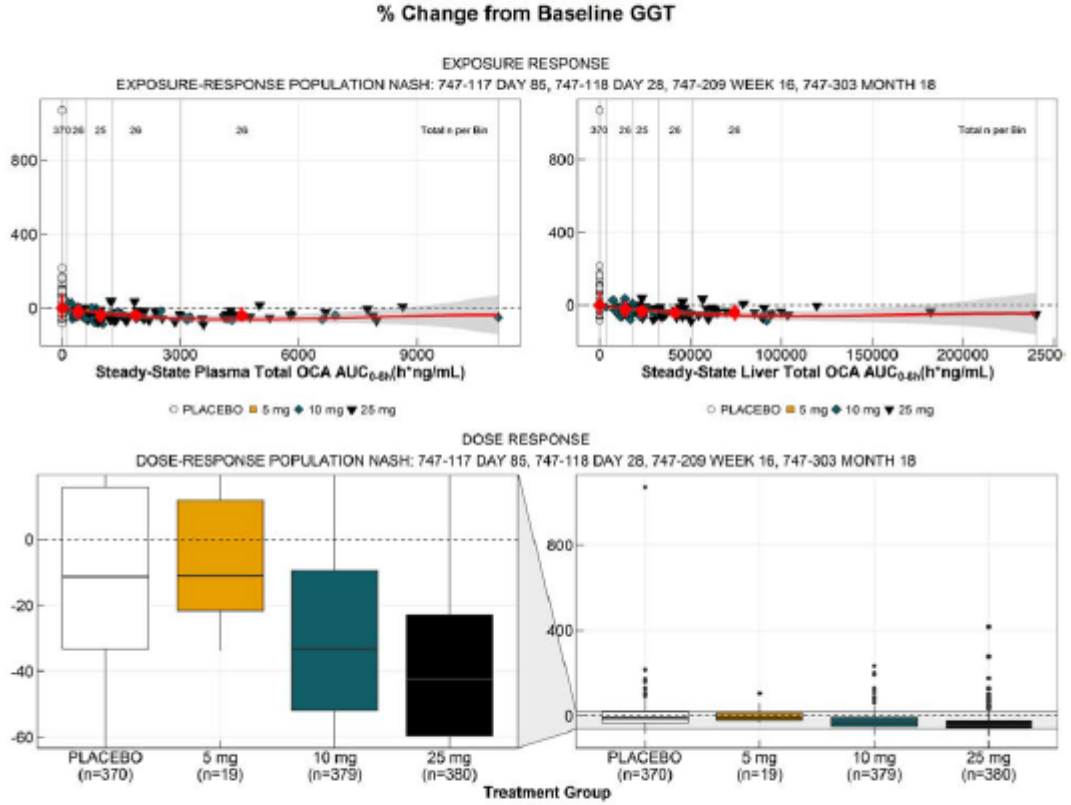


AST = aspartate aminotransferase; AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.

Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 47

Figure 37

Figure 35: Percent Change in GGT at End-of-Study Relative to Baseline for Placebo and OCA 5 mg, 10 mg, and 25 mg in Subjects with NASH Fibrosis - Studies 747-117, 747-118, 747-209, and 747-303



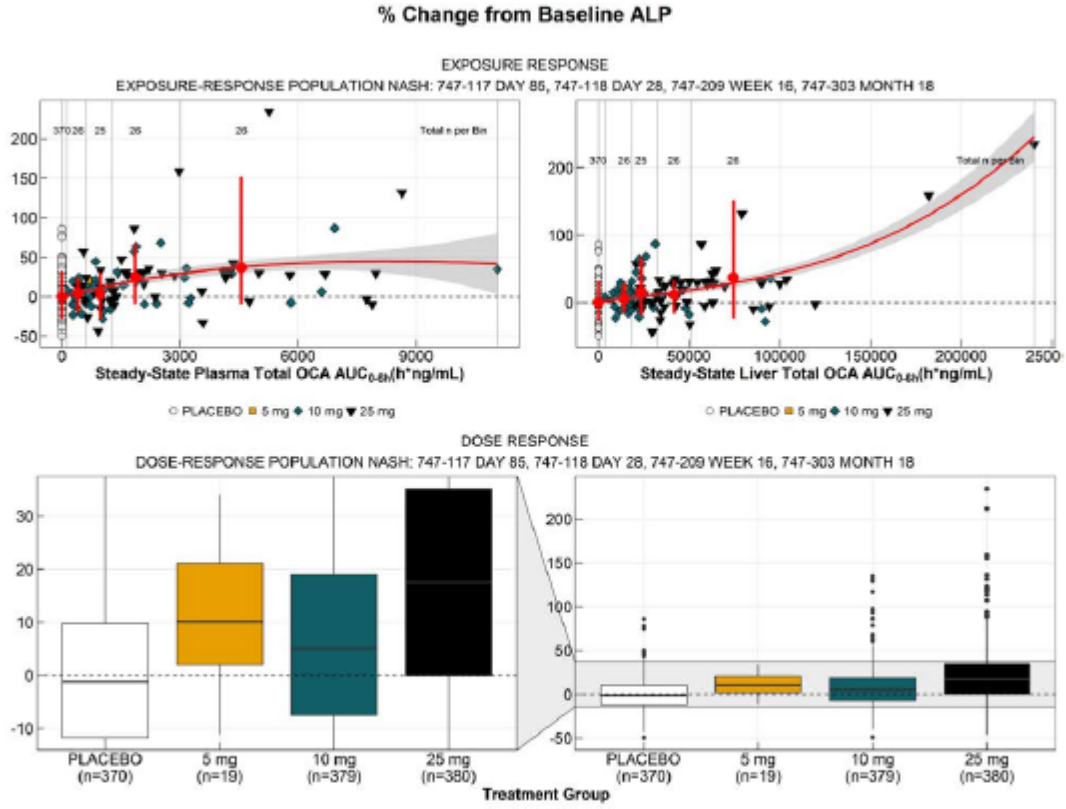
AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; GGT = gamma-glutamyl transferase; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.

Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 48

Alkaline Phosphatase

Figure 38

Figure 36: Percent Change in ALP at End-of-Study Relative to Baseline for Placebo and OCA 5 mg, 10 mg, and 25 mg in Subjects with NASH Fibrosis - Studies 747-117, 747-118, 747-209, and 747-303



ALP = alkaline phosphatase; AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.

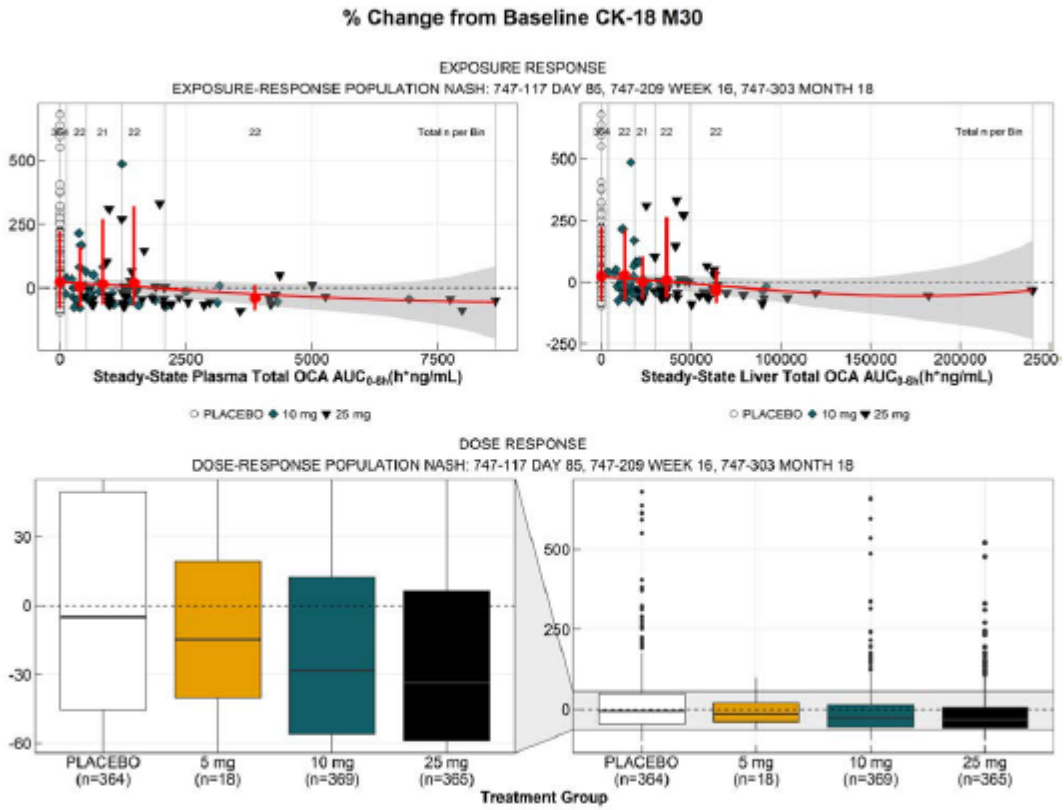
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 49

Apoptosis

CK-18: M30 and M65

Figure 39

Figure 39: Percent Change in CK-18 M30 at End-of-Study Relative to Baseline for Placebo and OCA 5 mg, 10 mg and 25 mg in NASH Subjects with Fibrosis - Studies 747-117, 747-118, 747-209 and 747-303

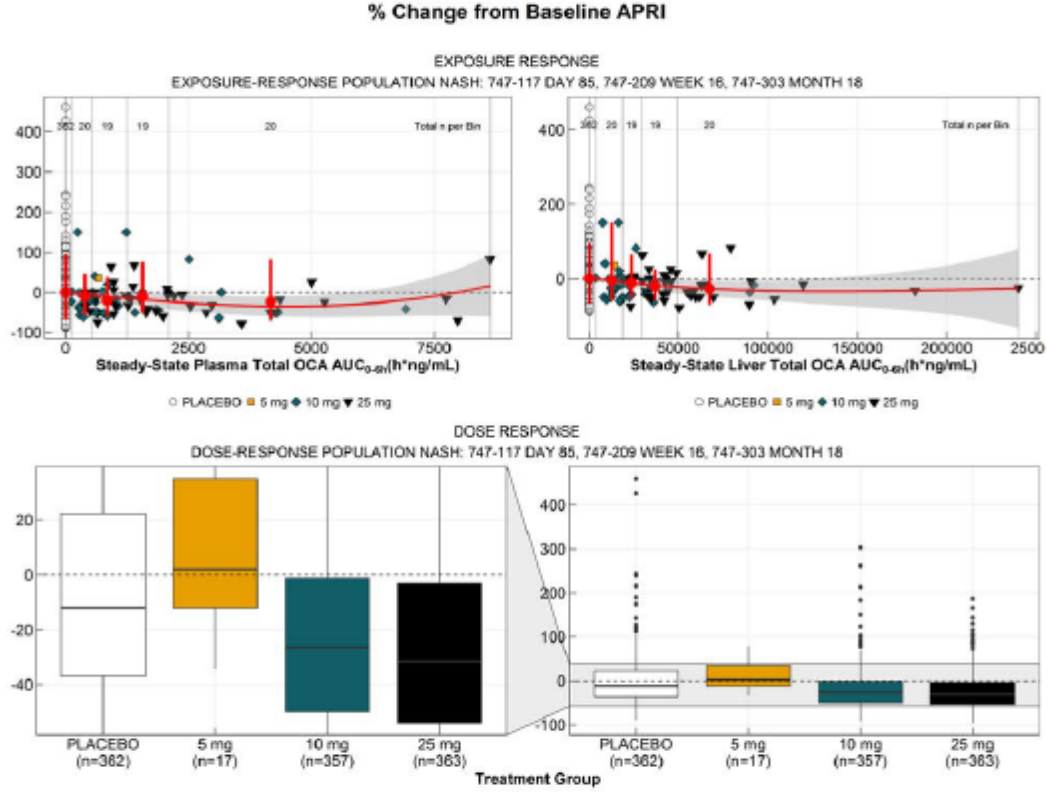


AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 27

Non-Invasive Markers of Fibrosis

Figure 40

Figure 41: Percent Change in APRI at End-of-Study Relative to Baseline for Placebo and OCA 5 mg, 10 mg and 25 mg in NASH Subjects with Fibrosis -Studies 747-117, 747-209, and 747-303

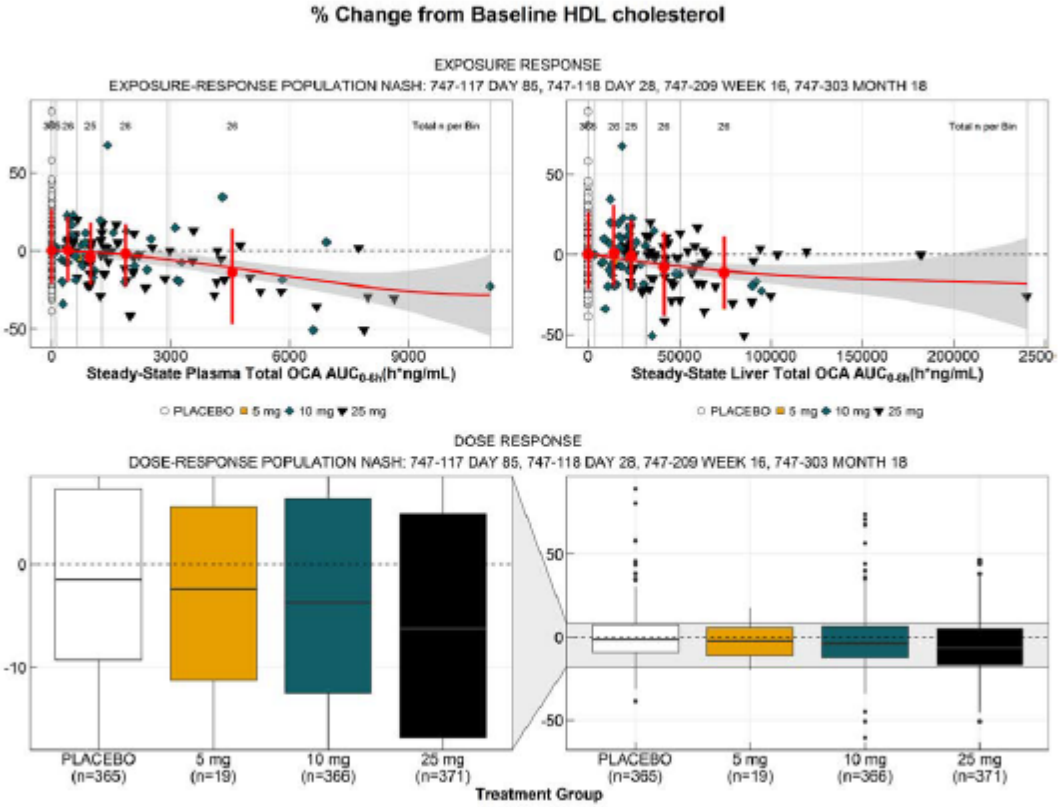


APRI = aspartate aminotransferase-to-platelet ratio index; AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 30

Lipid Homeostasis

Figure 41

Figure 44: Percent Change in Plasma HDL at End-of-Study Relative to Baseline for Placebo and OCA 5 mg, 10 mg, and 25 mg in NASH Subjects with Fibrosis - Studies 747-117, 747-209 and 747-303

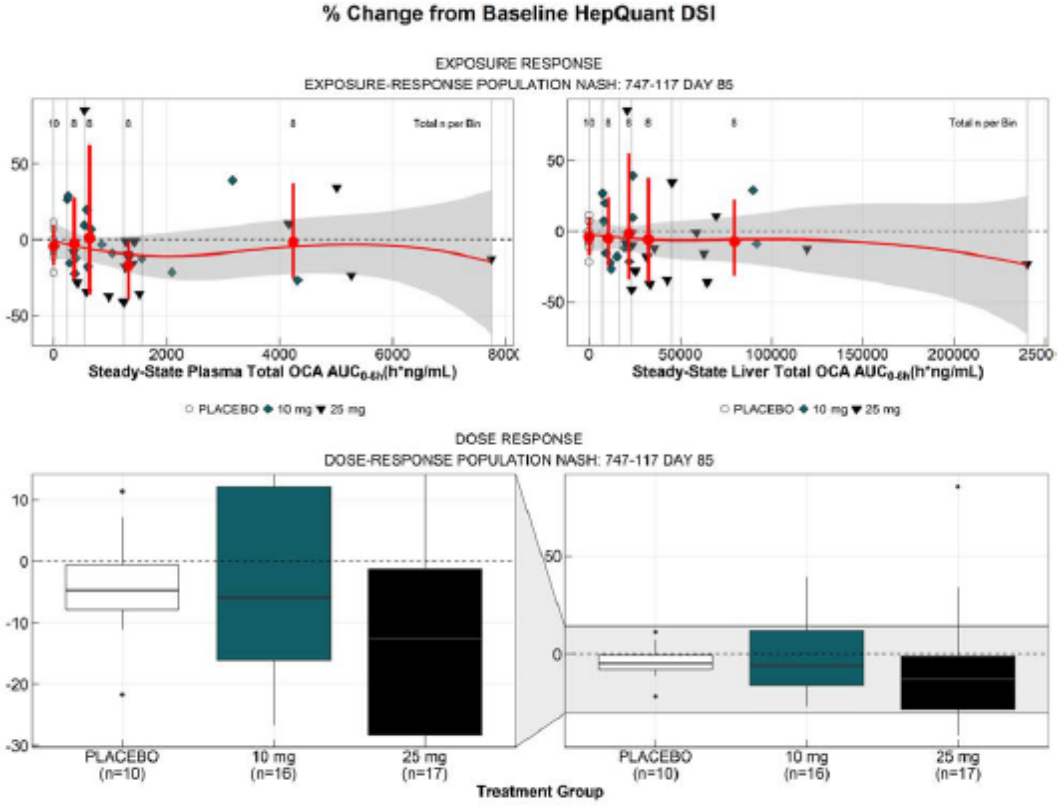


AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; HDL = high-density lipoprotein; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 42

Liver Function as Assessed by HepQuant

Figure 42

Figure 46: Percent Change in DSI at End-of-Study Relative to Baseline for Placebo and OCA 10 mg and 25 mg in NASH Subjects with Fibrosis -Study 747-117



AUC_{0-6h} = area under the concentration-time curve from time 0 to 6 hours postadministration; DSI = disease severity index; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PAR = pharmacometric analysis report.
Source: Module 5.3.5.3, PAR, OCA Exposure-Response and Dose-Response for NASH Fibrosis, Figure 56

3.3.3. Discussion on clinical pharmacology

The PK of OCA and its conjugates was sufficiently characterised through single- and multiple-dose, bridging bioequivalence, ADME, DDI, food effect, hepatic/renal impairment and QT studies.

Standard LC MS/MS and ELISA methodologies were used to characterise PK/PD profile of OCA and its metabolites.

Food effects

Food effects on OCA, tauro-OCA and glyco-OCA exposure (AUC and Cmax) were assessed across two dose levels (10 and 25 mg), showing no significant changes in exposure at none of the dose levels evaluated.

Distribution

The distribution of OCA through non compartmental analysis showed a volume of distribution at steady state of 210 L after IV administration, which demonstrates that is largely distributed into low-perfused compartments. The clearance of OCA after IV administration was 25 L/h showing a moderate-to-high clearance.

Excretion

Results from the radiolabel mass balanced study concluded OCA is almost completely excreted in feces (72%) compared to urine (2.83%). The total radioactivity recovered was less than 90%, even when samples collected beyond 504 hours were considered.

Metabolism

The metabolic route after oral administration of OCA demonstrates that glycine- and taurine-OCA analytes are the primary metabolites after OCA conjugation. Differences between NASH and helathy subjects have been characterized through the mass-balance study and a physiological PK model has been developed to characterize the PK and hepato-biliary/intestinal dispoistion of OCA in NASH patients. The evaluation of the physiological PK model will be provided in the section "Pharmacokinetics in the target population".

Pharmacokinetics in the target population

Population PK model

A population PK modelling strategy was implemented to characterize the time-course PK profiles of OCA, glyco-OCA, and tauro-OCA observations simultaneously after OCA administration using a sequential modelling approach: first, the base model was developed, then a covariate analysis was performed based on the significant covariate-parameter relationships previously explored and, at the last stage, the final population pharmacokinetic model was evaluated using the standard methodologies.

A high proportion (36%, 10%, and 19%) of BLQ data available for the population PK analysis was detected across the three analytes (OCA, glyco- and tauro-OCA), respectively. On the other hand, BLQ observations included in the analysis as LLOQ/2 were excluded from the analysis as they did not improve the model fitting. However, other methods to handle BLQ observations (M3 and M4) were not considered. BLQ observations provide information on the final parameter estimates that should be considered when significant BLQ observations are available (>5%). The Applicant has planned to conduct a joint PK analysis of NASH fibrosis with all active analytes and assessing the influence of BLQ observations in the parameter estimation.

The structural model includes a central compartment for OCA, tauro-OCA and glyco-OCA and an enterohepatic recirculation "gallbladder" compartment for glyco-OCA and tauro-OCA. In general, the structural model seems not able to properly characterize the observed behavior in any of the three analytes, based on the DV vs PRED correlations. Since the Applicant is committed to conduct a joint analysis including all the observations available (BLQ observations), additional efforts should be implemented to properly describe the overall behavior. Eleven random effects were incorporated into the model, which seems excessive and somehow artificial. In addition, a combined residual error was proposed to manage the difference between observed and predicted concentrations. The large proportional error of OCA (74%), glyco-OCA (51%) and tauro-OCA (52%) indicates that there is a lot of uncertainty, probably due to an inadequate structural PK structure. The Applicant is committed to conduct an empirical PK model with all the active analytes, which will consider the use of additive error model as suggested.

The emptying of gallbladder was assumed to occurred during 90 minutes after meal intake and constantly through a first-order process. However, the fraction of constant release from gallbladder seems to affect only glyco-OCA and in an excessively low proportion. A model refinement could improve model stability without compromising the overall fitting.

The final population PK model incorporates 32 covariate effects on several typical parameters of the population PK model. A significant reduction in the omega variances revealed the statistical significance of such relationships and a structural improvement was observed on glyco-OCA, whereas the structural

bias on OCA and tauro-OCA remained unchanged. Pc-VPC for multiple dose study revealed an over-estimation of the variability and a bias for all the dose tested and analytes, which undermine the ability of the model to serve as a solid tool for description of the data and dose selection assessment. The model qualification clearly justifies the need for an update in the population PK model through a joint analysis in order to provide a successful description of the data.

Physiological PK model in NASH patients

The proportion of BLQ observations of unconjugated, glyco- and tauro-OCA is significant (> 10%). The rationale (long run times) of using the M5 method for handling BLQ values is not supported. Currently, computational strategies of parallelization and optimal CPU's are available to short the runt times. A consequence of bias on parameter estimates is much more relevant and increases the burdens of using M5 method compared to M3/M4 strategies, which are largely supported in the literature. Therefore, the Applicant is requested to implement the M3/M4 strategies in the updated population PK model in NASH fibrosis in order to address for a precise and unbiased parameter estimation.

The sensitivity analysis conducted for the OCA Physiologyc PK model in healthy volunteers and NASH patients revealed an adequate consistency and precision of most of the PK parameters included.

Therefore, any conclusion derived from the model needs to be considered with great caution. In addition, new analyzes are needed to better characterize the observed behavior and, therefore, to consider the appropriate model for the proposed objective.

Special populations

The relevance of renal impairment in the PK exposure of OCA has been associated to a decrease hepatic uptake of OCA, leading to higher exposure of OCA in these patients. In addition, the clinical relevance of urinary excretion and renal clearance of OCA was negligible, suggesting that its inclusion in the population PK model may not increase its prediction capacity. Actual and modelling data show that the increase in total-OCA exposure due to renal impairment or NASH is not related to a decrease in intra-hepatic drug concentration.

The impact of hepatic impairment has been assessed based on the results of a dedicated hepatic study with patients with mild hepatic impairment and the population PK model developed. The results of the clinical study in patients with mild hepatic impairment reflected a 2.4-fold increase in total OCA AUC0-6h, which is somehow expected considering that OCA is mainly metabolized through the liver. Results from Study 747-103 reported a clinically relevant impact on AUC and Cmax for each analyte (>1.4 fold increase) in mild, moderate and severe hepatic imparied patients. Once the population PK model can describe the experimental observations in hepatic impaired patients and considering the large inter-individual variability observed on OCA, it is necessary to propose a dose recommendation that guarantees a similar exposure of OCA. Obeticholic acid is not aimed to be administered if patients show hepatic impairment or liver injury.

Differences in total OCA AUC0-6h between males and females were observed, but they were attributed to a different body weight distribution among both sub-groups of patients. Considering that higher body weight leads to less exposure of total OCA and the correlation observed between body weight and gender, the explanation seems reasonable.

The impact of body weight was evaluated through a simulation-based analysis from the population PK model on the relative change in AUC compared to the typical patient of 67 kg using extreme body weight values (40 and 134 kg). A significant change (50% higher AUC) is predicted in patients with low body weight (40 kg) and patients with high body weight (134 kg) would show a 42.6% lower AUC compared to a patient of 67 kg. A similar trend was observed when experimental total OCA AUC0-6h were represented across three body weight ranges (<84kg, 85-103kg and >103 kg). The analysis

confirmed the same relative change in exposure (43% increase in patients with <84kg and 19% reduction in patients with >103 kg). However, the absolute difference between median values of the three body weight ranges is significantly less compared to the difference in the median values from the forest plot analysis, which indicates that the forest plot analysis from the population PK model undermines the effect of body weight on the total OCA AUC. The Applicant discussed that no dose recommendation should be established based on body weight since no safety concern has been observed so far based on the body weight across the patients. However, it is expected that larger differences in exposure may occur in patients with extreme body weight values that may influence the safety profile.

Exposure relevant for safety evaluation

The Applicant provided the predicted exposure metrics (AUC, Cmax, Cavg) values of OCA, glyco-OCA and tauro-OCA in Phase 1 and 2. The results confirm the large variability with exposure metric ranges of 10 orders of magnitude, which makes quite uncertain to understand any exposure-response relationship. In addition, the results should be considered with caution as the population PK model developed is not validated enough to make any dose recommendation.

Secondary pharmacology: QTc prolongation

An exposure-QT analysis has been performed, evaluating the QTc prolongation on each exposure analyte available (unconjugated OCA, glyco-OCA, tauro-OCA and total-OCA. The upper limit of the 95% CI of the difference between placebo and OCA did not overcome the 10 ms. The model did not identify any QTcF prolongation in healthy volunteers and NASH patients. Additionally, it seems that both groups of populations show similar QTcF prolongation, so no differences due to disease status may exist.

Exposure-efficacy

A dose- and exposure-response relationship was established between total OCA AUC0-6h in plasma or liver to (i) achieving improvement of fibrosis by ≥ 1 stage with no worsening of NASH and (ii) the resolution of NASH with no worsening of fibrosis. Higher proportion of patients responding for OCA 25 mg were observed when exposure in plasma or liver were related to the response compared to dose levels, indicating that exposure metrics are better predictors than the dose level. An updated exposure-response logistic regression analysis allows to better characterize the relationship, showing a significant improvement in terms of efficacy at AUC >5500 h*ng/mL. In addition, post-hoc exposure metrics should be considered with caution, knowing that many concerns have been raised regarding the population and physiological PK models developed.

Exposure-safety

The incidence of hepatic disorder AEs was not related to total OCA dose nor exposure levels. These results suggest there is no clear increase in the probability of hepatic disorder AEs, even at higher plasma and liver exposures of OCA in subjects with liver fibrosis due to NASH.

Exposure-biomarker relationship

A clear dose/exposure relationship was established between total OCA exposure and biomarkers of FXR activation (C4, FGF-19 and bile acids). Surprisingly, better correlations were observed when steady-state plasma total OCA exposures were considered, rather than liver total OCA AUC0-6h. A significant change from baseline C4 was observed with lower plasma levels, indicating that this biomarker is able to establish a smooth and complete relationship with OCA plasma exposure. A similar behavior was observed when change from baseline total bile acids was considered. The increase from baseline FGF-19 is less evident and only appears at higher OCA plasma exposures. No relationship was established with OCA liver exposure levels. Based on the poor description of the mathematical model implemented

to describe the correlation between relative change in total bile acids and the proportion of patients with fibrosis improvement by ≥ 1 stage with no worsening of NASH, total bile acids cannot be used to inform on the efficacy.

The exposure-relationships between liver biomarkers revealed a robust correlation between plasma and liver exposure levels of total OCA. The dose-response relationship was less evident and only visible after >10 mg OCA administration. The correlation between change from baseline ALT and proportion of patients with fibrosis improvement by ≥ 1 stage with no worsening of NASH confirmed the adequacy of ALT as an informative biomarker of efficacy.

A dose-response relationship between OCA dose levels and apoptosis biomarkers was observed. As expected, a dose-dependent decrease in apoptosis biomarkers (CK-18 M30) from baseline was characterized. However, plasma and liver exposure levels of total OCA were not as informative as dose. The correlation between relative change from baseline CK-18 M30 and proportion of patients with fibrosis improvement by ≥ 1 stage with no worsening of NASH should be considered with caution, as it only explains a small reduction in the proportion of patients compared to the change in the apoptosis biomarker. Therefore, further justification is needed to consider this relationship as an informative correlation with efficacy- Such relationship is not aimed for dose selection.

No dose/exposure-response relationship was observed when non-invasive markers of fibrosis were considered.

A week exposure/dose-response relationship was observed when lipid homeostasis biomarkers were considered. The relative change from baseline HDL levels was more evident at 4th quartile of exposure (where also less observations were collected). The dose-response relationship was weak across the different dose levels considered.

3.3.4. Conclusions on clinical pharmacology

The clinical pharmacology properties have been partially characterized, but there are still relevant aspects that need to be improved in order to fully understand the pharmacokinetic and pharmacodynamic properties and implications of the administration of obeticholic acid. The Applicant is committed to update the population PK model and the PBPK model developed in a joint mathematical framework that would be of higher relevance for dose selection. Remaining questions regarding the impact of obeticholic acid in patients with extreme body weight and regarding the long-term stability period for the storage of samples used within studies 747-117, -207, -209, -301 and -303 should be clarified.

3.3.5. Clinical efficacy

Dose-response studies and main clinical studies

The proposed dose for this medicinal product consists on obeticholic acid, 25 mg once daily with or without food.

The Applicant has proposed the dose of 25 mg once daily taking into account the results of the efficacy data from FLINT Study (supportive phase 2b study) and 747-303 Study (pivotal Study phase 3)

Regarding Phase 2b FLINT study, subjects with biopsy-confirmed NASH were randomized to either OCA 25 mg or placebo once daily over a 72-week treatment period. In this study, a significantly greater percentage of subjects receiving OCA 25 mg compared with placebo achieved no worsening of fibrosis and an improvement in NAS ≥2 points following 72 weeks of treatment. Clinically meaningful and statistically significant improvements were also observed with OCA 25 mg treatment across multiple

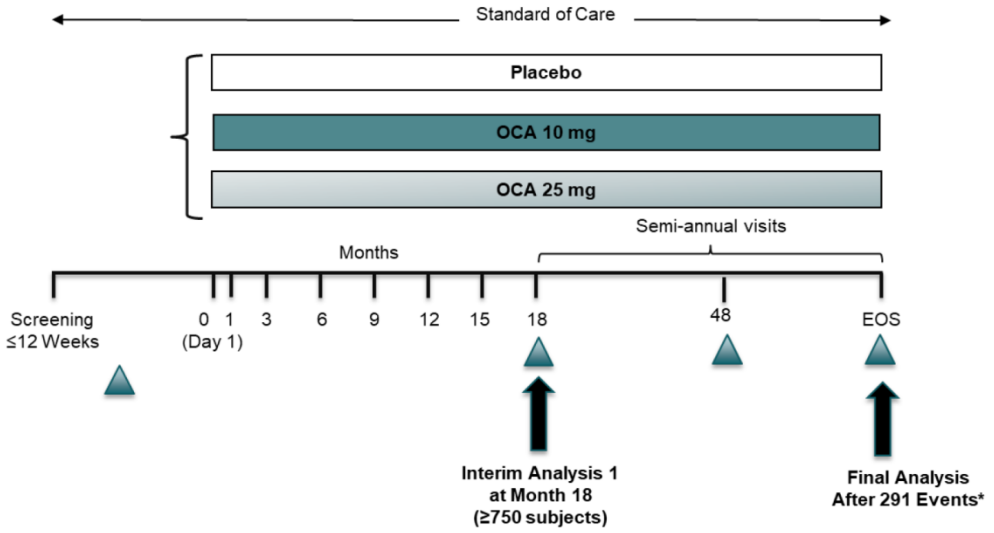
fibrosis-related and steatohepatitis-related histologic endpoints, as well as laboratory markers of hepatocellular injury, oxidative stress, synthetic liver function, and noninvasive measures of fibrosis.

In Study 747-303, subjects with biopsy-confirmed NASH fibrosis were evaluated over an 18-month treatment period. Treatment with OCA 25 mg resulted in an improvement in fibrosis and NASH. While some antifibrotic and anti-inflammatory activity was evident with OCA 10 mg, the response rates were significantly lower than those achieved with 25 mg (Table 25); therefore, OCA 25 mg is considered the target therapeutic dose for NASH fibrosis. Dose-dependent improvements in markers of hepatocellular injury (ie, ALT and AST), GGT, and noninvasive markers of fibrosis (ie, APRI and FIB-4) were also observed, with substantially greater responses with OCA 25 mg. The dose response was generally consistent across multiple subgroups, and regardless of subgroup, OCA 25 mg delivered superior efficacy relative to OCA 10 mg.

Main study

Study 747-303 (REGENERATE Study): A Phase 3, Double-Blind, Randomized, Long-Term, Placebo-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Obeticholic Acid in Subjects with Nonalcoholic Steatohepatitis

Figure 43 Study 747-303 Design



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

This Phase 3, double blind, randomized, long-term, placebo-controlled, multicenter, international study was designed to evaluate the effect of OCA on histological improvements of NASH, all-cause mortality, and liver-related clinical outcomes. The study was designed to enrol approximately 2370 subjects with NASH. The study population was planned to comprise approximately 2085 subjects with biopsy-confirmed, precirrhotic NASH and evidence of stage 2or stage 3 liver fibrosis, including approximately 60% with fibrosis stage 3 and approximately40% with fibrosis stage 2. An additional cohort of approximately 285 subjects with fibrosis stage 1 and ≥1 accompanying risk factor was enrolled to gather information on the safety of OCA and progression of liver disease in this population

This assessment report only collects data from the Month 18 Interim Analysis, which was performed after a planned minimum of 750 randomized subjects (the first sequential) with fibrosis stage 2 or

stage 3 reached their actual/planned Month 18 Visit (including subjects who discontinued before reaching the planned Month 18 Visit).

Methods

Study Participants

Main inclusion Criteria

Subjects were required to meet the following criteria in order to be included in the study:

1. **Histologic evidence of NASH** upon central read of a liver biopsy obtained no more than 6 months before Day 1 defined by presence of all 3 key histological features of NASH with a score of ≥1 for each and a combined NAFLD activity score (NAS) of 4 or greater out of possible 8 points according to NASH CRN criteria.
2. **Histologic** evidence of fibrosis stage 2 (perisinusoidal and portal/periportal) or stage 3 (bridging fibrosis) as defined by the NASH CRN scoring of fibrosis, or
3. **Histologic** evidence of fibrosis stage 1a or stage 1b (mild or moderate, zone 3 perisinusoidal) as defined by the NASH CRN scoring of fibrosis if accompanied by ≥1 of the following risk factors: Obesity (BMI ≥30 kg/m2), Type 2 diabetes diagnosed per 2013 American Diabetes Association criteria, ALT >1.5× upper limit of normal (ULN).
4. Subjects with a historical biopsy were either not taking or on stable doses of TZDs/glitazones or vitamin E for 6 months before Day 1.
5. Stable body weight (ie, not varying by >10% for ≥3 months) before Day 1.
6. Age ≥18 years on the date of signed informed consent form.

Main exclusion Criteria

Subjects were to be excluded from the study if they had chronic liver disease of other etiology, had liver cirrhosis, or had clinical evidence of hepatic decompensation. Key exclusion criteria were:

1. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year before Screening.
2. Clinical history of liver decompensation such as ascites (identified on physical exam), variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy (Grade I or greater based on West Haven classification), or hepatorenal/hepatopulmonary syndromes.
3. Current history of hepatic function impairment defined as Child-Pugh (CP) score of >=7 (CP B or C cirrhosis classification).
4. Subjects who in the Investigator's opinion are likely to develop a CP score of >=7 within the first 12 weeks of the study.
5. Any type of blood donation, including but not limited to whole blood, plasma, blood components, autologous or directed within 28 days before Day -1.
6. Hemoglobin HbA1c >9.5% within 28 days before Day -1.
7. Subjects with **recent history (within 1 year of Day 1) of significant cardiovascular or cerebrovascular disorders**,
8. **BMI >45 kg/m2** with ≥1 of the following comorbidities: Hypertension with blood pressure ≥140/90 mmHg if <60 years, ≥150/90 mmHg if ≥60 years, or on antihypertensive medication;

Hyperlipidemia defined as LDL cholesterol ≥160 mg/dL, total cholesterol ≥200 mg/dL, or on lipid lowering medication; Type 2 diabetes per 2013 American Diabetes Association criteria.

9. **LDL ≥190 mg/dL** and already on a stable dose of statin and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for ≥30 days at Screening.

Evidence of other forms of known chronic liver disease.

Treatments

Three treatment groups were evaluated in the double-blind phase of the study: placebo, OCA 10, or OCA 25. The test products were:

- OCA tablet; 10 mg; oral administration; bulk lot numbers B08809, B08813, B10793, B11624, B11626, B11627, and B16057
- OCA tablet; 25 mg; oral administration; bulk lot numbers B06175, B06419, B10794, B11628, B11629, B16054, and B16055
- Placebo tablet; matching in size and appearance to OCA tablets; oral administration; bulk lot numbers B08806, B11622, B11623, and B14244

Objectives

The primary objective of the study was to evaluate at 18 months the effect of OCA compared to placebo on Histological improvement in NASH by assessing the following primary endpoints using NASH Clinical Research Network (CRN) scoring criteria:

- Improvement in fibrosis by ≥ 1 stage with no worsening of NASH (no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis)
- Resolution of NASH with no worsening of fibrosis

NASH resolution is defined as the overall histopathologic interpretation of (1) "no fatty liver disease" or (2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a nonalcoholic fatty liver disease (NAFLD) activity score (NAS) of 0 for ballooning and 0 to 1 for inflammation.

The secondary objectives of the study:

To evaluate at 18 months the effect of OCA compared to placebo on histological improvement in NASH by assessing the following using NASH CRN scoring criteria:

- Improvement of fibrosis by ≥1 stage AND/OR resolution of NASH, without worsening of either
- No worsening of fibrosis and no worsening of NASH
- Histological progression to cirrhosis
- Improvement of fibrosis by >2 stages
- Improvement of each key of histological feature of NASH by >1 point (steatosis, lobular inflammation, and hepatocellular ballooning)
- Improvement of NAS by >2 points with no worsening of fibrosis
- Improvement of fibrosis and resolution of NASH as a composite endpoint as defined by both endpoints being met in the same subject
- Resolution of fibrosis

Outcomes/endpoints

Efficacy

The Primary Efficacy Endpoint for the Month 18 Interim Analysis are as follows:

- *Improvement of liver fibrosis by ≥ 1 stage (NASH CRN fibrosis score) with no worsening of NASH*
- *Resolution of NASH with no worsening of fibrosis.*

In a post-hoc analysis, resolution of NASH was defined as the absence of steatohepatitis based on pathologist's diagnostic assessment of the overall pattern of injury.

The original version of the protocol for Study 747-303 defined NASH resolution as the absence of definite steatohepatitis, based on the pathologist's overall assessment (ie, pathologist's assessment of absence of definite NASH based on overall pattern of injury rather than specific NAS parameters).

A Key Secondary Endpoint was:

1. Percentage of subjects with improvement of fibrosis by ≥ 1 Stage and/or resolution of NASH, without worsening of either.

Secondary Histologic Endpoints:

2. Percentage of subjects with no worsening of fibrosis and no worsening of NASH
3. Percentage of subjects with progression to cirrhosis
4. Percentage of subjects with improvement of fibrosis by ≥2 stages
5. Percentage of subjects with improvement of each key histologic feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning)
6. Percentage of subjects with improvement of NAS by ≥2 points with no worsening of fibrosis
7. Percentage of subjects with improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject
8. Percentage of subjects with resolution of fibrosis

Randomisation and blinding (masking)

Subjects are screened for a period of up to 12 weeks before entering the study. Subjects who met all eligibility criteria were randomized to receive OCA 10 mg, OCA 25 mg, or matching placebo in a 1:1:1 ratio, in addition to lifestyle modification guidance and local standard of care.

Randomization of subjects with fibrosis stage 2 or stage 3 was stratified by presence of type 2 diabetes at enrollment (yes/no) and use of thiazolidinediones (TZDs) or vitamin E at baseline (yes/no).

Statistical methods

The study was designed to enroll approximately 2370 subjects with liver fibrosis due to NASH.

The Month 18 Interim Analysis was to be performed after a planned minimum of 750 randomized subjects (the first sequential) with fibrosis stage 2 or stage 3 reached their actual/planned Month 18 Visit (including subjects who discontinued before reaching the planned Month 18 Visit).

For the primary efficacy endpoint of improvement of fibrosis of ≥1 stage, no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis at

Month 18, a sample size of 250 per group with an assumed 15% discontinuation rate was estimated to provide 98% power to demonstrate a statistically significant treatment difference between the OCA (10 mg and 25 mg) and placebo groups based on CMH test with a 2-sided type I error at the 0.01 level, assuming an adjusted response rate of 36.7% and 17.6% in the OCA (10 mg and 25 mg) and placebo groups, respectively. The adjustment was based on a 15% discontinuation rate applied to the response rate of 43.1% and 20.7% in the OCA (10 mg and 25 mg) and placebo groups, respectively, based on data from the FLINT study.

For the primary efficacy endpoint of NASH resolution with no worsening of fibrosis at Month 18, a sample size of 250 per group with an assumed 15% discontinuation rate was estimated to provide 91% power to demonstrate a statistically significant treatment difference between OCA (10 mg and 25 mg) and placebo groups based on CMH test with a 2-sided type I error at the 0.01 level, assuming an adjusted response rate of 17.1% and 5.4% in the OCA (10 mg and 25 mg) and placebo groups, respectively. The adjustment was based on a 15% discontinuation rate applied to the response rate of 20.1% and 6.3% in the OCA (10 mg and 25 mg) and placebo groups, respectively, based on data from the FLINT study.

The Month 18 Interim Analysis DCO date was prespecified to include all subjects' data for visits (scheduled or unscheduled) occurring on or before that date. The Interim Analysis Cohort included all randomized subjects (fibrosis stages 1 to 3) who received at least one dose of IP by the DCO.

The primary efficacy analyses at Month 18 compared placebo and each OCA dose, adjusting for multiplicity and using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata (diabetes at enrollment [yes/no] and use of TZDs or vitamin E at baseline [yes/no]). Any subject who discontinued from the study before the Month 18 biopsy visit and did not have a postbaseline biopsy assessment was considered a non-responder. Postbaseline biopsies collected for subjects who discontinued treatment before the Month 18 Visit were included in the Month 18 Interim Analysis of histologic endpoints regardless of the timing of the biopsy.

The two-sided Type I error (alpha) allocated to all testing at Month 18 was 0.02. Because there were two primary endpoints (only one of which needed to achieve statistical significance to meet the primary study objective) and two doses being tested, multiplicity adjustment was implemented with hierarchical testing. The inferential testing started with the two primary endpoints in comparing the OCA 25 mg and the placebo groups using the truncated Hochberg procedure (gamma = 0.1, critical values =0.011 and 0.01) with Type I error of 0.02.

If both primary endpoints achieved statistical significance at the OCA 25 mg dose level, the full alpha fraction was to be preserved and carried to compare the placebo and OCA 10 mg groups with respect to the primary endpoints using the truncated Hochberg procedure (gamma = 0.1). In this scenario, the placebo and OCA 10 mg groups were to be compared using the truncated Hochberg procedure with respect to the fibrosis and NASH primary efficacy endpoints with critical values of 0.011 and 0.01 against which the larger and smaller p-values were compared, respectively.

In the scenario where only one of the primary endpoints achieved statistical significance at the OCA 25 mg dose level (which occurred in Study 747-303), the preserved alpha of 0.009 was carried to compare the placebo and OCA 10 mg groups with respect to the primary endpoints using the truncated Hochberg procedure (gamma = 0.1). In this scenario, the placebo and OCA 10 mg groups were to be compared with respect to the fibrosis and NASH primary efficacy endpoints with critical values of 0.00495 and 0.0045 against which the larger and smaller p-values were compared, respectively.

Any subject who discontinued from the study prior to the Month 18 biopsy Visit and did not have a postbaseline biopsy assessment was considered a non-responder. Postbaseline biopsies collected for

subjects who discontinued treatment before the Month 18 Visit were included in the Month 18 Interim Analysis of histologic endpoints regardless of the timing of the biopsy.

The primary efficacy analysis at Month 18 compared OCA to placebo. The primary endpoints for the Month 18 Interim Analysis were as follows:

- Improvement of fibrosis by ≥1 stage with no worsening of NASH (no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis)
- Resolution of NASH with no worsening of fibrosis

The primary efficacy analysis at OCA 25 mg dose tested the following hypotheses using the ITT population:

- H01: The percentage of subjects with fibrosis improvement by 1 stage or more, no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis is equal between placebo and OCA 25 mg groups.
- H11: The percentage of subjects with fibrosis improvement by 1 stage or more, no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis is different between placebo and OCA 25 mg groups.
- H02: The percentage of subjects with NASH resolution and no worsening of fibrosis is equal between placebo and OCA 25 mg groups.
- H12: The percentage of subjects with NASH resolution and no worsening of fibrosis is different between placebo and OCA 25 mg groups.

The primary efficacy analysis at OCA 10 mg dose tested the following hypotheses using the ITT population:

- H01: The percentage of subjects with fibrosis improvement by 1 stage or more, no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis is equal between placebo and OCA 10 mg groups.
- H11: The percentage of subjects with fibrosis improvement by 1 stage or more, no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis is different between placebo and OCA 10 mg groups.
- H02: The percentage of subjects with NASH resolution and no worsening of fibrosis is equal between placebo and OCA 10 mg groups.
- H12: The percentage of subjects with NASH resolution and no worsening of fibrosis is different between placebo and OCA 10 mg groups.

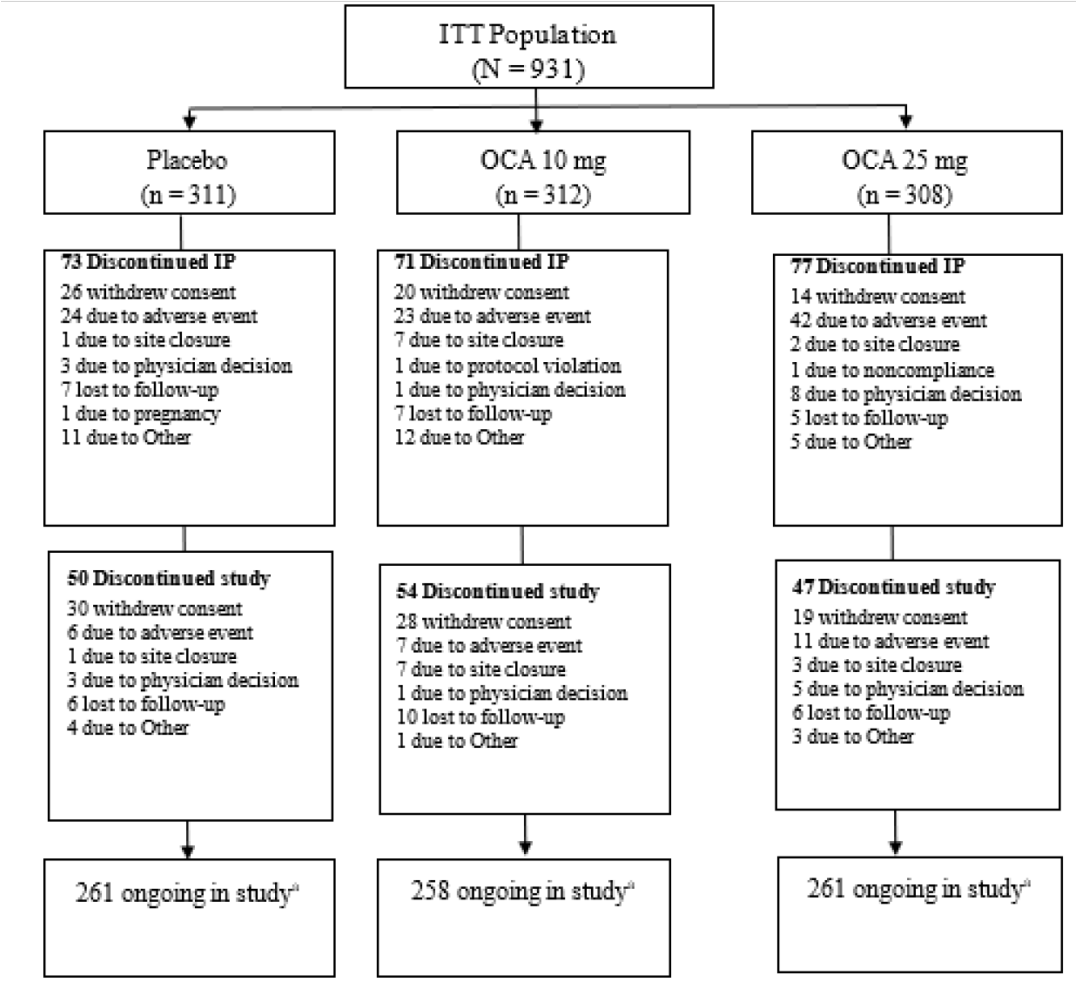
The secondary efficacy analyses compared placebo and each OCA dose separately (10 mg and 25 mg), using a CMH test stratified by randomization strata (diabetes at enrollment [yes/no] and use of TZDs or vitamin E at baseline [yes/no]). These analyses were conducted for the ITT, modified Intent-to-Treat (mITT), Per Protocol, and Full Efficacy Analysis populations.

Laboratory parameters (ALT, AST, GGT, ALP, total and direct bilirubin, albumin, INR, and platelets)

Results

Participant flow

Figure 44 Subject Disposition (ITT Population [N = 931])



[a] Ongoing includes subjects still on treatment and those who discontinued treatment but remain in the study.
ITT = intent-to-treat; IP = investigational product; OCA = obeticholic acid
Source: Table 14.1.1.2

First Subject Randomized: 09 December 2015

Date of Month 18 Interim Analysis Data Cut-Off: 26 October 2018

Last Subject Completed: Not Applicable, as the study is ongoing

Baseline data

Table 10 Demographic and Baseline Characteristics (ITT Population [N = 931])

	Placebo (N = 311)	OCA 10 mg (N = 312)	OCA 25 mg (N = 308)	Overall (N = 931)
Demographic Characteristics				
Mean (SD) age, years	54.5 (11.46)	54.7 (10.97)	55.0 (11.01)	54.7 (11.14)
Age subgroup, n (%)				
<65 years	246 (79)	249 (80)	251 (81)	746 (80)
≥65 years	65 (21)	63 (20)	57 (19)	185 (20)
≥75 years	2 (<1)	3 (<1)	2 (<1)	7 (<1)
Sex, n (%)				
Female	187 (60)	177 (57)	175 (57)	539 (58)
Male	124 (40)	135 (43)	133 (43)	392 (42)
Race, n (%)				
American Indian or Alaska Native	2 (<1)	0	5 (2)	7 (<1)
Asian	10 (4)	17 (6)	20 (7)	47 (6)
Black or African American	3 (1)	4 (1)	10 (3)	17 (2)
Native Hawaiian or Other Pacific Islander	1 (<1)	3 (1)	2 (<1)	6 (<1)
White	264 (94)	263 (92)	249 (87)	776 (91)
Ethnicity, n (%)				
Hispanic or Latino	52 (18)	42 (15)	47 (17)	141 (17)
Not Hispanic or Latino	230 (82)	244 (85)	235 (83)	709 (83)
Geographic region, n (%)				
Europe	69 (22)	72 (23)	68 (22)	209 (22)
North America	226 (73)	222 (71)	228 (74)	676 (73)
Rest of World	16 (5)	18 (6)	12 (4)	46 (5)
Mean (SD) BMI, kg/m^2	34.11 (5.92)	33.6 (5.56)	33.81 (5.38)	33.84 (5.62)
BMI subgroups, n (%)				
≥30 kg/m^2	232 (75)	227 (73)	233 (76)	692 (74)
≥35 kg/m^2	113 (36)	114 (37)	114 (37)	341 (37)
Disease Characteristics				
Fibrosis stage 2	142 (46)	130 (42)	139 (45)	411 (44)
Fibrosis stage 3	169 (54)	182 (58)	169 (55)	520 (56)
NAS, n (%)				
<6	94 (30)	101 (32)	100 (32)	295 (32)
≥6	215 (70)	211 (68)	208 (68)	634 (68)

	Placebo (N = 311)	OCA 10 mg (N = 312)	OCA 25 mg (N = 308)	Overall (N = 931)
Mean (SD) NAS	6.0 (1.12)	5.9 (1.10)	6.0 (1.07)	6.0 (1.10)
Mean (SD) steatosis score	1.9 (0.84)	1.9 (0.86)	1.9 (0.88)	1.9 (0.86)
Mean (SD) hepatocellular ballooning score	1.7 (0.45)	1.7 (0.46)	1.7 (0.44)	1.7 (0.45)
Mean (SD) lobular inflammation score	2.3 (0.75)	2.3 (0.72)	2.3 (0.72)	2.3 (0.73)
Stratification Factors				
Type 2 diabetes, n (%)	175 (56)	171 (55)	171 (56)	517 (56)
Concomitant TZD use	5 (2)	9 (3)	4 (1)	18 (2)
Concomitant Vitamin E use	42 (14)	34 (11)	32 (10)	108 (12)
Concomitant Medication Use				
Lipid lowering medication	175 (56)	170 (54)	160 (52)	505 (54)
Statins	144 (46)	142 (46)	127 (41)	413 (44)
Antidiabetic medications	167 (54)	171 (55)	159 (52)	497 (53)
Liver Biochemistry				
ALT (ULN = 55 U/L)				
≤ULN	128 (41)	130 (42)	114 (37)	372 (40)
>ULN to ≤3× ULN	159 (51)	163 (52)	175 (57)	497 (53)
>3× ULN	24 (8)	19 (6)	19 (6)	62 (7)
AST (ULN = 34 U/L)				
≤ULN	94 (30)	77 (25)	74 (24)	245 (26)
>ULN to ≤3× ULN	185 (59)	206 (66)	208 (68)	599 (64)
>3× ULN	32 (10)	29 (9)	26 (8)	87 (9)
Total Bilirubin (ULN = 20.5 µmol/L)				
≤ULN	296 (95)	300 (96)	284 (92)	880 (95)
>ULN	15 (5)	12 (4)	24 (8)	51 (5)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; ITT = intent-to-treat; NAFLD = nonalcoholic fatty liver disease; NAS = NAFLD activity score; OCA = obeticholic acid; SD = standard deviation; TZD = thiazolidinedione; ULN = upper limit of normal

Source: Table 14.1.3.2

Numbers analysed

At Month 18 Interim Analysis 1968 subjects randomized to investigational product had received at least1 dose of investigational product. These subjects comprised the Safety population.

The following analysis populations were evaluated and used for presentation and analysis of Month 18 Interim Analysis data:

Table 11

Population	Number of subjects	Fibrosis stage	Month 18 Interim Analysis
Safety	1968	1, 2 and 3	Randomized subjects who received ≥1dose of investigational product by the data cutoff (IA Cohort)
Full Efficacy Analysis	1218	1, 2 and 3	All subjects randomized by 15 Jul 2017 with any fibrosis stage (stage 1, 2, or 3) who received ≥1 dose of investigational product
ITT	931	2 and 3	Subset of the Full Efficacy Analysis population (includes subjects with fibrosis stage 2 and stage 3 only)

mITT	903	2 and 3	Subset of the ITT population excluding subjects who discontinued treatment (before the Month 18 Visit and without an end of treatment biopsy) between 13 Sep 2017 and 19 Dec 2017 due to withdrawal of consent, lost to follow up, and other reasons
PP	668	2 and 3	Subset of the ITT population who completed ≥15 months of treatment, had a Month 18/end of treatment biopsy, were on investigational product for ≥30 days immediately preceding the biopsy, and did not have any major protocol deviation

IA = interim analysis; ITT = Intent-to-Treat; mITT = modified Intent-to-Treat; PP = Per Protocol

The analysis populations for the Month 18 Interim Analysis are summarized by treatment group in table below.

Table 12 Month 18 Interim Analysis Populations by Treatment Group

	Fibrosis Stage	Placebo	OCA 10 mg	OCA 25 mg	Overall
All Randomized Subjects		657	653	658	1968
Safety	1, 2, and 3	657	653	658	1968
Full Efficacy Analysis	1, 2, and 3	407	407	404	1218
ITT	2 and 3	311	312	308	931
mITT	2 and 3	304	299	300	903
Per Protocol	2 and 3	224	226	218	668
PK	1, 2, and 3	0	25	32	57

ITT = intent-to-treat; mITT = modified intent-to-treat; OCA = obeticholic acid; PK = pharmacokinetic
Source: Table 14.1.1.1, Table 14.1.1.2, Table 14.1.1.3, Table 14.1.1.4, Table 14.1.1.5, and Table 14.1.1.6

Outcomes and estimation

Adequacy of liver biopsies used for histological evaluation

Liver biopsy specimens have a central role in the assessment of efficacy endpoints of 747-303 study, the primary efficacy endpoint is exclusively based on histological assessment of NASH and fibrosis. A systematic review defined the optimal liver biopsy as 20-25 mm in length and/or containing more than 11 complete portal tracts (1). Biopsies shorter than 20 mm and/or containing 6 to 10 complete portal tracts are considered "compromised" or "suboptimal" and those shorter than 10 mm and/or containing less than 6 complete portal tracts are considered "inadequate". Length criteria are considered even more important in NASH, due to the well-recognized regional variability. A diagnosis of definite NASH is more common in biopsies of at least 25 mm (2). 1) Cholongitas E, Senzolo M, Standish R, Marelli L, Quaglia A, Patch D et al. A systematic review of the quality of liver biopsy specimens. Am J Clin Pathol 2006;125(5):710-721. 2) Vuppalanchi R, Unalp A, Van Natta ML, Cummings OW, Sandrasegaran KE, Hameed T, et al. Effects of liver biopsy sample length and number of readings on sampling variability in nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:481-486.

Primary Endpoints:

Improvement of Fibrosis by ≥1 Stage with No Worsening of NASH

- The primary endpoint of the study was achieved in the OCA 25 mg group achieving an improvement in fibrosis by ≥1 stage with no worsening of NASH compared with placebo-treated

subjects (23.1% versus 11.9%, p = 0.0002). The OCA 25 mg: placebo response ratio was 1.94 (95% CI: 1.35, 2.78).

- 17.6% of subjects in the OCA 10 mg group achieved improvement of fibrosis by ≥1 stage with no worsening of NASH (p = 0.0446), with an OCA 10 mg: placebo response ratio of 1.48 (95% CI: 1.01, 2.18), thus providing evidence of a dose-response relationship.
- When the original definition was applied for the analysis of the primary endpoint of fibrosis improvement with no worsening of NASH (which excluded no worsening of steatosis), the overall response rates and the level of statistical significance compared with placebo were higher than those of the primary analysis that included steatosis as a component of NASH (26.9% for OCA 25 mg versus 13.5% for placebo, p <0.0001). The OCA 25 mg: placebo response ratio was 1.99 (95% CI: 1.43, 2.78).

Resolution of NASH with No Worsening of Fibrosis

- A greater percentage of subjects in the OCA 25 mg group (11.7%) achieved the second primary endpoint of resolution of NASH with no worsening of fibrosis compared with the placebo group (8.0%), but the difference was not statistically significant (p = 0.1268). The OCA 25 mg: placebo response ratio was 1.45 (95% CI: 0.90, 2.35). In the OCA 10 mg group, 11.2% of subjects achieved resolution of NASH with no worsening of fibrosis (p = 0.1814), with an OCA 10 mg: placebo response ratio of 1.39 (95% CI: 0.86, 2.25).
- When NASH resolution was defined based on pathologist's overall assessment, a significantly greater proportion of subjects in the OCA 25 mg group (23.1%) achieved NASH resolution based on absence of definite NASH with no worsening of fibrosis as compared with placebo (12.2%, p = 0.0004). The OCA 25 mg:placebo response ratio was 1.89 (95% CI: 1.32, 2.70).

Table 13 Summary of Primary Efficacy Endpoints (ITT Population [N = 931])

Endpoint	Placebo (N = 311)	OCA 10 mg (N = 312)	OCA 25 mg (N = 308)
Improvement of Fibrosis by ≥1 Stage with No Worsening of NASH[a]			
Number (%) of Responders	37 (11.9%)	55 (17.6%)	71 (23.1%)
Treatment Difference[b] (95% CI)	-	5.7% (0.2%, 11.3%)	11.1% (5.3%, 17.0%)
OCA:Placebo Response Ratio[c] (95% CI)	-	1.48 (1.01, 2.18)	1.94 (1.35, 2.78)
p-value Versus Placebo[d]	-	0.0446	0.0002
Resolution of NASH[e] with No Worsening of Fibrosis			
Number (%) of Responders	25 (8.0%)	35 (11.2%)	36 (11.7%)
Treatment Difference[b] (95% CI)	-	3.1% (-1.4%, 7.7%)	3.6% (-1.0%, 8.3%)
OCA:Placebo Response Ratio[c] (95% CI)	-	1.39 (0.86, 2.25)	1.45 (0.90, 2.35)
p-value Versus Placebo[d]	-	0.1814	0.1268

CI = confidence interval; ITT = intent-to-treat; NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; TZD = thiazolidinedione

Note: The ITT population comprised subjects in the Month 18 Interim Analysis Cohort with liver fibrosis stage 2 or stage 3 who were randomized by 15 July 2017 and received ≥1 dose of investigational product. Fibrosis stage is defined using the NASH CRN criteria. Baseline NASH CRN fibrosis stage, steatosis, lobular inflammation, and hepatocyte ballooning are defined using the findings of the centrally read biopsy slide used to determine study eligibility (ie, the unpaired screening read).

The analysis used the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).

[a] No worsening of NASH is defined as no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis.

[b] Common Treatment Risk Difference = 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 method is used to construct the confidence intervals

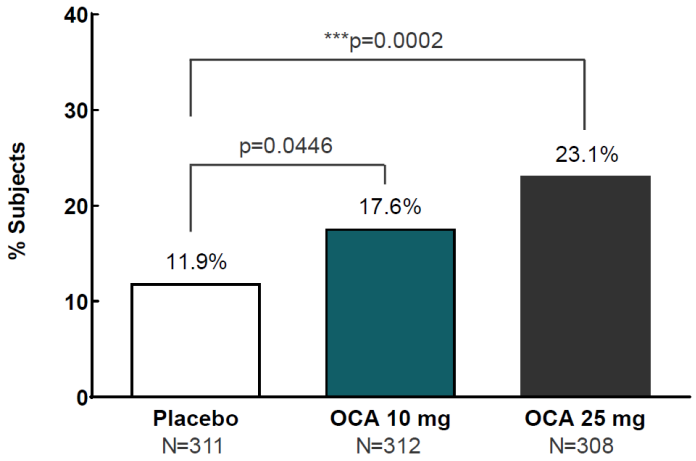
[c] Common Treatment / Placebo Response Ratio = Percentage of Responders in Active Treatment Arm / Percentage of Responders in Placebo, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no); the Mantel-Haenszel estimate of the common odds ratio and the associated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

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

[e] Resolution of NASH is defined as the overall histopathologic interpretation of (1) "no fatty liver disease" or (2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a NAS of 0 for ballooning and 0 to 1 for inflammation.

Source: Table 14.2.1.1.1

Figure 45 Primary Efficacy Endpoint: Improvement of Fibrosis by ≥1 Stage with No Worsening of NASH (ITT Population [N = 931])



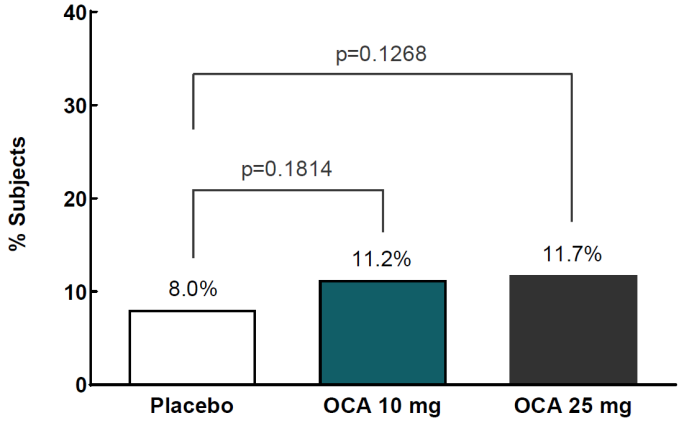
CRN = Clinical Research Network; ITT = intent-to-treat; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; TZD = thiazolidinedione

Notes: Fibrosis stage is defined using the NASH CRN criteria. Baseline NASH CRN fibrosis stage, steatosis, lobular inflammation, and hepatocyte ballooning are defined using the findings of the centrally read biopsy slide used to determine study eligibility (ie, the unpaired screening read).

The analysis used the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).

Source: Table 14.2.1.1.1

Figure 46 Primary Efficacy Endpoint: NASH Resolution with No Worsening of Fibrosis (ITT Population [N = 931])



CRN = Clinical Research Network; ITT = intent-to-treat; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; TZD = thiazolidinedione
Notes: Fibrosis stage is defined using the NASH CRN criteria. Baseline NASH CRN fibrosis stage, steatosis, lobular inflammation, and hepatocyte ballooning are defined using the findings of the centrally read biopsy slide used to determine study eligibility (ie, the unpaired screening read).
The analysis used the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).
Source: Table 14.2.1.1.1

Reproducibility of Results

For each primary endpoint, consistent results were observed across all analysis populations, and results were confirmed by sensitivity analyses. In general, the greatest response in fibrosis improvement by ≥1 stage with no worsening of NASH was observed in the PP population, whereas the greatest response in NASH resolution with no worsening of fibrosis was observed in the Full Efficacy Analysis population, which also included earlier stage subjects (fibrosis stage 1).

Key Secondary Endpoint

Improvement of Fibrosis by ≥1 Stage and/or Resolution of NASH Without Worsening of Either:

- In the OCA 25 mg group, nearly twice as many subjects (27.3%) achieved the key secondary endpoint compared to the placebo group (15.8%; p = 0.0005). The OCA 25 mg:placebo response ratio was 1.73 (95% CI: 1.27, 2.36).
- Higher response rates were observed for the key secondary endpoint when NASH resolution was evaluated based on pathologist's overall assessment, with more than one third of the subjects in OCA 25 mg group achieving the key secondary endpoint (34.7%) compared to the placebo group (18.3%; p <0.0001).
- Similar results were observed across analysis populations and were confirmed by sensitivity analyses.

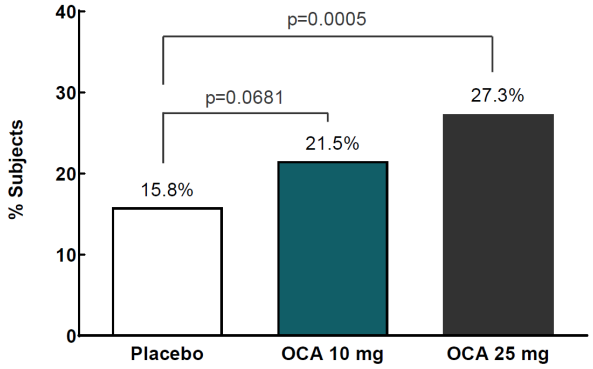
For the study to meet the primary efficacy objective, at least one of the two primary efficacy endpoints needed to achieve statistical significance.

The primary efficacy analysis was based on the Intent-to-Treat (ITT) population. The Month 18 Interim Analysis for the primary histologic endpoints was performed with an alpha level of 0.02. The primary clinical outcomes composite endpoint will be tested with a minimum alpha level of 0.03 to maintain the overall type I error at 0.05.

Results for the key secondary endpoint are presented with a nominal p-value as reference due to the fact that the hypothesis test could not be performed according to the pre-specified procedure. The percentage of subjects in the ITT population who achieved improvement of fibrosis by ≥1 stage and/or resolution of NASH without worsening of either was higher in the OCA 25 mg group (27.3%) than in the placebo group (15.8%, p = 0.0005). The OCA 25 mg:placebo response ratio was 1.73 (95% CI: 1.27, 2.36). Data are presented below.

Similar results were observed across the other analysis populations.

Figure 47 Key Secondary Endpoint: Improvement of Fibrosis by ≥1 Stage and/or Resolution of NASH Without Worsening of Either (ITT Population [N = 931])



CRN = Clinical Research Network; ITT = intent-to-treat; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; TZD = thiazolidinedione
Notes: Fibrosis stage is defined using the NASH CRN criteria. Baseline NASH CRN fibrosis stage, steatosis, lobular inflammation, and hepatocyte ballooning are defined using the findings of the centrally read biopsy slide used to determine study eligibility (ie, the unpaired screening read).
The analysis used the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).
Source: Table 14.2.2.1.1

Table 14 Key Secondary Endpoint: Improvement of Fibrosis by ≥1 Stage and/or Resolution of NASH Without Worsening of Either (ITT Population [N = 931])

	Placebo (N = 311)	OCA 10 mg (N = 312)	OCA 25 mg (N = 308)
Number (%) of Responders	49 (15.8%)	67 (21.5%)	84 (27.3%)
Treatment Difference[a] (95% CI)	-	5.7% (-0.4%, 11.8%)	11.5% (5.1%, 17.8%)
OCA:Placebo Response Ratio[b] (95% CI)	-	1.36 (0.98, 1.90)	1.73 (1.27, 2.36)
p-value Versus Placebo[c]	-	0.0681	0.0005

CI = confidence interval; CRN = Clinical Research Network; ITT = intent-to-treat; NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; TZD = thiazolidinedione
Notes: Resolution of NASH is defined as the overall histopathologic interpretation of (1) "no fatty liver disease" or (2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a NAS of 0 for ballooning and 0 to 1 for inflammation. Fibrosis stage is defined using the NASH CRN criteria. Baseline NASH CRN fibrosis stage, steatosis, lobular inflammation, and hepatocyte ballooning are defined using the findings of the centrally read biopsy slide used to determine study eligibility (ie, the unpaired screening read).
The ITT population comprised subjects in the Month 18 Interim Analysis Cohort with liver fibrosis stage 2 or stage 3 who were randomized by 15 July 2017 and received ≥1 dose of investigational product.
[a] Common treatment risk difference = percentage of responders in the active treatment group - percentage of responders in the placebo group, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no). The Mantel-Haenszel method is used to construct the CIs.
[b] Common treatment/placebo response ratio = percentage of responders in the active treatment group/percentage of responders in the placebo group, 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).
Source: Table 14.2.2.1.1

Table 15 Key Secondary Endpoint: OCA:Placebo Response Ratios by Analysis Population

OCA:Placebo Response Ratio (95% CI) p-value	Analysis Populations		
	ITT	Full Efficacy	Per Protocol
OCA 10 mg	1.36 (0.98, 1.90) 0.0681	1.35 (1.00, 1.82) 0.0502	1.44 (1.01, 2.05) 0.0407
OCA 25 mg	1.73 (1.27, 2.36) 0.0005	1.86 (1.40, 2.45) <0.0001	1.80 (1.29, 2.51) 0.0004

CI = confidence interval; ITT = intent-to-treat; OCA = obeticholic acid; TZD = thiazolidinedione
Note: Common treatment/placebo response ratio = percentage of responders in the active treatment group/percentage of responders in the placebo group, 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.
Source: Tables 14.2.2.1.1, 14.2.2.1.3, and 14.2.2.1.4

Other Secondary Histologic Endpoints:

This section summarizes the other secondary histologic endpoints, with a focus on the ITT and Per Protocol populations, and is organized as follows:

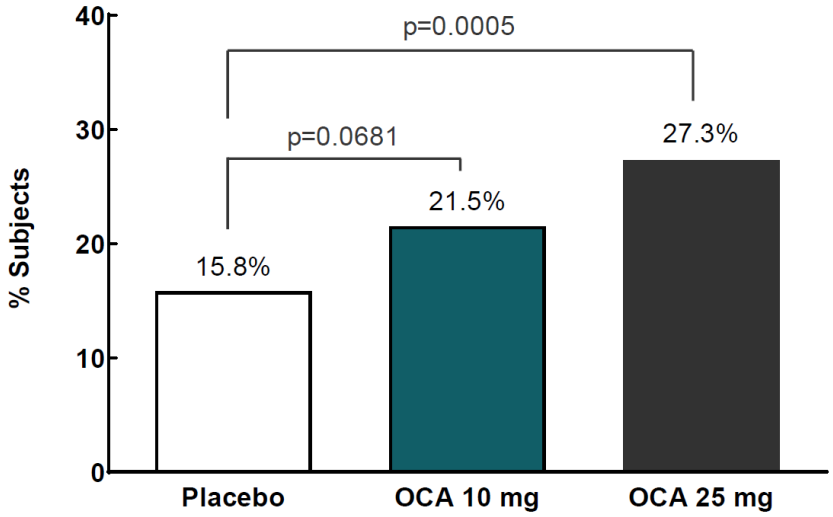
- Fibrosis-related secondary endpoints
- NASH-related secondary endpoints
- Composite endpoints

All p-values are provided as nominal p-values.

Fibrosis-Related Secondary Endpoints

Results of the analysis of fibrosis-related secondary endpoints substantiate the dose-dependent antifibrotic effect of OCA as demonstrated on the primary endpoint. Results for the Per Protocol and Full Efficacy Analysis populations were consistent with the ITT population.

Figure 48 Fibrosis-Related Secondary Histologic Endpoints (ITT Population [N = 931])



CRN = Clinical Research Network; ITT = intent-to-treat; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; TZD = thiazolidinedione
Notes: Fibrosis stage is defined using the NASH CRN criteria. Baseline NASH CRN fibrosis stage, steatosis, lobular inflammation, and hepatocyte ballooning are defined using the findings of the centrally read biopsy slide used to determine study eligibility (ie, the unpaired screening read).
The analysis used the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).
Source: Table 14.2.2.1.1

Table 16 Histological Fibrosis-Related Secondary Endpoints: OCA:Placebo Response Ratios by Analysis Population

Analysis Population	Number of Responders/Number of Subjects (% Responders) OCA:Placebo Response Ratio (95% CI) p-value			
	Improvement of Fibrosis by ≥2 Stages	Improvement of Fibrosis by ≥2 Stages and No Worsening of NASH	Resolution of Fibrosis	Progression to Cirrhosis
ITT				
Placebo	15/311 (4.8%)	12/311 **(3.9%)**	4/311 (1.3%)	15/311 (4.8%)
OCA 10 mg	19/312 (6.1%) 1.26 (0.65, 2.42) **0.4918**	17/**312 (5.4%)** **1.41 (0.69, 2.88)** **0.3496**	8/312 (2.6%) 1.97 (0.61, 6.39) 0.2499	16/312 (5.1%) 1.07 (0.54, 2.12) 0.8477
OCA 25 mg	30/308 (9.7%) 2.02 (1.11, 3.66) 0.0183	24/308 (7.8%) 2.02 (1.03, 3.94) 0.0363	10/308 (3.2%) 2.52 (0.81, 7.89) 0.0995	12/308 (3.9%) 0.81 (0.38, 1.69) 0.5681
Per Protocol				
Placebo	10/224 (4.5%)	8/224 (3.6%)	4/224 (1.8%)	13/224 (5.8%)
OCA 10 mg	16/226 (7.1%) 1.62 (0.75, 3.49) 0.2167	14/226 (6.2%) 1.77 (0.76, 4.14) 0.1823	8/226 (3.5%) 2.07 (0.64, 6.66) 0.2128	12/226 (5.3%) 0.91 (0.42, 1.94) 0.8029
OCA 25 mg	29/218 (13.3%) 3.05 (1.52, 6.08) 0.0008	23/218 (10.6%) 3.02 (1.38, 6.59) 0.0034	9/218 (4.1%) 2.36 (0.74, 7.56) 0.1350	9/218 (4.1%) 0.71 (0.31, 1.63) 0.4192
Full Efficacy				
Placebo	15/407 (3.7%)	12/407 (2.9%)	15/407 (3.7%)	15/407 (3.7%)
OCA 10 mg	19/407 (4.7%) 1.27 (0.66, 2.46) 0.4746	17/407 (4.2%) 1.42 (0.69, 2.92) 0.3387	18/407 (4.4%) 1.21 (0.62, 2.36) 0.5712	16/407 (3.9%) 1.05 (0.53, 2.09) 0.8786
OCA 25 mg	30/404 (7.4%) 2.04 (1.12, 3.72) 0.0168	24/404 (5.9%) 2.04 (1.04, 4.00) 0.0342	25/404 (6.2%) 1.74 (0.93, 3.27) 0.0787	12/404 (3.0%) 0.79 (0.38, 1.65) 0.5236

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

Notes: Fibrosis stage is defined using the NASH CRN criteria. Baseline NASH CRN fibrosis stage is defined using the findings of the centrally read biopsy slide used to determine study eligibility (ie, the unpaired screening read).

Note: Common treatment/placebo response ratio = percentage of responders in the active treatment group/percentage of responders in the placebo group, 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.

The analysis used the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).

Source: Tables 14.2.3.1.1, 14.2.3.1.3, 14.2.3.1.4, 14.4.2.1, 14.4.2.2, and 14.4.2.3

Shifts in Fibrosis Stage

Among subjects in the ITT population with available biopsy data at Month 18, 3 times as many subjects in the OCA 25 mg group had improved fibrosis (37.1%) as opposed to worsening fibrosis (13.5%), compared with a 1:1 ratio of improvement (22.8%) versus worsening (20.9%) with placebo (Figure 16), representing an approximate 14% favorable difference for the OCA 25 mg group compared to the placebo group, and an approximate 7% greater risk of worsening in the placebo group compared to the OCA 25 mg group. A dose response was observed in the OCA groups, with 27.8% of subjects in the OCA 10 mg group achieving a ≥1-stage improvement and 16.7% of subjects having a ≥1-stage worsening in fibrosis.

Figure 49 Shifts in Fibrosis Stage (ITT Population, Subjects with Baseline and Month 18 Biopsies [N = 777])

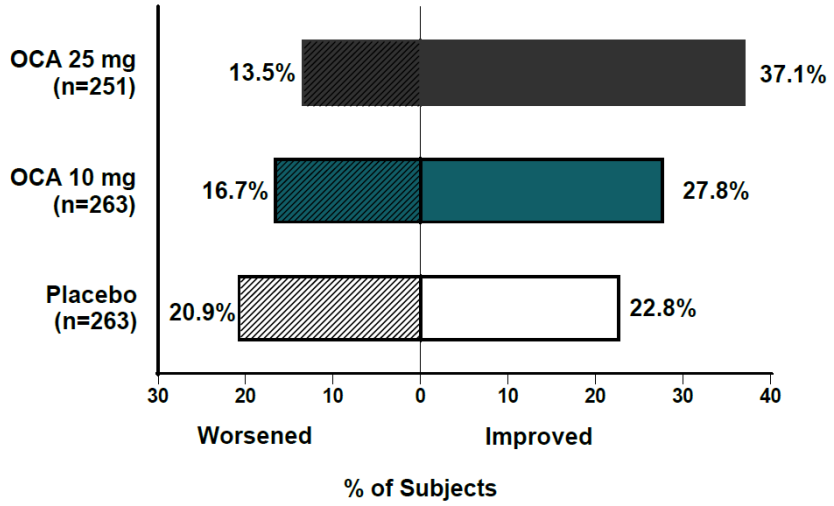


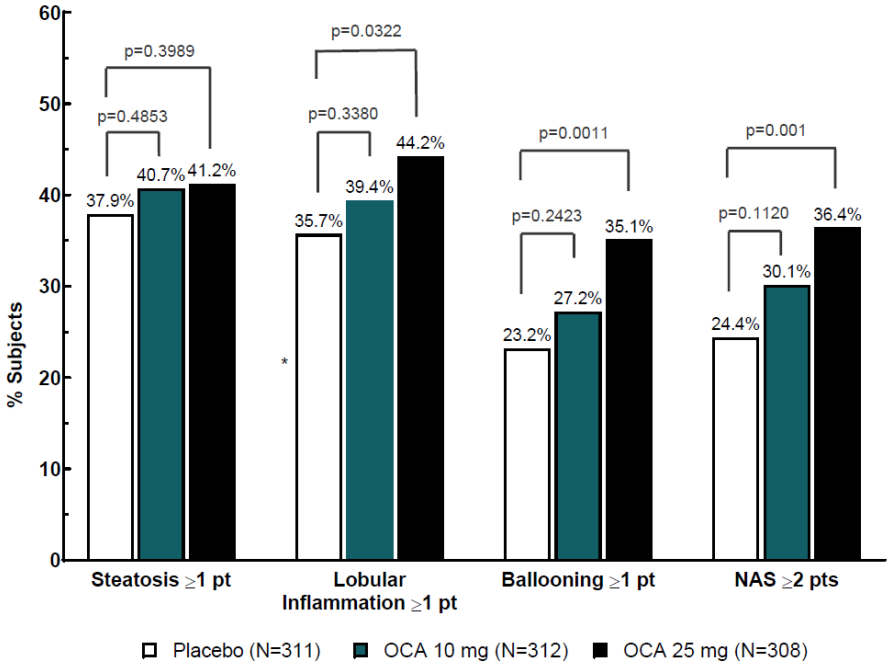
Table 17 Shifts in Fibrosis Stage (Full Efficacy Analysis Population, Subjects with Baseline and Month 18 Biopsies [N = 1011])

Fibrosis Stage at Month 18			Fibrosis Stage at Baseline		
			Stage 1 n = 79 (placebo) n = 77 (OCA 10 mg) n = 78 (OCA 25 mg)	Stage 2 n = 121 (placebo) n = 105 (OCA 10 mg) n = 115 (OCA 25 mg)	Stage 3 n = 142 (placebo) n = 158 (OCA 10 mg) n = 136 (OCA 25 mg)
Placebo (N=342)	0	(n = 15)	11	3	1
	1	(n = 60)	22	27	11
	2	(n = 102)	34	50	18
	3	(n = 150)	12	40	98
	4	(n = 15)	0	1	14
OCA 10 mg (N=340)	0	(n = 18)	10	8	0
	1	(n = 72)	34	27	11
	2	(n = 90)	24	39	27
	3	(n = 144)	9	28	107
	4	(n = 16)	0	3	13
OCA 25 mg (N=329)	0	(n = 25)	15	8	2
	1	(n = 90)	33	37	20
	2	(n = 91)	20	45	26
	3	(n = 111)	10	22	79
	4	(n = 12)	0	3	9

CRN = Clinical Research Network; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid
Note: Legend: improved; no change; worsened.
Fibrosis stage is defined using the NASH CRN criteria.
Baseline NASH CRN fibrosis stage is defined using the findings of the centrally read biopsy slide used to determine study eligibility (ie, the unpaired screening read).
Source: CSR 747-303 18Mo IA, Section 14, Table 14.2.9

NASH-Related Endpoints

Figure 50 NASH-Related Histologic Secondary Endpoints (ITT Population [N = 931])



CRN = Clinical Research Network; ITT = intent-to-treat; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; pt = point; TZD = thiazolidinedione
Notes: Baseline NASH CRN steatosis, lobular inflammation, and hepatocyte ballooning are defined using the findings of the centrally read biopsy slide used to determine study eligibility (ie, the unpaired screening read).
The analysis used the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no).
Source: Tables 14.2.4.1.1 and 14.2.5.1.1

Similar to the fibrosis shift analysis, a greater percentage of OCA-treated subjects compared to placebo-treated subjects had improvement in lobular inflammation (54% versus 43%), hepatocellular ballooning (42.8% versus 27.6%), and NAS (70.6% versus 55.2%). Conversely, a greater percentage of subjects in the placebo group had worsening or no change in histological features of NASH and NAS as compared to OCA-treated subjects.

Endpoints Related to Fibrosis and NASH

Additional secondary and exploratory histologic endpoints evaluated the simultaneous effects on both fibrosis and steatohepatitis in the same subjects.

- More subjects treated with OCA 25 mg demonstrated no worsening of fibrosis and no worsening of NASH compared to placebo (47.7% versus 37.6%; p = 0.0109). Halting of disease progression was dose dependent.
- More subjects treated with OCA 25 mg demonstrated an improvement in the composite endpoint of improvement of fibrosis by ≥1 stage AND resolution of NASH compared to placebo (7.5% versus 4.2%; p = 0.0796).
- OCA elicited greater improvement in the total SAF score (which comprised steatosis [NASH CRN scoring], activity [NASH CRN lobular inflammation score + hepatocellular ballooning score], and fibrosis stage [NASH CRN]) as compared to placebo. Reductions of ≥2 points in the total SAF score were achieved by 35.1% of subjects in the OCA 25 mg group (p = 0.0005 versus placebo), 27.6% of subjects in the OCA 10 mg group (p = 0.1475 versus placebo), and 22.5% of subjects in the placebo group.

Ancillary analyses

Sensitivity Analysis

A sensitivity analysis was conducted for the primary endpoint of fibrosis improvement with no worsening of NASH. The sensitivity analysis examined the effect of non-responder imputation for subjects in the ITT population who did not have a biopsy at Month 18 or at the time of early termination. Results of this completer analysis, which excluded subjects without a Month 18 biopsy, were consistent with those of the ITT population, suggesting that the imputation of no response for missing biopsies did not materially affect the conclusions of the primary analysis for the overall ITT population. As it is limited to subjects with available post-baseline biopsies for analysis, the response rate of 27.8% in the OCA 25 mg group is reflective of a true response rate and represents an increase of approximately 20% above the response rate of 23.1% for the ITT population.

Table 18 Sensitivity Analysis of Improvement of Fibrosis by ≥1 Stage with No Worsening of NASH (ITT Population Completer Analysis)

	Placebo (N = 311)	OCA 10 mg (N = 312)	OCA 25 mg (N = 308)
Number of Completers[a]	244	244	237
Number (%) of Responders	33 (13.5%)	48 (19.7%)	66 (27.8%)
Treatment Difference (95% CI)[b]	-	6.2% (-0.3%, 12.8%)	14.4% (7.3%, 21.5%)
OCA/Placebo Response Ratio (95% CI)[c]	-	1.46 (0.97, 2.21)	2.07 (1.42, 3.01)
p-value Versus Placebo[d]	-	0.0656	<0.0001

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

Notes: Fibrosis stage is defined using the NASH CRN criteria. Baseline NASH CRN fibrosis stage, steatosis, lobular inflammation, and hepatocyte ballooning are defined using the findings of the centrally read biopsy slide used to determine study eligibility (ie, the unpaired screening read).

[a] Includes subjects who completed 18 months of treatment and had a postbaseline biopsy performed within the Month 18 biopsy window (ie, 420 and 672 days).

[b] Common treatment risk difference = percentage of responders in the active treatment group - percentage of responders in the placebo group, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no). The Mantel-Haenszel method is used to construct the CIs.

[c] Common treatment/placebo response ratio = percentage of responders in the active treatment group/percentage of responders in the placebo group, 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.

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

Source: Table 14.2.1.13

A sensitivity analysis of completers was conducted for the endpoint of NASH resolution with no worsening of fibrosis in which subjects who did not have a Month 18 biopsy were excluded. Results of the completer analysis were consistent with those of the ITT population.

Table 19 Sensitivity Analysis of NASH Resolution with No Worsening of Fibrosis (ITT Population Completers Analysis)

Endpoint	Placebo (N = 311)	OCA 10 mg (N = 312)	OCA 25 mg (N = 308)
Number of Completers[a]	244	244	237
Number (%) of Responders	25 (10.2%)	33 (13.5%)	32 (13.5%)
Treatment Difference (95% CI)[b]	-	3.3% (-2.4%, 9.0%)	3.4% (-2.3%, 9.1%)
OCA/Placebo Response Ratio (95% CI)[c]	-	1.32 (0.82, 2.15)	1.33 (0.82, 2.17)
p-value Versus Placebo[d]	-	0.2553	0.2461

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

Notes: Fibrosis stage is defined using the NASH CRN criteria. Baseline NASH CRN fibrosis stage, steatosis, lobular inflammation, and hepatocyte ballooning are defined using the findings of the centrally read biopsy slide used to determine study eligibility (ie, the unpaired screening read).

[a] Includes subjects who completed 18 months of treatment and had a postbaseline biopsy performed within the Month 18 biopsy window (ie, 420 and 672 days).

[b] Common treatment risk difference = percentage of responders in the active treatment group - percentage of responders in the placebo group, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no). The Mantel-Haenszel method is used to construct the CIs.

[c] Common treatment/placebo response ratio = percentage of responders in the active treatment group/percentage of responders in the placebo group, 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.

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

Source: Table 14.2.1.13

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20 Summary of efficacy for trial 747-303

Title: A Phase 3, Double-Blind, Randomized, Long-Term, Placebo-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Obeticholic Acid in Subjects with Nonalcoholic Steatohepatitis		
Study identifier	747-303; EudraCT number 2015-002560-16; ClinicalTrials.gov identifier NCT02548351	
Design	This Phase 3, double-blind, randomized, long-term, placebo-controlled, multicenter, international study is designed to evaluate the effect of OCA on histological improvements of NASH, all-cause mortality, and liver-related clinical outcomes. The Month 18 Interim Analysis was performed after a planned minimum of 750 randomized subjects with fibrosis stage 2 or stage 3 reached their actual/planned Month 18 visit (including subjects who discontinued before reaching the planned Month 18 visit). The study is continuing according to protocol (ie, as a double-blind, placebo-controlled study), and subjects will be followed over an extended period for clinical outcomes to confirm clinical benefit as part of the End of Study (EOS) analysis.	
	Duration of main phase:	~7.5 years (EOS analysis)
	Duration of run-in phase:	≤12 weeks (Screening period)
	Duration of extension phase:	Not applicable
Hypothesis	Superiority of OCA for NASH (fibrosis stage 2 and 3) vs placebo (Month 18 Interim Analysis)	
Treatments groups	Placebo	PO, QD, N=657

	OCA 10 mg		PO, QD, N=653
	OCA 25 mg		PO, QD, N=658
Endpoints and definitions	Month 18 primary endpoint	Fibrosis improvement	Improvement of fibrosis by ≥1 stage with no worsening of NASH (no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis) per the NASH CRN scoring criteria
	Month 18 primary endpoint	NASH resolution	Resolution of NASH with no worsening of fibrosis NASH resolution is defined as the overall histopathologic interpretation of (1) "no fatty liver disease" or (2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a NAFLD activity score (NAS) of 0 for ballooning and 0 to 1 for inflammation
	Month 18 key secondary endpoint	Key secondary	Improvement of fibrosis by ≥1 stage AND/OR resolution of NASH[a], without worsening of either
Database lock	05 Feb 2019		

Results and Analysis for the Month 18 Interim Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT population defined as all subjects, randomized by 15 July 2017, fibrosis stages 2 and 3, who received ≥1 dose of investigational product			
Descriptive statistics and estimate variability	Treatment group	Placebo	OCA 10 mg	OCA 25 mg
	Number of subjects	311	312	308
	Fibrosis improvement [Number (%) of responders]	37 (11.9%)	55 (17.6%)	71 (23.1%)
	Treatment difference[b] (95% CI)	Not Applicable	5.7% (0.2%, 11.3%)	11.1% (5.3%, 17.0%)
	NASH resolution[a] [Number (%) of responders]	25 (8.0%)	35 (11.2%)	36 (11.7%)
	Treatment difference[b] (95% CI)	Not applicable	3.1% (-1.4%, 7.7%)	3.6% (-1.0%, 8.3%)
	Key secondary[a] [Number (%) of responders]	49 (15.8%)	67 (21.5%)	84 (27.3%)
	Treatment difference[b] (95% CI)	Not Applicable	5.7% (-0.4%, 11.8%)	11.5% (5.1%, 17.8%)
Effect estimate per comparison	Fibrosis improvement	Comparison groups	OCA 10 mg: Placebo	OCA 25 mg: Placebo
		Response ratio	1.48	1.94
		95% CI	1.01, 2.18	1.35, 2.78

		p-value	0.0446	0.0002
	NASH resolution[a]	Comparison groups	OCA 10 mg: Placebo	OCA 25 mg: Placebo
		Response ratio	1.39	1.45
		95% CI	0.86, 2.25	0.90, 2.35
		p-value	0.1814	0.1268
	Key secondary[a]	Comparison groups	OCA 10 mg: Placebo	OCA 25 mg: Placebo
		Response ratio	1.36	1.73
		95% CI	0.98, 1.90	1.27, 2.36
		p-value	0.0681	0.0005
Analysis description	**Secondary Histologic Analysis**			
	Treatment group	Placebo	OCA 10 mg	OCA 25 mg
	Number of subjects	311	312	308
Improvement of fibrosis by ≥2 stages	Number (%) of responders	15 (4.8%)	19 (6.1%)	30 (9.7%)
	RR (95% CI) CMH p-value	NA	1.26 (0.65, 2.42) 0.4918	2.02 (1.11, 3.66) 0.0183
Improvement of NAS ≥2-points with no worsening of fibrosis	Number (%) of responders	76 (24.4%)	94 (30.1%)	112 (36.4%)
	RR (95% CI) CMH p-value	NA	1.23 (0.95, 1.59) 0.1120	1.49 (1.17, 1.90) 0.0012
≥1-point improvement in hepatocellular ballooning	Number (%) of responders	72 (23.2%)	85 (27.2%)	108 (35.1%)
	RR (95% CI) CMH p-value	NA	1.18 (0.90, 1.54) 0.2423	1.51 (1.18, 1.95) 0.0011
≥1-point improvement in lobular inflammation	Number (%) of responders	111 (35.7%)	123 (39.4%)	136 (44.2%)
	RR (95% CI) CMH p-value	NA	1.10 (0.90, 1.35) 0.3380	1.24 (1.02, 1.50) 0.0322
≥1-point improvement in steatosis	Number (%) of responders	118 (37.9%)	127 (40.7%)	127 (41.2%)
	RR (95% CI) CMH p-value	NA	1.07 (0.88, 1.30) 0.4853	1.09 (0.90, 1.32) 0.3989
Improvement of fibrosis ≥1-stage and resolution of NASH[a,c]	Number (%) of responders	13 (4.2%)	23 (7.4%)	23 (7.5%)
	RR (95% CI) CMH p-value	NA	1.76 (0.91, 3.40) 0.0896	1.78 (0.92, 3.43) 0.0796
No worsening of fibrosis and no worsening of NASH[a,c]	Number (%) of responders	117 (37.6%)	127 (40.7%)	147 (47.7%)
	RR (95% CI) CMH p-value	NA	1.08 (0.89, 132) 0.4333	1.27 (1.06, 1.52) 0.0109

Analysis description	Other Histologic Analysis (Post-hoc)			
	Treatment group	Placebo	OCA 10 mg	OCA 25 mg
	Number of subjects	311	312	308
Resolution of NASH with no worsening of fibrosis[e]	Number (%) of responders	38 (12.2%)	51 (16.3%)	71 (23.1%)
	RR (95% CI) CMH p-value	NA	1.33 (0.91, 1.96) 0.1433	1.89 (1.32, 2.70) 0.0004

Notes:
CI = confidence interval, CMH = Cochran-Mantel-Haenszel test, NA = not applicable, RR = Response ratio (OCA:placebo response ratio)
[a] NASH resolution is defined as the overall histopathologic interpretation of (1) "no fatty liver disease" or (2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a nonalcoholic fatty liver disease (NAFLD) activity score (NAS) of 0 for ballooning and 0 to 1 for inflammation
[b] Common treatment risk difference = percentage of responders in the active treatment group - percentage of responders in the placebo group, 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] As defined by both endpoints being met in the same subject
[e] NASH resolution is defined as the absence of steatohepatitis based on pathologist's diagnostic assessment of the overall pattern of injury.

Analysis performed across trials (pooled analyses and meta-analysis)

An integrated efficacy database was constructed from the 2 long-term controlled studies (Study 747-303 and FLINT). For FLINT, only the FLINT (747-303-matched) Intent-to-Treat population (ITT), similar with respect to disease characteristics, was included. This matched subpopulation does not include subjects who did not have a Month 18 biopsy due to the modification of the protocol, resulting from early termination of the trial for efficacy.

The Full Efficacy Analysis population from Study 747-303 consists of 1218 subjects at all fibrosis stages who were randomized by 15 July 2017 and received ≥1 dose of IP.

For FLINT, the Full Efficacy Analysis population consists of 203 subjects, including the 747-303-matched ITT population as well as subjects with fibrosis stage 1 who had at least one of the following risk factors: obesity, type 2 diabetes, or ALT >1.5xULN.

The pooled analysis populations included the corresponding subjects from the placebo and OCA 25 mg groups from Study 747-303 and the FLINT study. As the OCA 10 mg dose was not administered in the FLINT study, it was not included in the pooled analyses. The pooled ITT population includes 747 subjects (374 subjects in the placebo group and 373 subjects in the OCA 25 mg group). The pooled PP population includes 557 subjects (279 subjects in the placebo group and 278 subjects in the OCA 25 mg group); the pooled Full Efficacy Analysis population includes 1014 subjects (515 subjects in the placebo group and 499 subjects in the OCA 25 mg group).

Inclusion and Exclusion criteria

Inclusion criteria for FLINT were somehow less stringent: for inclusion was required histologic evidence of definite or probable NASH based upon a liver biopsy obtained no more than 90 days prior to randomization and a NAS of 4 or greater with at least one in each component of the NAS score (steatosis scored 0 to 3, hepatocellular ballooning degeneration scored 0-2, and lobular inflammation scored 0 to 3).

Exclusion criteria were similar but not completely overlapping with Study 747-303.

Analysis of results

To facilitate the integration of efficacy data from Study 747-303 and FLINT, an efficacy subset of subjects from the FLINT study who are representative of the ITT population in Study 747-303 (referred to as the 747-303-matched ITT population) was defined.

Participants in the FLINT study who received at least one dose of IP and met the following criteria (based on local biopsies for determination of eligibility) at their randomization visit were included in the 747-303- matched ITT population:

1. Histologic evidence of definite steatohepatitis
2. Presence of all three key histologic features comprising the NAFLD Activity Score (NAS) with a score of at least one for each and a combined score of 4 or greater according to NASH CRN criteria
3. Histologic evidence of fibrosis stage 2 or 3 as defined by NASH CRN criteria
4. Would have reached the planned Month 18 biopsy at the time of study cessation due to protocol modification

A pooled analysis was performed on a population including the corresponding subjects from the placebo and OCA 25 mg groups from Study 747-303 and the FLINT study. As the OCA 10 mg dose was not administered in the FLINT study, it was not included in the pooled analyses. The pooled for the ITT population is shown in the table below:

In the pooled analysis the same primary endpoints as in Study 747-303 were used.

For the second primary endpoint (resolution of NASH with no worsening of fibrosis), evaluation of the OCA 25 mg pooled dose from the ITT population of combined studies demonstrated a consistent, "clinically meaningful effect" (judged by the Applicant) of OCA 25 mg on NASH resolution with no worsening of fibrosis. When pooled, the difference from placebo was statistically significant (p = 0.0248). The percentage of responders was 8.3% in the placebo group and 13.4% in the OCA 25 mg group. The OCA 25 mg:placebo response ratio was 1.61 (95% CI: 1.06, 2.46).

Clinical studies in special populations

Hepatic impairment

OCA has not been evaluated in subjects with decompensated cirrhosis (class B and C) and should not be used in patients with clinical signs or symptoms of cirrhosis.

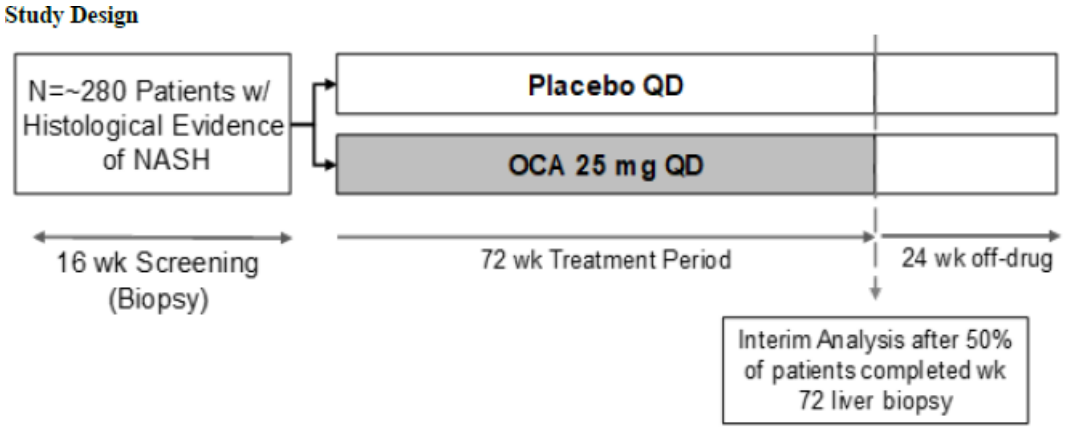
Renal impairment

No dose adjustment is recommended.

Supportive studies

The Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment (FLINT) Trial (supportive phase 2b study): Multi-center, randomized, double-masked, placebo-controlled, Phase 2b clinical trial to evaluate the efficacy and safety of treatment with either OCA 25 mg once daily or placebo in subjects with NASH

Figure 51



NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; QD = once daily; wk = weeks

Studied Period: 16 March 2011 (first subject enrolled) to 17 Sep 2014 (last subject completed)

Study participants

Inclusion Criteria

Subjects were required to meet the following criteria in order to be included in the study:

1. 18 years of age or older as of the initial screening interview and provision of consent
2. Histologic evidence of definite or probable NASH based upon a liver biopsy obtained no more than 90 days prior to randomization and a NAS of 4 or greater with at least one in each component of the NAS score (steatosis scored 0 to 3, hepatocellular ballooning degeneration scored 0-2, and lobular inflammation scored 0 to 3).

Exclusion Criteria

Subjects who met the following criteria were excluded from the study.

1. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to Screening (significant alcohol consumption was defined as more than 20 g/day in females and more than 30 g/day in males, on average)
2. Inability to reliably quantify alcohol consumption based upon local study physician judgment
3. Use of drugs historically associated with NAFLD (amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other known hepatotoxins) for more than 2 weeks in the year prior to randomization.
4. Prior or planned (during the study period) bariatric surgery (eg, gastroplasty, roux-en-Y gastric bypass)
5. Uncontrolled diabetes, defined as HbA1c 9.5% or higher within 60 days prior to enrollment
6. Presence of cirrhosis on liver biopsy
7. A platelet count below 100,000/mm3
8. Clinical evidence of hepatic decompensation
9. Evidence of other forms of chronic liver disease
10. Serum ALT greater than 300 U/L
11. Serum creatinine of 2.0 mg/dL or greater

12. Inability to safely obtain a liver biopsy
13. History of biliary diversion
14. Known positivity for human immunodeficiency virus (HIV) infection
15. Active, serious medical disease with likely life expectancy less than 5 years
16. Active substance abuse, including inhaled or injection drugs in the year prior to Screening
17. Pregnancy, planned pregnancy, potential for pregnancy and unwillingness to use effective birth control during the trial, breastfeeding
18. Participation in an IND trial in the 30 days before randomization
19. Any other condition which, in the opinion of the Investigator, would impede compliance or hinder completion of the study
20. Failure to give informed consent

A total of 283 subjects were randomised in FLINT Study (Placebo n= 142, OCA n = 141) and included in the ITT population.

Objectives:
The primary objective was to determine whether treatment with obeticholic acid (OCA) at 25 mg orally once daily for 72 weeks is better than placebo in improving liver histologic parameters as measured by the nonalcoholic fatty liver disease (NAFLD) activity score (NAS) in subjects with biopsy evidence of nonalcoholic steatohepatitis (NASH). Improvement of liver histologic parameters is defined as no worsening of the fibrosis score and a decrease in NAS by ≥2 points.

Endpoints:
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 two points. Worsening of the fibrosis score was defined as any numeric increase in the fibrosis score at the end of treatment compared to baseline. This definition of worsening of the fibrosis score is being used for all other endpoints unless otherwise specified.

Secondary Endpoints- Histology, Laboratory, and Symptoms and Exam:

Histology:

- Proportion of subjects with a change from a histological diagnosis (based on pathologist interpretation) of definite NASH or indeterminate for NASH to not NASH at end of treatment.
- Individual histological characteristics at end of treatment compared to baseline

Results:

Table 21 Demographic and Baseline Characteristics - ITT Population (N = 283)

Population	Placebo (N = 142)	OCA 25 mg (N = 141)	Overall (N = 283)
Age (years)			
Mean (SD)	51.0 (11.68)	52.0 (11.10)	51.5 (11.38)
SEM	0.98	0.93	0.68
Median (Min, Max)	53.0 (21, 75)	53.0 (18, 78)	53.0 (18, 78)
Sex, n (%)			
Female	89 (63)	98 (70)	187 (66)
Male	53 (37)	43 (30)	96 (34)
Race, n (%)			
White	111 (78)	123 (87)	234 (83)
Asian	10 (7)	6 (4)	16 (6)
Multi-racial	9 (6)	5 (4)	14 (5)
Black or African American	4 (3)	2 (1)	6 (2)
American Indian or Alaska Native	3 (2)	1 (<1)	4 (1)
Native Hawaiian or Other Pacific Islander	1 (<1)	1 (<1)	2 (<1)
Ethnicity, n (%)			
Hispanic or Latino	21 (15)	22 (16)	43 (15)
Not Hispanic or Latino	121 (85)	119 (84)	240 (85)
AST (U/L)			
Mean (SD)	58.0 (33.59)	64.1 (38.46)	61.1 (36.16)
SEM	2.82	3.24	2.15
Median (Min, Max)	48.0 (17, 180)	53.0 (21, 212)	51.0 (17, 212)
>3× ULN	9 (6)	11 (8)	20 (7)
ALT (U/L)			
Mean (SD)	82.4 (51.05)	82.8 (49.48)	82.6 (50.18)
SEM	4.28	4.17	2.98
Median (Min, Max)	65.5 (15, 294)	68.0 (13, 269)	67.0 (13, 294)
>3× ULN	17 (12)	18 (13)	35 (12)

Lipids			
Total Cholesterol (mg/dL)			
Mean (SD)	186.8 (47.12)	190.1 (45.24)	188.4 (46.14)
SEM	3.95	3.81	2.74
Median (Min, Max)	184.0 (63, 315)	189.0 (64, 354)	187.0 (63, 354)
HDL Cholesterol (mg/dL)			
Mean (SD)	44.3 (14.10)	42.5 (11.32)	43.4 (12.80)
SEM	1.19	0.96	0.76
Median (Min, Max)	41.0 (22, 114)	42.0 (20, 79)	42.0 (20, 114)
LDL Cholesterol (mg/dL)			
Mean (SD)	110.6 (41.55)	112.0 (37.84)	111.3 (39.71)
SEM	3.52	3.27	2.40
Median (Min, Max)	107.0 (22, 227)	110.5 (29, 279)	108.0 (22, 279)
Triglycerides (mg/dL)			
Mean (SD)	177.7 (152.87)	216.4 (277.74)	197.0 (224.40)
SEM	12.83	23.39	13.34
Median (Min, Max)	150.0 (25, 1507)	161.0 (55, 3100)	159.0 (25, 3100)
HbA1c (%)			
Mean (SD)	6.41 (0.992)	6.53 (1.083)	6.47 (1.039)
SEM	0.083	0.091	0.062
Median (Min, Max)	6.20 (4.7, 9.2)	6.30 (4.4, 9.2)	6.20 (4.4, 9.2)
Weight (kg)			
Mean (SD)	95.73 (18.06)	99.98 (23.070)	97.85 (20.781)
SEM	1.51	1.943	1.235
Median (Min, Max)	93.80 (61.3, 161.2)	98.20 (60.7, 176.1)	95.80 (60.7, 176.1)
Body Mass Index (kg/m^2)			
Mean (SD)	33.94 (5.863)	35.25 (6.692)	34.58 (6.309)
SEM	0.492	0.568	0.376
Median (Min, Max)	33.30 (23.8, 59.4)	34.37 (22.2, 53.8)	33.57 (22.2, 59.4)
Concomitant medications, n(%)			
Any Statin	52 (37)	51 (36)	103 (36)
Any Vitamin E or TZD	36 (25)	31 (22)	67 (24)
Baseline Diabetes			
n, %	74 (52)	75 (53)	149 (53)

Fibrosis Stage, n(%)			
F0	18 (13)	13 (9)	31 (11)
F1	36 (26)	47 (33)	83 (29)
F2	44 (31)	31 (22)	75 (27)
F3	41 (29)	46 (33)	87 (31)
F4	2 (1)	4 (3)	6 (2)
NAFLD Activity Score[a]			
Mean (SD)	5.1 (1.29)	5.3 (1.30)	5.2 (1.29)
SEM	0.11	0.11	0.08
Median (Min, Max)	5.0 (2, 8)	5.0 (2, 8)	5.0 (2, 8)
<6, n (%)	86 (62)	78 (55)	164 (58)
≥6, n (%)	55 (39)	63 (45)	118 (42)
Presence of Steatohepatitis, n (%)			
Not NAFLD	0 (0)	0 (0)	0 (0)
NAFLD, not NASH	14 (10)	13 (9)	27 (10)
Suspicious/borderline/indeterminate : Zone 3 Pattern	16 (11)	11 (8)	27 (10)
Suspicious/borderline/indeterminate : Zone 1, Periportal Pattern	0 (0)	3 (2)	3 (1)
Yes, definite	111 (79)	114 (81)	225 (80)
Missing, n	1	0	1

ALT = alanine aminotransferase; AST = aspartate aminotransferase; F = fibrosis stage; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; ITT = intent-to-treat; LDL = low-density lipoprotein; Max = maximum; Min = minimum; N = total subjects in a group; n = specific number of subjects within the group; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; SD = standard deviation; SEM = standard error of the mean; TZD = thiazolidinedione; ULN = upper limit of normal

[a] NAFLD Activity Score is a non-weighted sum of the steatosis grade (0 – 3), lobular inflammation grade (0 – 3), and hepatocellular ballooning grade (0 – 2) and ranges from 0 to 8.

Percentages are based on the number of subjects in the ITT population per group and overall.

Source: Section 14, Table 14.1.3.1 and Table 14.1.4.1.

Analysis Populations

Intent-to-Treat (ITT) Population: All randomized subjects who received at least one dose of the investigational product (OCA or placebo) were included in the ITT population.

Modified ITT (mITT) population: All subjects from the ITT population except those who did not receive an end of treatment biopsy due to protocol modification after stopping criteria for efficacy were met were included in the mITT population.

Per-Protocol (PP) Population: All subjects from the ITT population who had baseline and 72-week liver biopsies and no major protocol deviations that could impact efficacy conclusions were included in the PP Population. Treatment assignment was based on the randomized treatment.

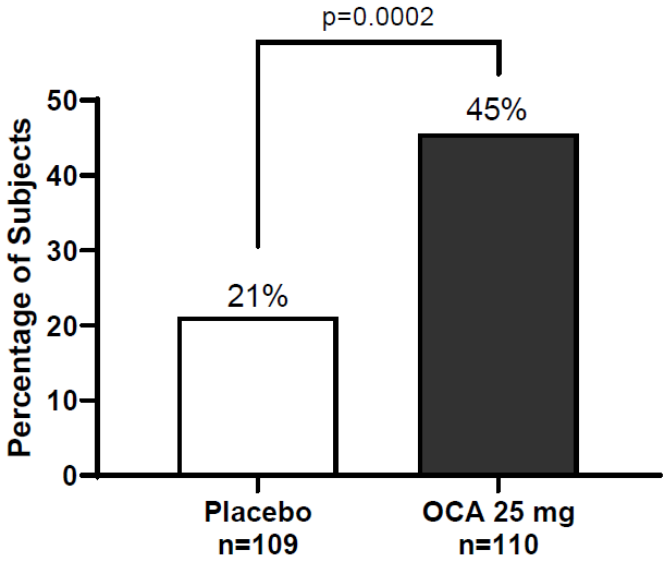
Efficacy Results:

The primary and secondary efficacy analyses were based on the mITT and PP populations, with the PP analyses serving as supportive.

Primary Efficacy Endpoint

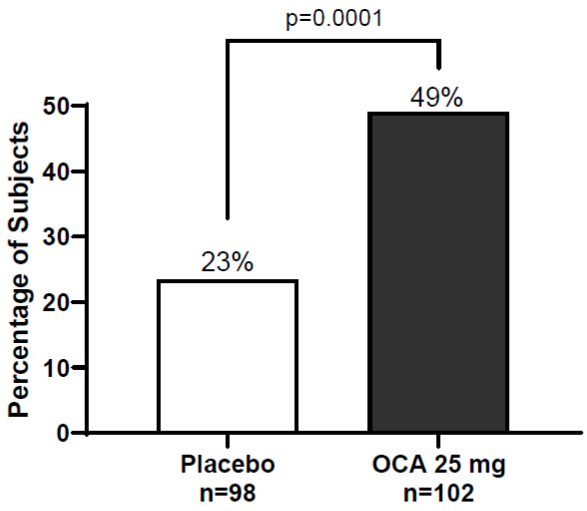
The primary endpoint of the study was achieved.

Figure 52 Primary Outcome Measure: Improvement in NAS by ≥2 Points with No Worsening of Fibrosis at Week 72 (mITT Population; N = 219)



mITT = modified Intent-to-Treat; NAS = nonalcoholic fatty liver disease activity score; OCA = obeticholic acid.
The primary outcome is defined as an improvement in histological features, which requires a decrease of two or more points in the total NAS and no worsening in the fibrosis score.
p-value and relative risk is based on a Cochran-Mantel-Haenszel chi-square test, stratified by center and diabetes status at randomization
Missing week 72 liver biopsy results are imputed as no improvement
Source: Table 14.2.1.1

Figure 53 Primary Outcome Measure: Improvement in NAS by ≥2 Points with No Worsening of Fibrosis at Week 72 (Per Protocol Population; N=200)



NAS = nonalcoholic fatty liver disease activity score; OCA = obeticholic acid.
The primary outcome is defined as an improvement in histological features, which requires a decrease of two or more points in the total NAS and no worsening in the fibrosis score.
p-value and relative risk is based on a Cochran-Mantel-Haenszel chi-square test, stratified by center and diabetes status at randomization
Source: Table 14.2.1.2

Table 22 Sensitivity Analysis on the Primary Endpoint: Improvement in NAS by ≥2 Points with No Worsening of Fibrosis at Week 72 (mITT Population; N=219)

	Improvement in NAS by ≥2 Points with No Worsening of Fibrosis at Week 72				
	OCA vs Placebo			No. of subjects	
Imputation Method for Missing Week 72 Biopsy Data	**Relative Risk[d]**	**95% CI**	**p-value**	**OCA**	**Placebo**
No Improvement in Either Treatment Group[a]	2.2	1.4 – 3.3	0.0002	110	109
Worst case scenario for OCA[b]¶	1.5	1.0 – 2.2	0.0215	110	109
Best case scenario for OCA[c]	2.5	1.7 – 3.8	<0.0001	110	109

CI = confidence interval; mITT = modified Intent-to-Treat; NAS = nonalcoholic fatty liver disease activity score; OCA = obeticholic acid
[a] Observations with missing Week 72 biopsy imputed as no improvement among subjects at risk of Week 72 biopsy
[b] Observations with missing Week 72 biopsy were imputed as improvement for subjects assigned to Placebo and no improvement for subjects assigned to OCA
[c] Observations with missing Week 72 biopsy were imputed as no improvement for subjects assigned to Placebo and improvement for subjects assigned to OCA
[d] p-value and relative risk is based on a Cochran-Mantel-Haenszel chi-square test, stratified by center and diabetes status at randomization.
Source: Table 14.2.1.1

Table 23 Response Rates and Relative Risk (95% CI) of Fibrosis-Related Secondary and Exploratory Endpoints (mITT and Per Protocol Populations)

Relative Risk OCA vs Placebo (p-value)	mITT Population (N=219)		Per Protocol Population (N=200)	
≥1 Stage Fibrosis Improvement	**OCA (N=110)**	**Placebo (N=109)**	**OCA (N=102)**	**Placebo (N=98)**
Response Rates	36/98 (37%)	19/ 94 (20%)	36/92 (39%)	19/83 (23%)
Relative Risk (OCA vs Placebo)	2.0 (1.2, 3.2)		1.9 (1.2, 3.1)	
p-value	0.0053		0.0071	
≥2 Stages Fibrosis Improvement	**OCA (N=110)**	**Placebo (N=109)**	**OCA (N=102)**	**Placebo (N=98)**
Response Rates	9/65 (14%)	4/72 (6%)	9/61 (15%)	4/62 (6%)
Relative Risk (OCA vs Placebo)	2.9 (1.0, 8.7)		2.7 (0.9, 7.9)	
p-value	NC		NC	
Fibrosis Resolution	**OCA (N=110)**	**Placebo (N=109)**	**OCA (N=102)**	**Placebo (N=98)**
Response Rates	16/98 (16%)	4/94 (4%)	16/92 (17%)	4/83 (5%)
Relative Risk (OCA vs Placebo)	4.2 (1.5, 11.8)		4.5 (1.5, 13.2)	
p-value	0.0019		0.0018	
Progression to Cirrhosis	**OCA (N=110)**	**Placebo (N=109)**	**OCA (N=102)**	**Placebo (N=98)**
Response Rates	2/108 (2%)	5/107 (5%)	2/101 (2%)	5/ 97 (5%)
Relative Risk (OCA vs Placebo)	0.2 (0.0, 1.5)		0.3 (0.0, 1.5)	
p-value	NC		NC	

CI = confidence interval; MITT = modified Intent-to-Treat; NC = not calculated; OCA = obeticholic acid.
Source: Table 14.2.2.1.1, Table 14.2.2.1.2, Table 14.2.2.5.1, and Table 14.2.2.5.2

Study D8602001: An Exploratory Study of DSP-1747 in Patients with Nonalcoholic Steatohepatitis (Phase 2 Study)

Studied Period:
Study initiation date (first subject consented): November 13, 2012
Study completion date (last subject completed): November 20, 2015

Study D8602001 was a double-blind, parallel-group, placebo-controlled, Phase 2 study in biopsy confirmed precirrhotic NASH, conducted in Japan by Sumitomo Dainippon Pharma, a efficacy and safety of OCA 10 mg, OCA 20 mg, or OCA 40 mg for 72 weeks compared with placebo in patients with NASH. The primary endpoint of the study was to evaluate the dose response for the improvement in NAS by ≥2 points with no worsening of fibrosis following 72 weeks of treatment

A total of 200 subjects 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 (~50 per group) for 72 weeks, with a subsequent follow-up period of 24 weeks. Thirty-one subjects (15.3%) discontinued

prematurely from the treatment phase: 11.8% to 26.0% of subjects in the OCA groups and 10.0% in the placebo group.

Demographics and baseline characteristics were generally similar across treatment groups. All subjects were Japanese, and the majority were males (62% to 72%). The mean subject age ranged from 46.4 to 50.2 years in the four groups. The mean weight (77.55 to 81.79 kg) and mean BMI (28.13 to 29.30 kg/m2) were lower than the average weight and BMI of typical NASH patients in North America. Mean NAS was approximately 6.3 in the OCA groups and 6.5 in the placebo group. In the placebo group, 50% of subjects had fibrosis stage ≤1, 26% had fibrosis stage 2, and 24% had fibrosis stage 3. In the total OCA group, 43% of subjects had fibrosis stage ≤1, 32% had fibrosis stage 2, and 25% had fibrosis stage 3. Common comorbid conditions were reflective of a NASH population and included type 2 diabetes (28% to 42% of subjects), hyperlipidaemia (66% to 76%), and hypertension (34% to 44%).

Efficacy Results:

Table 24 Dose-response Relationship of Pathological Improvement−Cochran-Armitage Test with Stratification According to Fibrosis Stage

	PLCB N=50	10MG N=50	20MG N=50	40MG N=50
Histological improvement				
Improved	10 (20.0%)	11 (22.0%)	14 (28.0%)	19 (38.0%)
Unimproved	40 (80.0%)	39 (78.0%)	36 (72.0%)	31 (62.0%)
Missing	5 (10.0%)	6 (12.0%)	6 (12.0%)	13 (26.0%)
Contrast coefficient			Adjusted p-value	Raw p-value
(-3, 1, 1, 1)			0.312	0.207
(-5, -1, 3, 3)			0.114	0.070
(-3, -1, 1, 3)			0.053	0.033

- The subjects for whom the Kleiner's fibrosis stage or NAS or both in Week 72 are missing are classified as "Unim proved"
- Adjusted p-values are calculated using the Cochran-Armitage test stratified by baseline value of Kleiner's fibrosis stage (stage 0 through 2, stage 3) with Permutation Resampling as multiple contrast tests
- Raw p-values are calculated using the Cochran-Armitage test stratified by baseline value of Kleiner's fibrosis stage (stage 0 through 2, stage 3)
- N: the number of ITT subjects
- Percentages are based on the number of ITT subjects.

Table 25 Comparison of the Percentage of Subjects with Pathological Improvement−Fisher's Exact Test

Statistic	10MG N=50	20MG N=50	40MG N=50	PLCB N=50
Improved	11	14	19	10
Percentage (95%CI)	22.0 (11.5, 36.0)	28.0 (16.2, 42.5)	38.0 (24.7, 52.8)	20.0 (10.0, 33.7)
Unimproved (Missing)	39 (6)	36 (6)	31 (13)	40 (5)
p-value (vs Placebo)	1.000	0.483	0.077	

- The subjects for whom observation are missing are classified as "Unimproved"
- N: the number of ITT subjects
- Percentages are based on the number of ITT subjects.
- 95%CI are calculated using Clopper-Pearson method.
- p-values are calculated using Fisher's exact test

Because of differences in the study population (Japanese patients) and dose regimen (doses of 10, 20, or 40 mg/day), data from Study D8602001 are not integrated or pooled with those of Study 747-303 and the FLINT study for efficacy. Owing to the differences in study population (Japanese subjects) and

OCA doses (10 mg, 20 mg and 40 mg), the efficacy results of Study D8602001 are not pooled with those of Study 747-303 and FLINT

3.3.6. Discussion on clinical efficacy

Obeticholic acid (OCA) is a selective agonist for the farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine. FXR is thought to be a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways.

Currently OCA is approved as Ocaliva 5 mg film-coated tablets and Ocaliva 10 mg film-coated tablets, indicated for the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

The initial intended indication was improvement of liver fibrosis and resolution of steatohepatitis in adult patients with significant liver fibrosis due to nonalcoholic steatohepatitis (NASH), without clinical signs or symptoms of cirrhosis. The wording of the indication was updated as part of the responses to the D120 LoQ to remove "resolution of steatohepatitis", see below.

The recommended dosage regimen is 25 mg once daily.

The efficacy of obeticholic acid (OCA) in the improvement of liver fibrosis and resolution of steatohepatitis in adult patients with significant liver fibrosis due to NASH is mainly based on one single pivotal phase III study (747-303) and the supportive phase II studies (FLINT and D8602001).

The Pivotal Study (747-303) in an ongoing study to support both initial conditional approval based on Month 18 Interim Analysis and full approval following confirmation of clinical benefit based on an End of Study (EOS). As this Month 18 Analysis Interim was performed using the data cut-off (DCO) of 26 Oct 2018.

Design and conduct of clinical studies

Pivotal Study 747-303

Study 747-303 is a Phase 3, randomized, multicentre international study double-blind, placebo-controlled, multi-dose, parallel-group study evaluating the effect of OCA on histologic improvements in NASH, all-cause mortality, and liver-related clinical outcomes. The inclusion of a placebo arm is accepted in view of the lack of approved drugs for NASH.

The study population includes 2085 subjects with biopsy-confirmed pre-cirrhotic NASH and evidence of stage 2 or 3 liver fibrosis mainly. Also, an additional cohort of patients with stage 1 (with at least one accompanying comorbidity) has been selected to get safety information. As it is recommended, the diagnosis of NASH and the inclusion of such patients in this clinical trial has been based on histological evaluation. In general, study inclusion and exclusion criteria reflect the target population of the claimed indication. Although, in the real world, NASH patients commonly have concurrent liver diseases (particularly virus- and alcoholic-related), patients with liver disease of other aetiology were excluded from the trial, to avoid possible confounders. This is correctly reflected in section 5.1 of the SmPC. Subjects with recent history (within 1 year of Day 1) of significant cardiovascular or cerebrovascular disorder were also excluded, because of the potential increase of CV risk due to OCA-impact on lipoprotein profile. This criterion surely has impacted on the number of old subjects included in the study and needs to be reflected in section 5.1 of the SmPC. Overall, 6218 subjects were screened, and 3738 subjects were considered ineligible for enrolment. Of the total subjects screened, 114 patients (1.8%) were ineligible due to evidence of other forms of known chronic liver disease and

28 (<1% of patients ineligible for enrolment) were excluded for recent history of significant atherosclerotic cardiovascular disease (ASCVD) including cerebrovascular disorders.

Most of the subjects (80%) were < 65 years and more than a half are female. Most subjects were obese. The ITT population comprised subjects with biopsy-confirmed, non-cirrhotic NASH and histological evidence of fibrosis stage 2 or stage 3.

Key histologic features of NASH were identical across treatment groups, with mean scores of 1.9, 1.7, and 2.3 for steatosis, hepatocellular ballooning, and lobular inflammation, respectively.

A similar percentage of subjects (55% to 56%) had diabetes at baseline across treatment groups, and 53% of subjects overall were receiving concomitant antidiabetic medications.

Of note, the majority of the enrolled population was from North America (73%, 676 patients) and only the 22% (209 patients) from EU. Moreover, the EU patients enrolled in the study seem to differ from the majority of US patients in terms of obesity, a risk factor for NASH (BMI ≥30 kg/m2 [61% vs. 79%] and ≥35 kg/m2 [26% vs. 40%], respectively). Also, lower proportions of EU subjects had baseline ALT and AST levels >ULN. However, the EU population enrolled is generally similar to the US population and US population results can be applied to the EU population. The subjects have been randomized to receive OCA 10 mg, OCA 25 mg or placebo, in addition to lifestyle modification guidance and local standard of care, as NASH is associated with other disorders as obesity, systemic hypertension, dyslipidemia and insulin resistance or diabetes. The EMA reflection paper recommends that patients enrolled in clinical trials for NASH undertake at least one unsuccessful attempt with weight-reducing diet before inclusion in the study. Patients were not required to have demonstrated an unsuccessful attempt at a weight-reducing diet at the time of inclusion. Only counselling during the study was conducted, however, in the presence of randomization it would be expected that patients either having or not followed such interventions would distribute equally across treatment arms.

Randomization of subjects with fibrosis stage 2 or stage 3 was stratified by presence of type 2 diabetes at enrolment (yes/no) and use of thiazolidinediones TZDs/glitazones or vitamin E at baseline (yes/no). It is important to know exactly the results in those patients treated with concomitant medication with potential NASH-modifying properties as TZDs/glitazones or vitamin E and liraglutide. The use of Cochran-Mantel-Haenszel test stratified by the randomization strata is considered adequate for the analysis of the primary efficacy endpoints. However, based on the baseline characteristic of the recruited population, the Poisson regression model, a more powerful statistical method, was also applied to the analysis of the primary endpoints, adjusting for treatments' effects (OCA 10 mg, OCA 25 mg, Placebo), strata (type 2 diabetes, TZDs/vitamin E), other covariates at baseline (age, sex, fibrosis stage), and study population based on clinical sites (EU, North America, rest of the world).Findings were consistent with the stratified Cochran-Mantel-Haenszel test.

A total of 2480 subjects across 345 sites globally were randomized to one of 3 treatment arms (Placebo, 10 mg OCA, 25 mg OCA) in a 1:1:1 ratio using a stratified block randomization schedule. The block size was 6. Only one central randomization list was used by all sites globally, with stratification also performed globally. Therefore, there was no separate randomization by centre or by site. The subjects were randomized in permuted blocks.

In general terms, the objectives were to evaluate the efficacy and safety of OCA at two different doses (10 mg and 25 mg QD) in subjects with NASH with fibrosis.

The Primary Efficacy Endpoints for the Month 18 Interim Analysis were:

- *Improvement of liver fibrosis by ≥ 1 stage (NASH CRN fibrosis score) with no worsening of NASH*
- *Resolution of NASH with no worsening of fibrosis*

In a post-hoc analysis, the Applicant changed the initial definition "Resolution of NASH" in the primary endpoint, to "Resolution of NASH with no worsening of fibrosis". The Applicant considers that NASH resolution based on the pathologist's overall assessment is a more reproducible and clinically relevant approach to determine presence or absence of definite NASH and is also the definition implemented in clinical practice and by the NASH CRN. This change has provided better results in this endpoint, as a matter of fact, with the first definition the results were not statistically significant and with the final definition the results achieved statistically significance.

On the other hand, in the initial Scientific Advice (2015), a co-primary endpoint comprising measures of the effects of OCA on improvement of fibrosis and on the resolution of NASH was considered acceptable:

- Improvement of 1 stage of fibrosis and no worsening of steatohepatitis (as defined by no increase in ballooning or inflammation); AND
- "Resolution of NASH" as defined by the overall histopathological interpretation (i.e. subjects would have a biopsy interpretation of "not NAFLD" or "simple steatosis" or "NAFLD without steatohepatitis") and no worsening of fibrosis.

This approach required that both endpoints achieve statistical significance for the primary efficacy analysis to be considered successful.

After the initial Scientific Advice, the Applicant considered that there was accumulated clinical evidence and emerging scientific literature indicated that either endpoint alone is predictive of clinical outcomes. Specifically:

1. Newer data are consistent with an existing strong body of literature that continues to support the contention that fibrosis predicts all-cause and liver-related mortality
2. Presence of definite NASH as well as individual histologic features of steatohepatitis such as hepatocellular ballooning also contribute to a decline in survival, and
3. NASH activity positively correlates with fibrosis progression.

Therefore, it was the Applicant's assessment that fibrosis improvement without worsening of NASH or NASH resolution without worsening of fibrosis can each individually reasonably predict clinical outcomes, and achievement of either endpoint alone would be reflective of improvement in overall disease severity.

Based on this the Applicant revisited the topic at the subsequent 2018 follow up procedure and requested to change the co-primary endpoint analysis to an analysis that requires either of the two components of the initial co-primary to be met for statistical success. This position was adopted by the FDA in the granting of either of the two endpoints sufficient for the pivotal measure of efficacy as is now reflected in the draft FDA guidance.

In addition, the analysis for the primary efficacy endpoints presented in the Pivotal Study 747-303 were assessed by the Applicant according exclusively to the Statistical Analysis Plan (Final Version, dated 08 Jan 2019) and not with latest version of the protocol (Protocol 747-303, Version 7, dated 11 Apr 2018).

The methodology proposed by the Applicant in the SAP was completely different to the one presented in the latest version of the protocol. A relevant modification was with regard to the multiplicity adjustment to control the overall Type 1 error; in the protocol for the Month 18 interim analysis was planned to be tested at 0.01 and the final analysis at 0.04, while in the SAP, the interim analysis was tested at 0.02 and the final analysis at 0.03.

Also, the strategy to test the different histological endpoints was completely changed in both documents; the Version 7 of the protocol proposed a simple sequential testing order to assess the primary endpoints, whilst the SAP suggested the Truncated-Hochberg procedure (Gamma = 0.1).

There was no mention of the changes described in the SAP within any protocol and in the SAP there were no justification for those modifications. It is remarkable as well, that the statistical analysis plan (08/01/2019) was dated later than the version 7 of the protocol (11/04/2018) and even than the date of month 18 interim analysis data cut-off (26/10/2018).The CHMP declined to endorse this view in the written advice to the Applicant and their position was consolidated by the publication following the November CHMP meeting (at exactly the same time as the advice was provided) of a CHMP draft Reflection Paper specifying the co- primary endpoint requirement, for consultation.

The key secondary endpoint was percentage of subjects with improvement of fibrosis by > 1 Stage and/or resolution of NASH, without worsening of either. Additionally, the secondary histologic endpoints (fibrosis-related endpoints and NASH-related endpoints) have been assessed as well as secondary no histologic endpoints (change and percentage change from baseline in liver biochemistry and markers of function (ALT, AST, GGT, alkaline phosphatase [ALP], total and direct bilirubin, albumin, international normalized ratio [INR], and platelets)).

Statistical analyses. The overall study sample size was estimated based on the clinical outcome composite endpoint analysis at the End of Study, which is acknowledged.

For the analysis of the primary efficacy endpoints at month 18, a gatekeeping approach with propagation of α=0.01 from the histological endpoints to the clinical endpoints was applied, together with a hierarchical statistical testing for both OCA doses and key secondary endpoint. Hochberg adjustment was used for the two endpoints within each OCA dose arm.

Analysis of the Clinical outcomes composite endpoint at EOS. Two formal interim analyses will be performed on the end-of-study endpoint prior to final database lock. Sequential testing has been planned to use the O'Brien-Fleming type alpha-spending function to control for type 1 error, which is agreed.

FLINT Study (Supportive phase 2b)

The Applicant has submitted this predecessor study which was stopped early for efficacy based on a planned interim analysis showing that the primary endpoint of the trial had been met.

It was a multicentre, randomized, double-masked, placebo-controlled, Phase 2b clinical trial evaluated the efficacy and safety of treatment with either OCA 25 mg once daily or placebo in subjects with NASH.

Subjects were screened for up to 16 weeks (112 days). Subjects who satisfied all inclusion criteria and none of the exclusion criteria were randomized to receive daily doses of either OCA (25 mg) or placebo for 72 weeks, at which time the investigational product was stopped. The subjects were to return for safety visits (Weeks 2 and 4) and follow-up visits every 12 weeks after randomization (Weeks 12, 24, 36, 48, 60, and 72), with a final off-drug follow-up visit 24 weeks after the end of treatment (Week 96).

The subjects had histologic evidence of definite or probable NASH based upon a liver biopsy obtained no more than 90 days prior to randomization and a NAS of 4 or greater with at least 1 in each component of the NAS score (steatosis scored 0 to 3, ballooning degeneration scored 0 to 2, and lobular inflammation scored 0 to 3).

The inclusion / exclusion criteria are acceptable.

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 two points.

The secondary endpoints consisted of histology endpoints, Laboratory values and Symptoms and Exam data.

Study D8602001

Study D8602001 was a double-blind, parallel-group, placebo-controlled, Phase 2 study in biopsy confirmed pre-cirrhotic NASH, conducted in Japan to assess the efficacy and safety of OCA 10 mg, OCA 20 mg, or OCA 40 mg for 72 weeks compared with placebo in patients with NASH.

After the 72 weeks, there was a subsequent follow-up period of 24 weeks to assess the off-drug response.

The primary endpoint of the study was to evaluate the dose response for the improvement in NAS by ≥2 points with no worsening of fibrosis following 72 weeks of treatment.

A total of 200 subjects 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 (~50 per group).

Demographics and baseline characteristics were generally similar across treatment groups. Mean NAS was approximately 6.3 in the OCA groups and 6.5 in the placebo group. In the placebo group, 50% of subjects had fibrosis stage ≤1, 26% had fibrosis stage 2, and 24% had fibrosis stage 3. In the total OCA group, 43% of subjects had fibrosis stage ≤1, 32% had fibrosis stage 2, and 25% had fibrosis stage 3. Common comorbid conditions were reflective of a NASH population and included type 2 diabetes (28% to 42% of subjects), hyperlipidaemia (66% to 76%), and hypertension (34% to 44%).

It is acknowledged that this study provides supportive information however, there are differences in the study population and dose regimen.

Efficacy data and additional analyses

Pivotal Study 747-303

In the Month 18 Interim analysis, the ITT population comprised 931 subjects. The ITT population comprised subjects with biopsy-confirmed, noncirrhotic NASH and histological evidence of fibrosis stage 2 (44%) or stage 3 (56%). Mean NAS was 6.0 overall and was comparable across treatment groups. Key histologic features of NASH were identical across treatment groups, with mean scores of 1.9, 1.7, and 2.3 for steatosis, hepatocellular ballooning, and lobular inflammation, respectively.

A similar percentage of subjects (55% to 56%) had diabetes at baseline across treatment groups, and 53% of subjects overall were receiving concomitant antidiabetic medications. A total of 54% of subjects were receiving concomitant lipid-lowering medications, and 44% were receiving statins. Baseline concomitant use of NASH-modifying agents, TZDs and vitamin E, was infrequent (2% and 12%, respectively), and was generally balanced across treatment groups.

As would be expected in a population with NASH fibrosis, mean baseline AST and ALT levels were elevated but well balanced across treatment groups; 60% of subjects had ALT >ULN with 7% being >3× ULN, and 74% of subjects had AST >ULN with 9% being >3× ULN. Total bilirubin was within normal range at baseline for the majority (95%) of subjects.

The Applicant defined a mITT as a Subset of the ITT population excluding subjects who discontinued treatment (before the Month 18 Visit and without an end of treatment biopsy). Having a mITT of 903 subjects, means that of the initial ITT population of 931 subjects, 28 subjects discontinued treatment before the month 18 visit without the end of treatment biopsy. Any subject who discontinued from the

study prior to the Month 18 Visit and did not have a postbaseline biopsy assessment, was considered a non responder.

Primary endpoint results

Improvement of fibrosis is the main target of the first primary endpoint. Long-term follow-up studies have showed that fibrosis stage is the most important determinant of the risk of liver-related death in patients with NAFLD. In spite of their retrospective nature, these studies provide evidence that discrete fibrosis categories dramatically influence future outcomes and allow to infer that liver fibrosis regression may correspond to a significant benefit in terms of reduction of liver-related deaths. However, this qualitative correlation should be translated into a quantitative correlation before accepting the use of these histological endpoints as surrogate markers of clinical benefit. A patient level prognostic factor is not considered enough to accept surrogacy.

NASH resolution is the main target of the second primary endpoint. The role of NASH in NAFLD progression is unclear. Most importantly, neither NASH presence nor its different grades measured by NAS have shown per se long-term prognostic value in NAFLD patients in long-term follow-up studies.

Regarding *Improvement of Fibrosis by ≥1 Stage with No Worsening of NASH*, treatment with OCA 25 mg had a response with statically significance compared to placebo (23.1% versus 11.9%, p = 0.0002). OCA 10 mg group showed improvement in fibrosis; however, the results are not statistically significant according to the new study design detailed in the SAP. It is remarkable that, in case the original study design (Version 7 of the protocol) would have been maintained, the results are exactly the same as the final design described in the statistical analysis plan.

With respect to the composite primary endpoint, *Resolution of NASH with No Worsening of Fibrosis,* the difference in the number of responders was not statistically significant for each group compared to placebo: OCA 25 mg group (11.7%) (p = 0.1268) and OCA 10 mg group (11.2%) (p = 0.1814).

As it has been previously mentioned, in a post-hoc analysis the Applicant changed the initial definition of "*Resolution of NASH*" in the primary endpoint. When NASH resolution was defined based on the pattern of injury (pathologist's overall assessment), a significantly greater proportion of subjects in the OCA 25 mg group (23.1%; p= 0.0004) achieved NASH resolution based on absence of definite NASH with no worsening of fibrosis as compared with placebo.

Following the *Reflection Paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH) (EMA/CHMP/299976/2018)*, efficacy in these two composites should be demonstrated in co-primary fashion, meaning that both will have to independently demonstrate a statistically significant and clinically relevant difference to placebo. This requirement is thought to take account of the uncertainties associated with a strategy to account for the long-term outcomes later.

This requirement has not been fulfilled as only *Improvement of Fibrosis by ≥1 Stage with No Worsening of NASH* has been successful.

For both primary endpoints, the response was dose dependent. The response with OCA 10 mg was lower than that achieved with the 25 mg dose.

The histologic benefit of OCA was consistent across analysis populations and subgroups of interest and was further confirmed by several sensitivity analyses. The beneficial effect on histologic endpoints was accompanied by consistent improvements in other markers of liver health including liver biochemistry and non-invasive markers of fibrosis and NASH, as well as in cardiometabolic parameters.

This first primary endpoint (improvement of fibrosis by at least 1 stage) was met with OCA 25 mg but not with OCA 10 mg. Responders were 23%, and the gain over placebo was limited to +11.1%, with

OCA/placebo response ratio of 1.94 (95% IC: 1.35-2.78; p=0.0002); the second primary endpoint (resolution of NASH) did not meet statistical significance for either OCA doses. The OCA/placebo response ratio was 1.45 (95% CI: 0.90-2.35; p=0.1268). Results of the primary analysis were confirmed by all pre-planned sensitivity analyses.

A post hoc analysis of the second component of the primary endpoint (Resolution of NASH with no worsening of fibrosis) using a different definition of NASH resolution, by a pathologist's overall assessment and not by overall histopathologic interpretation AND NAS score, showed statistically significant results for the 25 mg dose (but not for the lower dose), with 23.1% of responders, a gain over placebo of 10.8%, and an OCA/placebo response ratio of 1.89 (95% CI: 1.32-2.70; p=0.0004).

The applicant specifies in the CSR of study 747-303 that, by applying the overall pathologist's assessment, it is possible to discriminate from presence of "definite NASH" and "absence of definite NASH", with the consequence that a treatment responder is considered a subject with "absence of definite NASH". It seems that the applicant's diagnosis of "absence of definite NASH" by overall pathologist's assessment can be placed in a "grey area" between the world-wide recognised diagnoses of "definite NASH" and of "NAFLD not NASH", the latter characterised by the steatosis, minimal degree of inflammation and absence of ballooning injury. The Applicant clarified that "absence of definite NASH" indicates a histologic pattern by which a clear diagnosis of NASH cannot be done because the diagnostic features that are characteristic of NASH (steatosis, ballooning) are minimal, but more generic signs of liver disease (especially inflammation) are still present. The main limitation of this definition is that it is highly dependent by the reader's ability to notice or not subtle diagnostic signs of the disease. Moreover, it is at least in part independent by signs of disease severity, in particular severe inflammation. Therefore, the meaning of "absence of definite NASH" can be very different from "NASH resolution" in terms of improvement of NASH. In support of the reliability of results obtained with the post-hoc analysis, the applicant puts forward the higher concordance (intra- and inter-observer) in central biopsy reads obtained with the second definition of NASH compared to the original one, and concludes that the pathologists' assessment of the overall pattern of injury is a more reproducible and clinically relevant approach to determine presence or absence of definite NASH. It is recognized that intra- and inter-observer variability in liver biopsy evaluation is a problem that cannot currently be eliminated and that concordance in reading biopsies in the 747-303 study was better than that obtained in other large studies.

Key secondary endpoint

For "*Improvement of Fibrosis by ≥1 Stage and/or Resolution of NASH Without Worsening of Either",* OCA 25 mg showed improvement in nearly twice as many subjects (27.3%; p= 0.0005). The responder rates in the post-hoc analysis using the second definition of resolution of NASH were also higher.

The number of non-white subjects in study 747-303 was low, which appears in line with epidemiological data available from registries and other studies. The geographic distribution appears similar across North America, Europe and Rest of the World regions.

The results were favourable for secondary histologic endpoints as % of subjects with no worsening of fibrosis and no worsening of NASH, % of subjects with improvement of fibrosis by ≥2 stages, % of subjects with improvement of NAS by ≥2 points with no worsening of fibrosis.

Results on secondary endpoints, overall, showed a better performance of 25 mg OCA compared to placebo, with no improvement in steatosis.

It is acknowledged that steatosis, *per se*, is considered less relevant than the other components of liver damage (cell injury, inflammation and especially fibrosis) for the risk of progression toward cirrhosis and liver complications. EMA reflection paper addresses the case of drugs for NASH and fibrosis that target

fibrosis formation with minor or no effects on steatosis. If an indication in fibrosis in NASH is claimed, it is advised to use intermediate primary endpoints assessing a strong effect on fibrosis (e.g., fibrosis regression of at least 2 stages without worsening of NASH). In the OCA 25 mg group 9.7% of subjects (PLB 4.8% difference about 5%) had improvement of fibrosis by ≥2 stages, and 7.8% of patients (PLB 3.9% difference about 4%) had improvement of fibrosis by ≥2 stages and no worsening of NASH. Of note, when the endpoint for fibrosis was ≥ 2 stages a statistically significant difference was achieved in study 747-303 only if the effect on NASH worsening was not considered in the endpoint definition. Apart from the formal statistical significance, the proportion of patients who benefited from OCA 25 mg over placebo is considered limited, especially when the more stringent criteria of ≥ 2 stages fibrosis improvement is considered.

No dose adjustment is recommended in patient with renal impairment in the proposed SmPC. Similar increases in total OCA exposure were found across all degrees of renal impairment, raising the concern that renal impairment may impact on OCA uptake and concentration at the target site. The increased plasma exposure to OCA in patients with mild renal impairment (eGRF 60-89 mL/min/1.73m^2) corresponds to a substantially higher placebo corrected OCA 25 mg benefit on fibrosis improvement ≥1 stage with no worsening of NASH compared to patients with normal renal function (20.4% vs. 7.2%, respectively), and similar results have been registered for other endpoints. Overall, treatment with OCA 25 mg resulted in greater histological improvement, regardless of baseline renal impairment status.

FLINT Study (Supportive phase 2b):

Subjects were screened for up to 16 weeks and those who satisfied all inclusion criteria and none of the exclusion criteria were randomized to receive daily doses of either OCA (25 mg) or placebo for 72 weeks, at which time the investigational product was stopped. The subjects were to return for safety visits (Weeks 2 and 4) and follow-up visits every 12 weeks after randomization (Weeks 12, 24, 36, 48, 60, and 72), with a final off-drug follow-up visit 24 weeks after the end of treatment (Week 96).

The study was stopped early for efficacy based on a planned interim analysis showing that the primary endpoint of the trial had been met.

Analysis of the primary endpoint was conducted using the mITT and PP populations.

The secondary histological endpoints were analyzed using the mITT and PP populations. Modified ITT (mITT) population corresponds with all subjects from the ITT population except those who did not receive an end of treatment biopsy due to protocol modification after stopping criteria for efficacy were met were included in the mITT population.

The primary endpoint of the study, Improvement in NAS≥ 2 points with no worsening of fibrosis following 72 weeks of treatment, was achieved for the mITT population, in which a significantly greater percentage of OCA-treated subjects (50 (45%)) compared with placebo (23 (21%)) (p = 0.0002, RR: 2.2 95% CI [1.4 to 3.3]).

The results in secondary endpoints as Fibrosis improvement by at least one stage at Week 72, Improvement in the hallmark histologic features of NASH: hepatocellular ballooning, lobular inflammation, steatosis show that OCA 25 mg is effective at improving fibrosis.

In general terms, these data provide supportive evidence that treatment with OCA is associated with meaningful improvement in histologic endpoints.

In view of the results of the studies 747-303 and FLINT, the dose of OCA 25 mg once a day has shown improvements for the endpoints in both studies, however the dose of 10 mg in the main study 747-303 showed a lower effect, not getting statistically significant improvements for primary endpoints.

An integrated efficacy analysis of the 25 mg OCA dose, based on pooled data from the 2 long-term controlled studies (Study 747-303 and matched population form FLINT) was presented. However, the matched population from FLINT study had milder histologic grade of markers of liver injury and inflammation, and showed a better response to treatment. To characterizing the heterogeneity of effects across studies, a random-effect meta-analysis was requested to analyse pooled data. Findings were consistent with the stratified Cochran-Mantel-Haenszel test previously used.

Study D8602001

A total of 200 subjects 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 for 72 weeks, with a subsequent follow-up period of 24 weeks. Thirty-one subjects (15.3%) discontinued prematurely from the treatment phase: 11.8% to 26.0% of subjects in the OCA groups and 10.0% in the placebo group.

The results for the primary endpoint of the study, to evaluate the dose response for the improvement in NAS by ≥2 points with no worsening of fibrosis following 72 weeks of treatment, showed a trend for a dose-response relationship for the percentage of OCA-treated subjects who achieved the primary endpoint of improvement in NAS by ≥2 points with no worsening of fibrosis; more subjects treated with OCA 20 mg and OCA 40 mg achieved the primary endpoint compared with OCA 10 mg and placebo (20% in the placebo group, 22% in the OCA 10 mg group, 28% in the OCA 20 mg group, and 38% in the OCA 40 mg group). The difference in response to the primary endpoint between subjects in the OCA 40 mg group and the placebo group was statistically significant (p = 0.0496).

Revised indication wording

As part of the responses to the D120 LoQ the applicant proposed a revised indication targeting only improvement of liver fibrosis. Even if, as discussed above, the CHMP Draft Reflection Paper (EMA 2018) recommends a co-primary endpoint (i.e. statistical significance required on a composite endpoint based on improvement on fibrosis *and* an additional one addressing resolution of NASH) for a conditional marketing approval to be considered in the context of NASH treatment, the applicant argues that achievement of either endpoint alone (fibrosis improvement without worsening of NASH or NASH resolution without worsening of fibrosis) would be reflective of improvement in overall disease severity and therefore sufficient to support approval in the revised indication.

Even in a scenario where either fibrosis improvement or NASH resolution could be considered as independent/acceptable 'intermediate' (histologic) endpoints in the context of treatment of patients with stage 2-3 fibrosis due to NASH, the underlying issue remains that the demonstrated effect in any of them should be of such a magnitude that it could be reasonably expected to translate in/predict clinical benefit in the long-term. With this in mind achieving (mere) statistical significance in an endpoint reflecting an improvement in fibrosis only, appears difficult to accept unless such (interim) results were particularly compelling, i.e. to also compensate for the safety profile of a treatment intended to be given chronically to patients who are most suffering from several comorbidities. This is also related to the fact that, as outlined above, even if liver fibrosis can indeed be acknowledged as a strong predictor of morbidity and mortality in NASH at a patient level, surrogacy, not at patient level but at trial/population level, for this endpoint in the intended setting has not been established and it is therefore difficult to ascertain the level of 'fibrosis improvement' / antifibrotic effect needed (quantitatively) to translate into an effect in a hard endpoint(s) (clinical outcomes) reflecting clinical benefit in the targeted population.

In study 747-303 the administration of OCA 25 mg showed a positive but limited effect on liver fibrosis in patients with NASH when compared to placebo. The magnitude of this effect varies according to the endpoints, ranging from 3.9% of patients when the most stringent criteria were adopted (≥ 2 stages fibrosis improvement and no worsening of NASH in the same patient), a secondary endpoint for which

statistical significance was not shown, to 14.3% of patients when only ≥ 1 stage fibrosis improvement was sought.

Data from the FLINT study support the benefit of OCA 25 mg for fibrosis improvement ≥ 1 stage, showing higher response rates over placebo than those obtained in the 747-303 study, but a non-significant difference from placebo for fibrosis improvement ≥ 2 stages was reported.

The other provided supportive evidence of OCA effect on the histologic endpoints for fibrosis (i.e. results from non-invasive biomarkers such as liver stiffness (TE) and fibrosis-4 (FIB-4) index) can be considered to support the extent of the improvement of liver fibrosis measured by histologic examination but do not add strength in terms of surrogacy of liver-related clinical outcomes.

To justify the clinical value of the observed statistically significant effect with OCA 25 mg in liver fibrosis (only) data from two models/approaches undertaken to 'estimate' the clinical benefit of achieving the endpoint of improvement in fibrosis ≥1 stage and no worsening of steatohepatitis with OCA treatment were provided: i) a Markov cost-effectiveness model developed to compare the "natural" progression toward cirrhosis and decompensation of patients with NASH and stage 2 and 3 fibrosis compared to that expected in those treated with OCA 25 mg, and ii) a simulation exercise by a Poisson model to project annual mortality rates as well as mortality rate ratios (OCA: placebo).

Although the above outlined exercises could be useful and of help for predictions, the long-term benefit in terms of reduction of liver-related morbidity and mortality expected by OCA 25 mg treatment cannot be reliably inferred by the simulations proposed based on models that rely on strong assumptions and are informed by inadequate source data and variables, among others a key limitation is not considering the risk associated to OCA long-term therapy which could potentially significantly change the effect of the drug on mortality, overall limiting the reliability of the proposed predictions.

Additional efficacy data needed in the context of a conditional MA

As of Sep 2019, the pivotal study was fully enrolled with a total of 2480 subjects randomized (approximately 2190 of whom with fibrosis stage 2 or stage 3). The study is continuing in a blinded fashion, and subjects will be followed up over an extended period until the EOS analysis in order to evaluate the effect of OCA on all-cause mortality and liver-related clinical outcomes, together with the long-term safety of OCA.

It is recognized that NASH is a metabolic disease with high cardiovascular disease burden leading to advanced liver fibrosis that can significantly increase morbidity and mortality of affected subjects and negatively impact their quality of life. The increasing prevalence of NASH and the lack of approved pharmacological treatment options is also acknowledged. With this in mind and provided a positive benefit/risk balance for OCA 25 mg in the proposed indication could eventually be concluded the requirements for a CMA could be considered met. It is however to be highlighted that notwithstanding the efforts of the applicant to ensure study completion (see above) the risk of feasibility issues, particularly to keep patients in the placebo arm, if the drug will be on the market is still considered high.

3.3.7. Conclusions on clinical efficacy

For an indication to be granted to OCA for the treatment on liver fibrosis and resolution of steatohepatitis in adult patients with significant liver fibrosis due to NASH, without clinical signs or symptoms of cirrhosis, demonstration of a statistically significant and clinically relevant difference to placebo in the two composite endpoints of fibrosis improvement without worsening of NASH and NASH resolution without worsening of fibrosis was expected. However, results from study 747-303 at the

month 18 interim analysis did only show and effect of OCA 25 mg in the improvement of liver fibrosis by ≥ 1 stage with no worsening of NASH, but not for resolution of NASH.

As part of the responses to the D120 LoQ the applicant proposed a revised indication targeting only improvement of liver fibrosis. In such a context it is expected that the demonstrated effect in fibrosis improvement is compelling: of such a relevant magnitude that it could be reasonably expected to translate in/predict clinical benefit in the long-term (and to also compensate for the safety profile of a treatment intended to be given chronically to patients who are most suffering from several metabolic and CV comorbidities).

However, evidence of efficacy currently available is considered limited as the proportion of responders is low and the reported gain over placebo small.

Reduction in liver fibrosis is generally considered a prognostic factor at patient level of long-term clinical benefit. However, the surrogacy of this endpoint for liver-related outcomes (e.g. progression toward cirrhosis) and mortality is based on retrospective observations and has not been formally demonstrated. A positive effect also on the second primary endpoint, steatohepatitis, would have increased the confidence that the effect on fibrosis could translate into a clinically relevant change in patient outcomes. However, in the current scenario notable uncertainty remains whether the observed effect is reasonably likely to translate into clinical benefit in the long-term in the targeted population. This scenario is further complicated by the risk that long-term treatment efficacy on hard endpoints will not be assessable if a CMA is granted and a high dropout rate occurs in the placebo arm of the trial. This risk remains high even if the applicant's efforts to ensure retention of subjects and study completion are acknowledged.

3.3.8. Clinical safety

The clinical safety information submitted includes approximately 3,200 subjects treated with at least one dose of OCA in clinical studies, including over 1700 subjects with liver fibrosis due to NASH.

Exposure to the intended therapeutic dose of OCA 25 mg in this patient population is 860 subjects. A total of 658 subjects had ≥6 months exposure to OCA 25 mg, and 530 subjects had ≥12 months exposure.

The clinical safety database is supported by data from healthy volunteer/special population, subjects treated with up to 500 mg of OCA as well as data from subjects with PBC and other chronic liver diseases. OCA exposure information also includes subjects with compensated Child-Pugh A cirrhosis due to NASH, the majority of whom are from an ongoing randomized, double-blind, placebo-controlled Phase 3 study (Study 747-304) in that population.

The safety topics of special interest that the Applicant has identified in the population of interest are pruritus, hepatic TEAEs, cardiovascular disorders, including dyslipidaemia TEAEs, gallbladder disease, renal safety and glycemic parameters.

Patient exposure

The clinical safety database includes data from the following studies:

- 17 clinical pharmacology studies in healthy subjects and special populations:
  14 studies conducted in healthy subjects, two studies conducted in healthy subjects and subjects with hepatic impairment (747-103, 747-118), and one study conducted in healthy subjects and subjects with renal impairment (747-120)

- Two clinical pharmacology studies conducted in subjects with liver fibrosis due to NASH: one study to characterize the pharmacokinetics (PK) of OCA (747-117) and one study to assess the effects of OCA and atorvastatin on lipoprotein metabolism (747-209)
- Three long-term, double-blind (DB), placebo-controlled studies in subjects with liver fibrosis due to NASH: 747-303, FLINT, and D8602001.
- One open-label (OL) long-term safety extension study in subjects with liver fibrosis due to NASH (747-209 Long-Term Safety Extension [LTSE])

  In addition, several studies have been evaluated in other chronic liver diseases. Data from these studies will be included as part of the exposure analyses; Study 747-304 (NASH cirrhosis) is an ongoing blinded study and is not part of the exposure analysis.

A summary of exposure in subjects in the All Treated Subjects (Pool 1) is provided in table below for the Safety Population. Overall, approximately 3200 subjects have been treated with OCA in clinical studies.

Table 26 Extent of Exposure for All Treated Subjects (Pool 1): Safety Population (All Follow-up)

Parameter	Clin Pharm		NASH Studies					Other Studies (Other Indications)			All Pooled Studies	
	Healthy Subjects and Special Populations		Clin Pharm		DB, Controlled		LTSE					
	Placebo N = 88	Total OCA N = 879	Placebo N = 32	Initial OCA[a] N = 103	Placebo N = 849	Total OCA N = 1602	Crossover OCA[b] N = 21	Placebo N = 181	Initial OCA[a] N = 459	Crossover OCA[b] N = 119	Placebo N = 1150	Total OCA N = 3183
Average daily dose[c]												
n	0	879	0	103	0	1461	21	0	459	119	0	3042
Median (Q1, Q3)	0.0 (0.0, 0.0)	10.0 (0.7, 25.0)	0.0 (0.0, 0.0)	10.1 (9.9, 24.6)	0.0 (0.0, 0.0)	13.8 (10.0, 25.0)	10.0 (9.8, 24.1)	0.0 (0.0, 0.0)	10.0 (8.1 25.0)	8.7 (5.0, 12.8)	0.0 (0.0, 0.0)	10.0 (9.7, 25.0)
Min, Max	0, 0	1, 500	0, 0	5, 25	0, 0	1, 40	7, 25	0, 0	2, 66	2, 39	0, 0	1, 500
Number of days on IP												
n	88	879	32	103	849	1602	21	181	459	119	1150	3183
Median (Q1, Q3)	5.0 (5.0, 5.0)	2.0 (2.0, 18.0)	111.5 (85.0, 112.5)	269.0 (85.0, 567.0)	499.0 (267.0, 590.0)	496.0 (240.0, 605.0)	432.0 (342.0, 482.0)	160.0 (84.0, 357.0)	355.0 (43.0, 1536.0)	852.0 (386.0, 1750.0)	376.0 (112.0, 536.0)	257.0 (18.0, 554.0)
Min, Max	1, 12	1, 29	85, 115	15, 715	1, 1044	1, 1047	28, 582	3, 378	3, 2976	7, 2918	1, 1044	1, 2976
≥1 dose and <1 week, n (%)	78 (88.6)	559 (63.6)	0 (0.0)	0 (0.0)	12 (1.4)	10 (0.6)	0 (0.0)	1 (0.6)	7 (1.5)	0 (0.0)	91 (7.9)	576 (18.1)
≥1 week and <1 month, n (%)	10 (11.4)	320 (36.4)	0 (0.0)	2 (1.9)	17 (2.0)	48 (3.0)	1 (4.8)	3 (1.7)	67 (14.6)	5 (4.2)	30 (2.6)	443 (13.9)
≥1 month and <3 months, n (%)	0 (0.0)	0 (0.0)	11 (34.4)	41 (39.8)	48 (5.7)	109 (6.8)	1 (4.8)	81 (44.8)	114 (24.8)	4 (3.4)	140 (12.2)	269 (8.5)
≥3 months and <4 months, n (%)	0 (0.0)	0 (0.0)	21 (65.6)	4 (3.9)	18 (2.1)	59 (3.7)	0 (0.0)	4 (2.2)	10 (2.2)	1 (0.8)	43 (3.7)	74 (2.3)
≥4 months and <6 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.9)	51 (6.0)	89 (5.6)	2 (9.5)	22 (12.2)	6 (1.3)	2 (1.7)	73 (6.3)	102 (3.2)

≥6 months and <12 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0	3 (2.9)	122 (14.4)	257 (16.0)	3 (14.3)	48 (26.5)	30 (6.5)	13 (10.9)	170 (14.8)	306 (9.6)
≥12 months and <15 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)	70 (8.2)	124 (7.7)	7 (33.3)	22 (12.2)	16 (3.5)	18 (15.1)	92 (8.0)	167 (5.2)
≥15 months and <18 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	16 (15.5)	245 (28.9)	375 (23.4)	6 (28.6)	0 (0.0)	32 (7.0)	5 (4.2)	245 (21.3)	434 (13.6)
≥18 months and <24 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	32 (31.1)	164 (19.3)	329 (20.5)	1 (4.8)	0 (0.0)	24 (5.2)	9 (7.6)	164 (14.3)	395 (12.4)
≥24 months and <36 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	102 (12.0)	202 (12.6)	0 (0.0)	0 (0.0)	28 (6.1)	10 (8.4)	102 (8.9)	240 (7.5)
≥36 months and <48 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.7)	1 (0.8)	0 (0.0)	9 (0.3)
≥48 months and <60 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (2.0)	37 (31.1)	0 (0.0)	46 (1.4)
≥60 months and <72 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	88 (19.2)	6 (5.0)	0 (0.0)	94 (3.0)
≥72 months and <84 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (3.3)	5 (4.2)	0 (0.0)	20 (0.6)
≥84 months and <96 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	3 (2.5)	0 (0.0)	7 (0.2)
≥96 months, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (<0.1)

IP = investigational product; LTSE = long-term safety extension; max = maximum; min = minimum; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; Q1 = first quartile; Q3 = third quartile

[a] Initial OCA includes all subjects who initially received OCA in double-blind or primary treatment phase.

[b] Crossover OCA includes all subjects who were initially randomized to placebo in double-blind phase and switched to OCA in LTSE phase. A total of 19 subjects who received OCA 10 mg (10 subjects) or placebo (nine subjects) in the double-blind phase were re-randomized to receive OCA 25 mg in the LTSE phase (Study 747-209 LTSE CSR).

[c] Average daily dose = sum of doses taken during the study/duration of treatment. Average daily dose is not summarized for FLINT.

Note: Denominators for percentages are based on N, the number of subjects in the population.

Source: ISS, Table 1.5.8

Subject disposition for all healthy subjects and subjects with NASH in controlled studies is summarized in table below.

Table 27 Subject Disposition in All Controlled Studies in Healthy Subjects and Subjects with NASH (Pool 2)

	Clinical Pharmacology		NASH Studies				All Pooled Studies	
	Healthy Subjects and Special Populations		Clinical Pharmacology		DB, Controlled			
Number of Subjects (%)	Placebo (N = 88)	Total OCA (N = 879)	Placebo (N = 32)	Total OCA (N = 103)	Placebo (N = 849)	Total OCA (N = 1502)	Placebo (N = 969)	Total OCA (N = 2484)
Completed study	87 (98.9)	853 (97.0)	32 (100)	97 (94.2)	147 (17.3)	150 (10.0)	266 (27.5)	1100 (44.3)
Discontinued study	1 (1.1)	26 (3.0)	0 (0.0)	6 (5.8)	122 (14.4)	205 (13.6)	123 (12.7)	237 (9.5)
Ongoing in study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	580 (68.3)	1147 (76.4)	580 (59.9)	1147 (46.2)
Completed study phase for primary endpoint assessment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	473 (55.7)	782 (52.1)	473 (48.8)	782 (31.5)
Subjects Discontinued from IP	1 (1.1)	23 (2.6)	0 (0.0)	6 (5.8)	136 (16.0)	284 (18.9)	137 (14.1)	313 (12.6)
Withdrawal by subject	0 (0.0)	6 (26.1)	0 (0.0)	0 (0.0)	40 (32.5)	65 (24.8)	40 (32.3)	71 (24.4)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	2 (1.6)	0 (0.0)
Adverse event	1 (100)	8 (34.8)	0 (0.0)	3 (50.0)	43 (35.0)	126 (48.1)	44 (35.5)	137 (47.1)
Site terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	9 (3.4)	1 (0.8)	9 (3.1)
Non-compliance with study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.7)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)	2 (0.8)	2 (1.6)	2 (0.7)
Physician decision	0 (0.0)	1 (4.3)	0 (0.0)	1 (16.7)	3 (2.4)	15 (5.7)	3 (2.4)	17 (5.8)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	13 (10.6)	20 (7.6)	13 (10.5)	21 (7.2)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)
Progression of disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)
Other	0 (0.0)	8 (34.8)	0 (0.0)	1 (16.7)	17 (13.8)	23 (8.8)	17 (13.7)	32 (11.0)

DB = double-blind; IP = investigational product; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid
Note: For each reason for IP discontinuation, denominators for percentages are based on the total number of subjects who discontinued the IP. Reason for IP discontinuation was not collected in FLINT.
Source: ISS, Table 1.1.5

All Studies in Subjects with NASH (Except Open-Label, Uncontrolled Studies; Pool 3)

This pool comprised 2486 subjects. The percentage of subjects who completed clinical pharmacology studies was 94.2% in the OCA group and 100% in the placebo group. Across the pooled studies, the percentage of subjects who were ongoing in their studies at the time of the DCO was 71.5% in the OCA group and 65.8% in the placebo group, with all subjects being from the DB studies. Investigational product discontinuation rates (pooled studies) were generally similar between the OCA and placebo groups (18.1% and 15.4%, respectively). The reasons for investigational product discontinuation in this pool were consistent with all studies in all dose groups (the most common being AE and withdrawal by subject).

Studies in Healthy Subjects and Special Populations

Subject disposition in the clinical pharmacology studies in healthy subjects and special populations is summarized in table below. This population comprised 967 subjects. The majority of subjects in each study and treatment group completed their studies (90.9% to 100%). Investigational product discontinuations were rare and occurred in similar percentages across studies and treatment groups (1.1% to 9.1%). No one reason for investigational product discontinuation appeared to be more common than the other reasons.

Table 28 Subject Disposition in Clinical Pharmacology Studies in Healthy Subjects and Special Populations: Safety Population

	PK/ Bioavailability[a, b]	PK/ Initial Tolerability[b, c]		PK/ Intrinsic[d]	PK/ DDI[e]	Secondary Pharmacology[f]		Biocomp/ Bioequiv[g]
Number of Subjects (%)	**Total OCA (N = 44)**	**Placebo (N = 24)**	**Total OCA (N = 124)**	**Total OCA (N = 92)**	**Total OCA (N = 236)**	**Placebo (N = 64)**	**Total OCA (N = 63)**	**OCA (N = 320)**
Completed study	40 (90.9)	24 (100.0)	120 (96.8)	91 (98.9)	231 (97.9)	63 (98.4)	62 (98.4)	309 (96.6)
Discontinued study	4 (9.1)	0 (0.0)	4 (3.2)	1 (1.1)	5 (2.1)	1 (1.6)	1 (1.6)	11 (3.4)
Subjects discontinued from IP	4 (9.1)	0 (0.0)	3 (2.4)	1 (1.1)	4 (1.7)	1 (1.6)	1 (1.6)	10 (3.1)
Withdrawal by subject	3 (75.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)
Adverse event	1 (25.0)	0 (0.0)	2 (66.7)	1 (100.0)	1 (25.0)	1 (100.0)	1 (100.0)	2 (20.0)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	6 (60.0)

DDI = drug-drug interaction; IP = investigational product; MAD = multiple ascending dose; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PK = pharmacokinetic; SAD = single ascending dose;

[a] 747-104, D8601002 Food Effect

[b] D8601002 had two parts: a double-blind, placebo-controlled, randomized, SAD/MAD to investigate the safety and pharmacokinetics of DSP-1747 and an open-label, single-dose, two-period, crossover study to determine the effect of food on the pharmacokinetics of DSP-1747 in healthy Japanese male subjects.

[c] D8601002 SAD/MAD, and 747-101, 747-102, 747-105, and 747-107.

[d] 747-103, 747-118, and 747-120.

[e] 747-109, 747-110, 747-111, 747-112, and 747-114.

[f] 747-108.

[g] 747-115 and 747-116.

Note: For each reason for IP discontinuation, denominators for percentages are based on the total number of subjects who discontinued the IP.

Source: ISS, Table 1.1.4

Adverse events

An overview of TEAEs occurring in the Safety Population is shown in table below. In general, the TEAE profiles were consistent across studies, with a few exceptions noted.

Table 29 Overview of Treatment-Emergent Adverse Events in the Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population

Parameter	747-303			FLINT		D8602001		Pooled		
	Placebo N = 657	OCA 10 mg N = 653	OCA 25 mg N = 658	Placebo N = 142	OCA 25 mg N = 141	Placebo N = 50	OCA 10 mg N = 50	Placebo N = 849	OCA 10 mg N = 703	OCA 25 mg N = 799
Total number of TEAEs	[redacted]			280	366	228	161	4058	4118	4665
Total number of SAEs				39	48	3	8	135	112	179
Number (%) of subjects reporting at least one										
TEAE	548 (83.4)	579 (88.7)	601 (91.3)	87 (61.3)	105 (74.5)	47 (94.0)	44 (88.0)	682 (80.3)	623 (88.6)	706 (88.4)
TEAE by severity[a]										
Mild	161 (24.5)	163 (25.0)	130 (19.8)	29 (20.4)	20 (14.2)	31 (62.0)	26 (52.0)	221 (26.0)	189 (26.9)	150 (18.8)
Moderate	293 (44.6)	323 (49.5)	338 (51.4)	36 (25.4)	54 (38.3)	16 (32.0)	16 (32.0)	345 (40.6)	339 (48.2)	392 (49.1)
Severe	87 (13.2)	89 (13.6)	130 (19.8)	15 (10.6)	23 (16.3)	0 (0.0)	2 (4.0)	102 (12.0)	91 (12.9)	153 (19.1)
Life-threatening	5 (0.8)	4 (0.6)	2 (0.3)	7 (4.9)	6 (4.3)	0 (0.0)	0 (0.0)	12 (1.4)	4 (0.6)	8 (1.0)
Death	2 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	3 (0.4)
TEAE by relationship to IP[b] n (%)										
Not related	[redacted]			66 (46.5)	53 (37.6)	20 (40.0)	24 (48.0)	327 (38.5)	220 (31.3)	184 (23.0)
Related				21 (14.8)	52 (36.9)	27 (54.0)	20 (40.0)	355 (41.8)	403 (57.3)	522 (65.3)
Related TEAE with severity ≥3, n (%)				4 (2.8)	8 (5.7)	0 (0.0)	2 (4.0)	18 (2.1)	12 (1.7)	55 (6.9)
AE leading to discontinuation of IP[c] n (%)	41 (6.2)	39 (6.0)	83 (12.6)	NA	NA	1 (2.0)	3 (6.0)	NA	NA	NA
SAE, n (%)	75 (11.4)	72 (11.0)	93 (14.1)	17 (12.0)	24 (17.0)	2 (4.0)	6 (12.0)	94 (11.1)	78 (11.1)	117 (14.6)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IP = investigational product; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] Subjects reporting more than one AE are counted only once using the highest severity. AEs are graded for severity using CTCAE Version 4.03.

[b] Subjects reporting more than one AE are counted only once using the closest relationship to investigational product. Not related events include those reported as "unlikely" or "not related" to the investigational product; related events include those reported as "possibly related," "probably related," or "definitely related" to the investigational product.

[c] Reason for IP Discontinuation was not collected in FLINT.

Denominators for percentages are based on N, the number of subjects in the population.

AEs with missing severity are counted in the "severe" group. AEs with missing relationship are counted in the "related" group.

Source: ISS, Table 2.1.1.1

A summary of common TEAEs experienced during the long-term, DB, placebo-controlled studies is shown in table below. The common TEAEs experienced during the long-term, DB, placebo-controlled studies were generally similar across the three studies. The most common TEAEs were pruritus and low-density lipoprotein increased.

Table 30 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Affecting At Least 10% of Any Group in the Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

System Organ Class Preferred Term, n (%)	747-303			FLINT		D8602001		Pooled		
	Placebo N = 657	OCA 10 mg N = 653	OCA 25 mg N = 658	Placebo N = 142	OCA 25 mg N = 141	Placebo N = 50	OCA 10 mg N = 50	Placebo N = 849	OCA 10 mg N = 703	OCA 25 mg N = 799
Number (%) of subjects with any TEAE	548 (83.4)	579 (88.7)	601 (91.3)	87 (61.3)	105 (74.5)	47 (94.0)	44 (88.0)	682 (80.3)	623 (88.6)	706 (88.4)
Skin and subcutaneous tissue disorders	180 (27.4)	245 (37.5)	377 (57.3)	22 (15.5)	43 (30.5)	11 (22.0)	14 (28.0)	213 (25.1)	259 (36.8)	420 (52.6)
Pruritus	112 (17.0)	175 (26.8)	316 (48.0)	11 (7.7)	39 (27.7)	4 (8.0)	10 (20.0)	127 (15.0)	185 (26.3)	355 (44.4)
Gastrointestinal disorders	265 (40.3)	279 (42.7)	297 (45.1)	29 (20.4)	36 (25.5)	26 (52.0)	9 (18.0)	320 (37.7)	288 (41.0)	333 (41.7)
Nausea	77 (11.7)	72 (11.0)	83 (12.6)	7 (4.9)	10 (7.1)	0 (0.0)	0 (0.0)	84 (9.9)	72 (10.2)	93 (11.6)
Constipation	35 (5.3)	65 (10.0)	70 (10.6)	3 (2.1)	6 (4.3)	3 (6.0)	3 (6.0)	41 (4.8)	68 (9.7)	76 (9.5)
Abdominal pain	63 (9.6)	66 (10.1)	67 (10.2)	5 (3.5)	7 (5.0)	2 (4.0)	0 (0.0)	70 (8.2)	66 (9.4)	74 (9.3)
Diarrhoea	79 (12.0)	44 (6.7)	49 (7.4)	6 (4.2)	8 (5.7)	5 (10.0)	0 (0.0)	90 (10.6)	44 (6.3)	57 (7.1)
Abdominal pain upper	35 (5.3)	46 (7.0)	45 (6.8)	3 (2.1)	6 (4.3)	5 (10.0)	2 (4.0)	43 (5.1)	48 (6.8)	51 (6.4)
Infections and infestations	282 (42.9)	266 (40.7)	282 (42.9)	28 (19.7)	38 (27.0)	33 (66.0)	26 (52.0)	343 (40.4)	292 (41.5)	320 (40.1)
Nasopharyngitis	41 (6.2)	34 (5.2)	45 (6.8)	1 (0.7)	3 (2.1)	27 (54.0)	21 (42.0)	69 (8.1)	55 (7.8)	48 (6.0)
Investigations	188 (28.6)	236 (36.1)	232 (35.3)	1 (0.7)	5 (3.5)	10 (20.0)	6 (12.0)	199 (23.4)	242 (34.4)	237 (29.7)
Low density lipoprotein increased	47 (7.2)	109 (16.7)	115 (17.5)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	47 (5.5)	109 (15.5)	116 (14.5)
Musculoskeletal and connective tissue disorders	208 (31.7)	202 (30.9)	211 (32.1)	16 (11.3)	17 (12.1)	18 (36.0)	11 (22.0)	242 (28.5)	213 (30.3)	228 (28.5)
Arthralgia	55 (8.4)	50 (7.7)	50 (7.6)	2 (1.4)	0 (0.0)	5 (10.0)	2 (4.0)	62 (7.3)	52 (7.4)	50 (6.3)
General disorders and administration site conditions	144 (21.9)	138 (21.1)	143 (21.7)	11 (7.7)	12 (8.5)	10 (20.0)	5 (10.0)	165 (19.4)	143 (20.3)	155 (19.4)
Fatigue	88 (13.4)	79 (12.1)	71 (10.8)	4 (2.8)	3 (2.1)	3 (6.0)	1 (2.0)	95 (11.2)	80 (11.4)	74 (9.3)

MedDRA = Medical Dictionary for Regulatory Activities; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; TEAE = treatment-emergent adverse event
Note: Denominators for percentages are based on N, the number of subjects in the population.
Note: Adverse events are coded to MedDRA version 18.1.
Note: Subjects may have more than one event per system organ class and preferred term. At each level of subject summarization, a subject is counted once if he/she reported one or more events at that level.
Source: ISS, Table 2.1.1.9

TEAEs that were prespecified as adverse events of special interest (AESIs) as part of the ISS included TEAEs that were assessed as frequently occurring with OCA (including PBC experience), TEAEs that constitute common comorbid conditions of patients with NASH, TEAEs that were clinically related to the dose limiting toxicities observed in nonclinical studies, TEAEs for which imbalances were observed in individual studies, and laboratory changes that were generally considered to be associated with adverse outcomes.

Seven AESIs were identified in the population of interest.

Pruritus

Pruritus has been the most frequent TEAE associated with OCA treatment in both the PBC and NASH clinical development programs as well as in the PBC post-marketing setting. Pruritus is identified as an adverse drug reaction (ADR) in the labeling of Ocaliva for PBC and is categorized as the only important identified risk for OCA within the currently approved and effective European Union (EU) Risk Management Plan (RMP). The exact pathogenesis of the pruritic effect of OCA is unknown, although it is currently hypothesized to be associated with an on-target FXR effect (Patel 2018, Chen 2019).

Hepatic TEAEs

The primary nonclinical toxicity observed with OCA was reversible hepatocellular injury and elevated serum liver transaminases at high doses, consistent with well-established prototypical bile acid toxicity. These hepatic effects accurately predicted the dose-limiting toxicity of OCA observed in clinical studies; dose-related mean increases in ALT and AST were observed in healthy subjects at high doses (100 mg

and 250 mg), which were reversible after cessation of dosing. In PBC clinical studies, a dose-response relationship was observed for the occurrence of liver-related adverse reactions with OCA. The dose-limiting toxicity is related to exposure in the liver, which is known to be higher in subjects with hepatic impairment and decompensated cirrhosis. Therefore, a comprehensive evaluation of hepatic safety was performed due to the known safety profile of OCA, as well as the underlying potential for liver injury and hepatic impairment in a patient population with chronic liver disease.

Cardiovascular Disorders, Including Dyslipidemia TEAEs

A systematic approach to the surveillance and management of cardiovascular risk was undertaken to evaluate the potential impact on cardiovascular safety of the known FXR-mediated effects of OCA on lipid metabolism, which include an increase in LDLc (mostly driven by an increase in large, buoyant LDL particles, considered to be less atherogenic than small, dense LDL particles) and a decrease in HDLc concentrations, against a decrease in triglycerides and VLDLc. This evaluation was of particular importance given the increased prevalence of atherosclerotic cardiovascular disease (ASCVD) in NASH (Anstee 2013).

Gallbladder Disease

Gallbladder disease (including cholelithiasis and cholecystitis) was evaluated because of its known association with NASH (Yener 2010), similar risk factors commonly seen in the NASH patient population (ie, obesity, dyslipidemia, type 2 diabetes, insulin resistance, and metabolic syndrome), and biological plausibility for an association between OCA exposure and the development or exacerbation of gallstones (ie, increased lithogenicity of bile due to higher cholesterol saturation resulting from decreased bile acid concentration in gallbladder bile) (Al-Dury 2019).

Renal Safety

Renal exposure to OCA is negligible, as OCA and its conjugates primarily exist within the gut-liver axis due to extensive enterohepatic recirculation, and there is no exposure-response relationship for markers of renal function (creatinine, Module 2.7.2, Section 3.8.3.10). While non-clinical evidence indicates that FXR activation, including by OCA, may have anti-fibrotic and reno-protective effects (Jiang 2007, Wang 2009, Levi 2011, Hu 2012, Bae 2014, Gai 2016), it has been reported that exposure to OCA was associated with a small reduction in estimated glomerular filtration rate (eGFR) in a posthoc analysis of FLINT (Corey 2016).

Glycemic Parameters

Nonclinical studies have consistently indicated that OCA-mediated FXR activation improves insulin signalling and insulin-stimulated glucose uptake (Rizzo 2006, Maneschi 2013), and a clinical proof-of-concept study using the euglycemic hyperinsulinemic glucose clamp (Study 747-203) showed that OCA treatment improved insulin sensitivity in patients with presumed NAFLD and type 2 diabetes (Mudaliar 2013). Conversely, the FLINT study indicated possibly greater hepatic insulin resistance, as estimated by the homeostatic model assessment of insulin resistance (HOMA-IR) with OCA 25 mg treatment compared with placebo (although baseline insulin levels were higher in the OCA 25 mg group, and HOMA-IR values exhibited significant variability over the course of the study), and Study 747-209 showed modest increases in fasting plasma glucose, hemoglobin A1c (HbA1c), and fasting serum insulin after 16 weeks of treatment with OCA compared with placebo (although the relatively small sample size and concomitant introduction of atorvastatin limited interpretation).

In light of these seemingly conflicting results, and given the frequent occurrence of impaired glucose tolerance and type 2 diabetes in patients with NASH, it was important to assess the effects of OCA treatment on glucose homeostasis, based on evaluation of TEAEs, as well as glycemic laboratory parameters.

Serious adverse events and deaths

Across the three studies, the majority of TEAEs were mild or moderate in severity; however, the incidence of mild TEAEs was higher and the incidence of severe TEAEs was lower in Study D8602001 than in the FLINT study and Study 747-303. The incidence of moderate TEAEs was similar across the three studies. Life-threatening TEAEs and TEAEs with an outcome of death occurred in the FLINT study and Study 747-303 only, with similar incidence between these studies.

In the pooled analysis, severe TEAEs occurred in 153 (19.1%) subjects in the OCA 25 mg group, in 91 (12.9%) subjects in the OCA 10 mg group, and in 102 (12.0%) subjects in the placebo group. The difference in incidence of severe TEAEs across treatment groups was mostly driven by pruritus (37 [4.6%] subjects in the OCA 25 mg group and three [0.4%] subjects each in the OCA 10 mg and placebo groups). The incidence of life-threatening TEAEs and TEAEs leading to death was low and similar across the treatment groups (<1.5%).

Similar results were observed in the 18-month follow-up analysis of the Safety Population

Based on the totality of data, serious liver-related AEs, hepatic impairment, severe pruritus, and gallbladder disease were identified as having OCA dosing implications.

Subjects with Liver Fibrosis due to NASH

Across treatment groups, the majority of TEAEs were mild or moderate in severity. No apparent relationship between the incidence of severe TEAEs and OCA dose was observed. Severe TEAEs occurred in two (4.8%) subjects in the OCA 25 mg group (procedural pain and wrist fracture), in one (2.4%) subject in the OCA 10 mg group (fatigue), and in three (15.0%) subjects in the OCA 5 mg group (nephrolithiasis, breast cancer stage IV, and hypertensive crisis); no severe TEAEs occurred in the placebo group. Across treatment groups, no life-threatening TEAEs or TEAEs leading to death were observed.

There were two deaths (both in subjects with cirrhosis) during or after the LTSE phase of Study 747-209 (Study 747-209 CSR). One death occurred in a cirrhotic subject who transitioned from placebo in the DB phase to OCA 25 mg in the LTSE phase. The death was due to renal failure and liver failure. This subject had a history of NASH cirrhosis with hepatic impairment and presumptive evidence of portal hypertension and experienced a severe and protracted intercurrent illness (with vomiting, diarrhea, weight loss, and some degree of pre-renal azotemia related to volume status) prior to the serious hepatic TEAE.

A second death occurred 100 days after study discontinuation in a cirrhotic subject who had been randomized to OCA 10 mg during the DB phase and continued on OCA 10 mg during the LTSE phase. The subject had a history of NASH cirrhosis with hepatic impairment and evidence of portal hypertension and experienced SAEs of bacteremia, cholecystitis acute, seizure, and hepatic encephalopathy, which all resolved during the study. Additional follow-up information after study termination indicated that the subject died on Study Day 304; no additional detail shave been provided.

Studies in Subjects with Liver Fibrosis (Including Stage 4) due to NASH

Regardless of cirrhosis status, the majority of TEAEs were mild or moderate in severity in both OCA-treated subjects overall and in placebo-treated subjects. In OCA-treated subjects overall, three (13.6%) subjects with cirrhosis and three (3.7%) subjects without cirrhosis had severe TEAEs. The difference in the incidence of severe TEAEs was not driven by a single PT (breast cancer stage IV [OCA 5 mg group], hypertensive crisis [OCA 5 mg group], and fatigue [OCA 10 mg group]) and was not related to dose. No severe TEAEs occurred in the placebo group. No life-threatening TEAEs or TEAEs leading to death were observed regardless of cirrhosis status.

Deaths in All Treated Subjects

There were seven deaths in the NASH fibrosis clinical development program.

Table 31 Listing of all Deaths That Occurred in the OCA Development Program

Study ID	Subject ID	Treatment group	Primary Cause of Death System Organ Class/ Preferred Term	Relationship to IP
Double-Blind, Placebo-Controlled Studies in Subjects with NASH				
747-303	[redacted]	OCA 25 mg	Neoplasms benign, malignant and unspecified (including cysts and polyps)/ Glioblastoma	Investigator assessment: Not related Intercept assessment: Same
	[redacted]	Placebo	Neoplasms benign, malignant and unspecified (including cysts and polyps)/ Bone cancer	Investigator assessment: Not related Intercept assessment: Same
	[redacted]	Placebo	Cardiac disorders/ Cardiac arrest	Investigator assessment: Not related Intercept assessment: Same
FLINT	[redacted]	OCA 25 mg	Cardiac disorders/ Cardiac failure congestive	Investigator assessment: Not applicable Intercept assessment: Definitely not related
			Nervous system disorders/ Cerebrovascular accident	Investigator assessment: Definitely not related Intercept assessment: Probably not related
			Nervous system disorders/ Hypoxic-ischaemic encephalopathy	Investigator assessment: Definitely not related Intercept assessment: Probably not related
			Respiratory, thoracic and mediastinal disorders/ Acute respiratory distress syndrome	Investigator assessment: Definitely not related Intercept assessment: Same
	[redacted]	OCA 25 mg	Cardiac disorders/ Myocardial ischemia	Investigator assessment: Possibly related Intercept assessment: Probably not related
			Cardiac disorders/ Myocardial infarction	Investigator assessment: Possibly related Intercept assessment: Probably not related
LTSE Phase Data in Subjects with NASH				
747-209 LTSE	[redacted]	Placebo-OCA 25 mg	Renal and urinary disorders/ Acute kidney injury	Investigator assessment: Unlikely related Intercept assessment: Possibly related
			Hepatobiliary disorders/ Hepatic failure	Investigator assessment: Unlikely related Intercept assessment: Possibly related
	[redacted]	OCA 10 mg-OCA 10 mg	Unknown	Not applicable

ID = identification; IP = investigational product; LTSE = long-term safety extension; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid.

[a] A second death occurred 100 days after study discontinuation in a subject with cirrhosis due to NASH who had been randomized to OCA 10 mg during the double-blind phase and continued on OCA 10 mg during the LTSE phase.

Table 32 Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term in the Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

System Organ Class Preferred Term	747-303			FLINT		D8602001		Pooled		
	Placebo (N = 657)	OCA 10 mg (N = 653)	OCA 25 mg (N = 658)	Placebo (N = 142)	OCA 25 mg (N = 141)	Placebo (N = 50)	OCA 10 mg (N = 50)	Placebo (N = 849)	OCA 10 mg (N = 703)	OCA 25 mg (N = 799)
Number (%) of subjects with any TEAE leading to death	2 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	3 (0.4)
Cardiac disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.3)
Cardiac failure congestive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Myocardial ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiac arrest	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Glioblastoma	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Bone cancer	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypoxic-ischaemic encephalopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Acute respiratory distress syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

MedDRA = Medical Dictionary for Regulatory Activities; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; TEAE = treatment-emergent adverse event
Note: Denominators for percentages are based on N, the number of subjects in the population. Adverse events are coded to MedDRA version 18.1. Subjects may have more than one event per system organ class and preferred term. At each level of subject summarization, a subject is counted once if he/she reported one or more events at that level.
Source: ISS, Table 2.1.1.47

Laboratory findings

Hepatic biochemical analysis and analysis of renal function, glucose regulation, and lipid metabolism are discussed in more detail in this section. For all other hematology, chemistry, and urinalysis assessments, no clinically meaningful changes were noted.

Serum markers of hepatocellular injury, ALT, AST:

ALT and AST values generally declined over time in all treatment groups, but the decrease was generally more pronounced in the OCA groups. In the pooled analyses, OCA produced dose-dependent and sustained decreases in ALT and AST over time compared with placebo [for pooled population only]. The increase in ALT and AST from Month 18 to Month 24 was driven by the off-treatment period of FLINT.

ALT and AST values over time were also analyzed by baseline fibrosis stage and by worst fibrosis stage on study. These subgroup analyses produced generally similar results to those in the overall Safety Population, ie, dose-dependent and sustained decreases in ALT and AST with OCA treatment regardless of fibrosis stage at baseline.

Shifts from baseline to postbaseline worst value in ALT and AST are presented in table below.

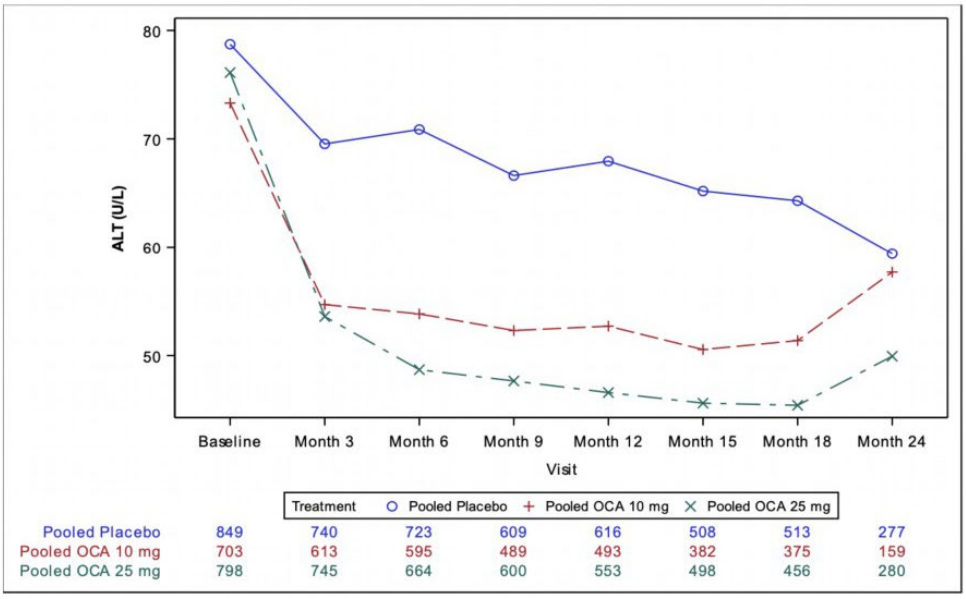
Similar results were observed in the 18-month follow-up of the Safety Population

Table 33 Mean ALT and AST Observed and Change from Baseline at Month 18 -Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

Parameter Visit Statistic	Pooled		
	Placebo N = 849	OCA 10 mg N = 703	OCA 25 mg N = 799
ALT (U/L)			
Baseline (n)	849	703	798
Mean (SD)	78.7 (51.59)	73.3 (48.14)	76.1 (52.33)
Month 18, observed (n)	513	375	456
Mean (SD)	64.3 (45.01)	51.4 (41.93)	45.4 (35.60)
Change from baseline to Month 18 (n)	513	375	456
Mean (SD)	-16.0 (48.45)	-24.3 (42.21)	-36.6 (54.00)
AST (U/L)			
Baseline (n)	849	703	799
Mean (SD)	56.3 (35.63)	53.8 (33.37)	55.8 (33.96)
Month 18, observed (n)	514	372	457
Mean (SD)	46.9 (28.69)	39.6 (29.25)	36.2 (21.73)
Change from baseline to Month 18 (n)	514	372	457
Mean (SD)	-9.3 (34.05)	-13.6 (31.21)	-21.8 (35.64)

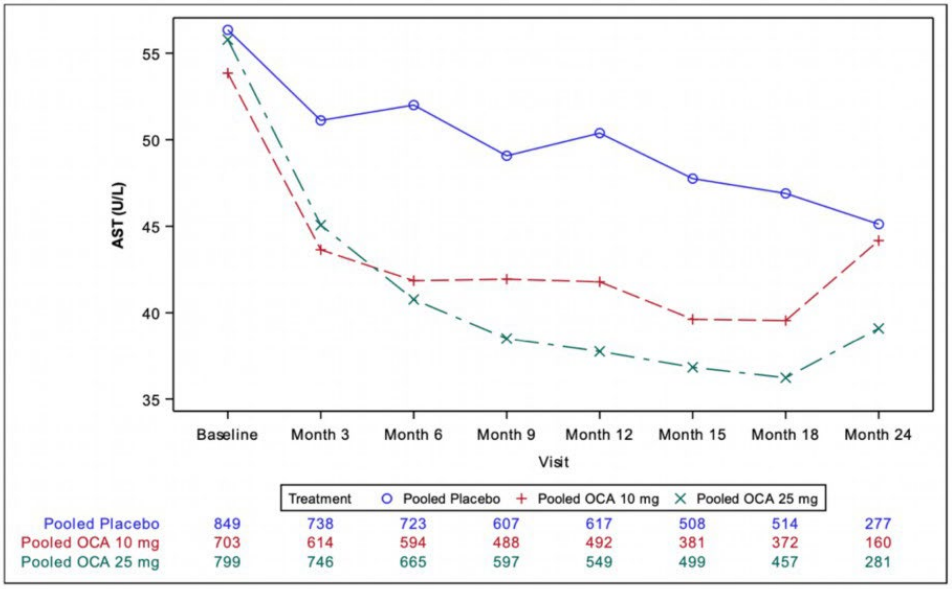
ALT = alanine aminotransferase; AST = aspartate aminotransferase; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; SD = standard deviation
Note: The baseline value is defined as the mean of all available evaluations prior to the first administration of investigational product.
Source: ISS, Table 3.1.3.2

Figure 54 Mean ALT by Visit - Pooled Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)



ALT = alanine aminotransferase; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid
Note: Baseline is defined as the mean of all available evaluations prior to the first administration of investigational product.
Source: ISS, Figure 3.1.1

Figure 55 Mean AST by Visit - Pooled Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)



AST = aspartate aminotransferase; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid
Note: Baseline is defined as the mean of all available evaluations prior to the first administration of investigational product.
Source: ISS, Figure 3.1.1

Table 34 Worst Shift from Baseline in ALT and AST - Pooled Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

Parameter	Pooled								
	Placebo (N = 849) Baseline			OCA 10 mg (N = 703) Baseline			OCA 25 mg (N = 799) Baseline		
Worst Postbaseline	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ALT									
	n = 824			n = 689			n = 779		
	≤ULN	>ULN - ≤3× ULN	>3× ULN	≤ULN	>ULN - ≤3× ULN	>3× ULN	≤ULN	>ULN - ≤3× ULN	>3× ULN
≤ULN	182 (22.1)	35 (4.2)	0	230 (33.4)	53 (7.7)	0	247 (31.7)	104 (13.4)	2 (0.3)
>ULN - ≤3× ULN	121 (14.7)	356 (43.2)	16 (1.9)	62 (9.0)	268 (38.9)	13 (1.9)	76 (9.8)	276 (35.4)	32 (4.1)
>3× ULN	1 (<0.1)	56 (6.8)	57 (6.9)	1 (<0.1)	35 (5.1)	27 (3.9)	1 (<0.1)	20 (2.6)	21 (2.7)
AST									
	n = 824			n = 689			n = 780		
	≤ULN	>ULN - ≤3× ULN	>3× ULN	≤ULN	>ULN - ≤3× ULN	>3× ULN	≤ULN	>ULN - ≤3× ULN	>3× ULN
≤ULN	115 (14.0)	30 (3.6)	0	145 (21.0)	50 (7.3)	1 (<0.1)	140 (17.9)	71 (9.1)	1 (<0.1)
>ULN - ≤3× ULN	146 (17.7)	366 (44.4)	16 (1.9)	61 (8.9)	321 (46.6)	11 (1.6)	80 (10.3)	377 (48.3)	28 (3.6)
>3× ULN	3 (0.4)	95 (11.5)	53 (6.4)	2 (0.3)	51 (7.4)	47 (6.8)	6 (0.8)	49 (6.3)	28 (3.6)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; ULN = upper limit of normal range
Note: Denominators for percentages are based on the number of subjects with nonmissing baseline and postbaseline measurements for the given parameter. The baseline value is defined as the mean of all available evaluations prior to the first administration of the investigational product.
Source: ISS, Table 3.1.7

Serum markers of cholestasis, ALP and GGT:

ALP is a liver biomarker of interest due to an identified FXR-dependent transcriptional regulation of phospholipase D that leads to an increase in soluble ALP.

Consistent with this known pharmacodynamic effect of FXR activation, more subjects experienced shifts in ALP from baseline ≤ULN to postbaseline >ULN to ≤1.5× ULN in the total OCA group compared with the placebo group.

In the pooled analysis, a modest increase in ALP was observed from baseline over time in the OCA 25 mg group, while no change from baseline was observed in the OCA 10 mg or placebo groups [for pooled population only]).

With respect to GGT, dose-dependent reductions from baseline were observed with OCA treatment, with reductions from baseline values evident at Month 3 and sustained through Month 18 [for pooled population only]). A modest decrease in ALP and a modest increase in GGT were observed from Month 18 to Month 24 in the OCA 25 mg group, which were driven by the off-treatment period of FLINT; no significant change in ALP and GGT was observed in the placebo and OCA 10 mg groups from Month 18 to Month 24.

ALP and GGT values over time were also analyzed by baseline fibrosis stage and by worst fibrosis stage on study. These subgroup analyses produced generally similar results as the overall Safety Population, ie, dose-dependent and sustained decreases in GGT and a modest increase in ALP values over time in the OCA 25 mg group regardless of baseline fibrosis stage.

Shifts from baseline to postbaseline worst value in ALP are presented below. More subjects experienced shifts in ALP from baseline ≤ULN to postbaseline >ULN to ≤1.5× ULN in the OCA 25 mg group compared with the OCA 10 mg and placebo groups. The proportion of subjects who experienced shifts in ALP from baseline >ULN to ≤1.5× ULN to postbaseline >1.5× ULN was similar across treatment groups. The proportion of subjects who experienced shifts in ALP from baseline ≤ULN to postbaseline >1.5× ULN was low overall but higher in the OCA 25 mg and OCA 10 mg groups compared with the placebo group.

Table 35 Mean ALP and GGT Observed and Change from Baseline at Month 18 - Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

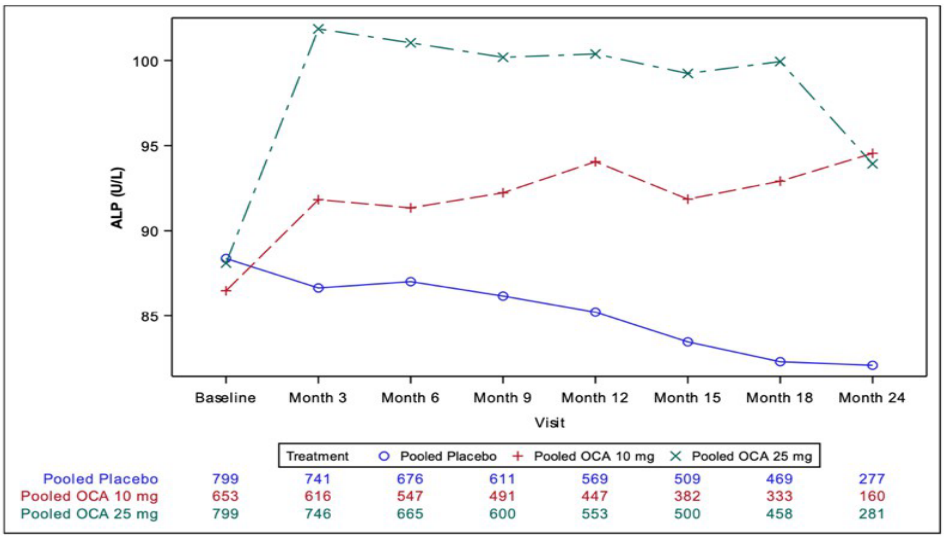
Parameter Visit Statistic	Pooled		
	Placebo N = 849	OCA 10 mg N = 703	OCA 25 mg N = 799
ALP (U/L)			
Baseline (n)	799	653	799
Mean (SD)	88.4 (32.67)	86.5 (28.97)	88.1 (32.60)
Month 18, observed (n)	469	333	458
Mean (SD)	82.3 (29.46)	92.9 (35.25)	99.9 (38.27)
Change from baseline to Month 18 (n)	469	333	458
Mean (SD)	-2.4 (18.61)	6.6 (23.58)	14.8 (26.74)
GGT (U/L)			
Baseline (n)	849	703	799
Mean (SD)	92.4 (113.13)	90.2 (106.59)	89.5 (104.68)
Month 18, observed (n)	513	377	458
Mean (SD)	74.6 (84.59)	67.1 (116.97)	45.8 (67.84)
Change from baseline to Month 18 (n)	513	377	458
Mean (SD)	-7.5 (51.50)	-22.5 (77.94)	-39.1 (76.01)

ALP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; SD = standard deviation

Notes: The baseline value is defined as the mean of all available evaluations prior to the first administration of the investigational product. ALP is not summarized for D8602001 since the normal range is substantially different from the other studies.

Source: ISS, Table 3.1.3.2

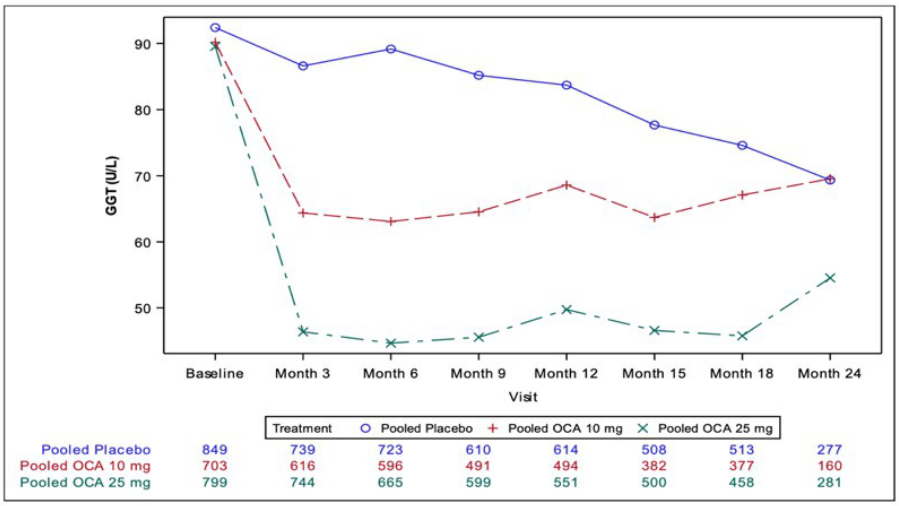
Figure 56 Mean ALP by Visit - Pooled Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)



Pooled Placebo	799	741	676	611	569	509	469	277
Pooled OCA 10 mg	653	616	547	491	447	382	333	160
Pooled OCA 25 mg	799	746	665	600	553	500	458	281

ALP = alkaline phosphatase; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid
Note: Baseline is defined as the mean of all available evaluations prior to the first administration of the investigational product.
Source: ISS, Figure 3.1.1

Figure 57 Mean GGT by Visit - Pooled Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)



Pooled Placebo	849	739	723	610	614	508	513	277
Pooled OCA 10 mg	703	616	596	491	494	382	377	160
Pooled OCA 25 mg	799	744	665	599	551	500	458	281

GGT = gamma-glutamyl transferase; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid
Note: Baseline is defined as the mean of all available evaluations prior to the first administration of the investigational product.
Source: ISS, Figure 3.1.1

Figure 58 Worst Shift from Baseline in ALP - Pooled Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

Worst Postbaseline	Pooled								
	Placebo (N = 849) Baseline			OCA 10 mg (N = 703) Baseline			OCA 25 mg (N = 799) Baseline		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	n = 824			n = 689			n = 780		
	≤ULN	>ULN - ≤1.5× ULN	>3× ULN	≤ULN	>ULN - ≤1.5× ULN	>1.5× ULN	≤ULN	>ULN - ≤1.5× ULN	>1.5× ULN
≤ULN	725 (88.0)	4 (0.5)	0	604 (87.7)	3 (0.4)	0	589 (75.5)	4 (0.5)	0
>ULN - ≤1.5× ULN	48 (5.8)	35 (4.2)	1 (<0.1)	51 (7.4)	13 (1.9)	0	129 (16.5)	19 (2.4)	4 (0.5)
>1.5× ULN	3 (0.4)	3 (0.4)	5 (0.6)	10 (1.5)	8 (1.2)	0	22 (2.8)	11 (1.4)	2 (0.3)

ALP = alkaline phosphatase; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; ULN = upper limit of normal range
Note: Denominators for percentages are based on the number of subjects with non-missing baseline and postbaseline measurements for the given parameter. The baseline value is defined as the mean of all available evaluations prior to the first administration of the investigational product.
Source: ISS, Table 3.1.7

Serum Markers of Liver Synthetic Function, bilirubin, direct bilirubin, INR and platelet counts:

No clinically significant changes over time or differences across treatment groups were observed with respect to total bilirubin, direct bilirubin, INR, and platelet counts [for pooled population only]).

Similarly, irrespective of baseline fibrosis stage (stage 0/1, stage 2, or stage 3) or worst fibrosis stage on study (stage 0/1, stage 2, stage 3, or stage 4), no clinically significant changes over time or differences across treatment groups were observed with respect to total bilirubin, direct bilirubin, INR, and platelet counts.

Shifts from baseline to postbaseline worst value in total bilirubin and direct bilirubin are presented in table below.

Table 36 Mean Total Bilirubin, Direct Bilirubin, INR, and Platelet Count Observed and Change from Baseline at Month 18 - Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

Parameter Visit Statistic	Pooled Placebo N = 849	Pooled OCA 10 mg N = 703	Pooled OCA 25 mg N = 799
Bilirubin (mg/dL)			
Baseline (n)	849	703	798
Mean (SD)	0.663 (0.337)	0.661 (0.303)	0.676 (0.341)
Month 18, observed (n)	513	375	457
Mean (SD)	0.683 (0.362)	0.680 (0.343)	0.659 (0.333)
Change from baseline to Month 18 (n)	513	375	457
Mean (SD)	0.027 (0.222)	0.007 (0.207)	-0.021 (0.235)
Direct bilirubin (mg/dL)			
Baseline (n)	849	701	797
Mean (SD)	0.235 (0.102)	0.251 (0.094)	0.240 (0.110)
Month 18, observed (n)	497	363	447
Mean (SD)	0.232 (0.115)	0.252 (0.113)	0.222 (0.127)
Change from baseline to Month 18 (n)	497	363	447
Mean (SD)	0.006 (0.076)	-0.005 (0.076)	-0.009 (0.096)

INR (ratio)			
Baseline (n)	798	653	799
Mean (SD)	1.05 (0.087)	1.07 (0.099)	1.05 (0.089)
Month 18, observed (n)	466	333	453
Mean (SD)	1.05 (0.100)	1.05 (0.116)	1.02 (0.096)
Change from baseline to Month 18 (n)	465	333	453
Mean (SD)	0.00 (0.098)	-0.01 (0.125)	-0.02 (0.098)
Platelet count (10^9/L)			
Baseline (n)	848	701	798
Mean (SD)	240.95 (66.379)	240.29 (64.671)	242.38 (67.318)
Month 18, observed (n)	508	374	457
Mean (SD)	241.80 (70.795)	242.13 (70.925)	250.97 (74.989)
Change from baseline to Month 18 (n)	508	373	457
Mean (SD)	0.38 (38.078)	3.79 (37.337)	9.51 (38.166)

INR = international normalized ratio; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; SD = standard deviation
Notes: The baseline value is defined as the mean of all available evaluations prior to the first administration of the investigational product.
Source: ISS, Table 3.1.3.2

Table 37 Worst Shift from Baseline in Total Bilirubin and Direct Bilirubin - Pooled Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

Parameter	Pooled								
	Placebo (N = 849) Baseline			OCA 10 mg (N = 703) Baseline			OCA 25 mg (N = 799) Baseline		
Worst Postbaseline	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total bilirubin									
	n = 824			n = 689			n = 779		
	≤ULN	>ULN - ≤2× ULN	>2× ULN	≤ULN	>ULN - ≤2× ULN	>2× ULN	≤ULN	>ULN - ≤2× ULN	>2× ULN
≤ULN	701 (85.1%)	3 (0.4%)	0	586 (85.1%)	4 (0.6%)	0	652 (83.7%)	9 (1.2%)	0
>ULN - ≤2× ULN	72 (8.7%)	34 (4.1%)	1 (<0.1%)	68 (9.9%)	26 (3.8%)	0	67 (8.6%)	41 (5.3%)	0
>2× ULN	2 (0.2%)	10 (1.2%)	1 (<0.1%)	0	4 (0.6%)	1 (<0.1%)	2 (0.3%)	7 (0.9%)	1 (<0.1%)
Direct bilirubin									
	n = 824			n = 687			n = 778		
	≤ULN	>ULN - ≤2× ULN	>2× ULN	≤ULN	>ULN - ≤2× ULN	>2× ULN	≤ULN	>ULN - ≤2× ULN	>2× ULN
≤ULN	761 (92.4%)	2 (0.2%)	0	632 (92.0%)	1 (<0.1%)	0	718 (92.3%)	1 (<0.1%)	0
>ULN - ≤2× ULN	41 (5.0%)	15 (1.8%)	0	40 (5.8%)	14 (2.0%)	0	31 (4.0%)	22 (2.8%)	0
>2× ULN	3 (0.4%)	2 (0.2%)	0	0	0	0	5 (0.6%)	1 (<0.1%)	0

NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; ULN = upper limit of normal range
Note: Denominators for percentages are based on the number of subjects with nonmissing baseline and postbaseline measurements for the given parameter. The baseline value is defined as the mean of all available evaluations prior to the first administration of the investigational product.
Source: ISS, Table 3.1.7

Suspected Hepatic Injury or Decompensation:

The proportion of subjects meeting any of the Study 747-303 protocol-specified laboratory criteria for drug interruption and close monitoring of potential hepatic injury or decompensation was also low and similar across treatment groups in the pooled analysis. The criteria for direct bilirubin and creatinine accounted for the majority of entries, but the proportion of subjects meeting these criteria did not differ between treatment groups. With the exception of the ALP criterion, which was met by a higher proportion of OCA-treated subjects than placebo-treated subjects, no other imbalances were observed between treatment groups with respect to each criterion. Although more OCA-treated subjects met the ALP criterion as compared with placebo, the proportion remained low (<1.5%) and, again, is consistent with the known pharmacodynamic effect of FXR activation.

Table 38 Liver Laboratory Criteria for Monitoring for Suspected Hepatic Injury or Decompensation- Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

Criteria	Pooled		
	Placebo (N = 849) n/nn (%)	OCA 10 mg (N = 703) n/nn (%)	OCA 25 mg (N = 799) n/nn (%)
Overall	76/824 (9.2)	77/689 (11.2)	73/780 (9.4)
Direct bilirubin	22/824 (2.7)	21/687 (3.1)	25/778 (3.2)
Creatinine	36/822 (4.4)	39/689 (5.7)	36/778 (4.6)
ALT	4/824 (0.5)	3/689 (0.4)	1/779 (0.1)
AST	8/824 (1.0)	4/689 (0.6)	4/780 (0.5)
ALP	1/824 (0.1)	5/689 (0.7)	11/780 (1.4)
Bilirubin	14/824 (1.7)	9/689 (1.3)	8/779 (1.0)
INR	2/761 (0.3)	4/638 (0.6)	2/764 (0.3)
GGT	3/824 (0.4)	5/689 (0.7)	2/779 (0.3)
Albumin	0/822 (0.0)	0/689 (0.0)	2/778 (0.3)
Platelet count	5/821 (0.6)	3/685 (0.4)	3/776 (0.4)
Sodium	0/822 (0.0)	1/689 (0.1)	1/778 (0.1)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; INR = international normalized ratio; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid

Notes: Denominator (nn) is based on subjects with baseline and at least one post-baseline data for each parameter. Specific criteria for each parameter are listed in the Statistical Analysis Plan, Section 10.5.5. These match the protocol-specified criteria in Study 747-303.

Source: ISS, Table 3.1.17

Serum Markers of Renal Function

Serum markers of renal function included eGFR, serum creatinine, and urinary albumin-to-creatinine ratio. Based on the pooled analysis, no clinically significant changes over time or differences across treatment groups were observed for any of these parameters.

Table 39 Mean Observed and Change from Baseline in Renal Function Laboratory Parameters at Month 18 - Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

Parameter Visit Statistic	Pooled		
	Placebo N = 849	OCA 10 mg N = 703	OCA 25 mg N = 799
eGFR (mL/min/1.73 m^2)			
Baseline (n)	765	646	741
Mean (SD)	94.3 (16.67)	95.0 (16.04)	93.1 (17.56)
Month 18, observed (n)	479	355	436
Mean (SD)	94.3 (17.10)	94.7 (17.24)	92.3 (18.51)
Change from baseline to Month 18 (n)	479	355	436
Mean (SD)	-0.3 (8.32)	-0.4 (8.54)	-1.2 (10.10)
Creatinine (mg/dL)			
Baseline (n)	849	703	799
Mean (SD)	0.788 (0.182)	0.773 (0.177)	0.793 (0.188)
Month 18, observed (n)	514	377	458
Mean (SD)	0.787 (0.185)	0.790 (0.205)	0.799 (0.191)
Change from baseline to Month 18 (n)	514	377	458
Mean (SD)	-0.010 (0.095)	-0.004 (0.114)	-0.003 (0.117)
Urine albumin/creatinine (mg/g)			
Baseline (n)	634	633	638
Mean (SD)	32.999 (93.398)	37.889 (120.151)	45.776 (235.227)
Month 18, observed (n)	356	363	389
Mean (SD)	37.402 (163.184)	42.524 (191.168)	48.280 (195.595)
Change from baseline to Month 18 (n)	337	345	372
Mean (SD)	3.248 (95.444)	9.950 (130.675)	-7.107 (148.851)

eGFR = estimated glomerular filtration rate; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; SD = standard deviation

Notes: The baseline value is defined as the mean of all available evaluations prior to the first administration of the investigational product.

Source: ISS, Table 3.4.1.2

Serum Markers of Glycemic Control

Serum markers of glycemic control included fasting plasma glucose, fasting serum insulin, and HbA1c.

Based on the pooled analysis, mean fasting plasma glucose concentrations increased across all three treatment groups over time. Similar results were observed for HbA1c (mean [SD] change from baseline values at Month 3: 0.26% [0.770] in the OCA 25 mg group, 0.21% [0.732] in the OCA 10 mg group, and 0.04% [0.576] in the placebo group), with no clinically meaningful differences across treatment groups at Month 18 [for pooled population only]). Mean fasting serum insulin concentrations increased modestly from baseline in the OCA 25 mg and OCA 10 mg groups and decreased slightly in the placebo group (for pooled population only).

Table 40 Mean Observed and Change from Baseline Glucose, HbA1c, and Insulin at Month 18 - Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

Parameter Visit Statistic	Pooled		
	Placebo N = 849	OCA 10 mg N = 703	OCA 25 mg N = 799
Glucose (mg/dL)			
Baseline (n)	840	690	790
Mean (SD)	117.5 (37.89)	119.3 (41.34)	117.5 (37.38)
Month 18, observed (n)	512	373	455
Mean (SD)	119.7 (41.64)	120.6 (40.58)	125.2 (46.42)
Change from baseline to Month 18 (n)	507	365	450
Mean (SD)	4.3 (39.13)	3.5 (45.19)	8.4 (41.04)
HbA1c (%)			
Baseline (n)	837	689	789
Mean (SD)	6.47 (1.090)	6.47 (1.162)	6.51 (1.164)
Month 18, observed (n)	511	372	455
Mean (SD)	6.50 (1.185)	6.64 (1.386)	6.64 (1.325)
Change from baseline to Month 18 (n)	504	364	450
Mean (SD)	0.08 (0.819)	0.20 (1.064)	0.16 (0.953)
Insulin (mU/L)			
Baseline (n)	786	639	783
Mean (SD)	30.094 (37.001)	31.280 (41.009)	33.236 (47.320)
Month 18, observed (n)	477	340	466
Mean (SD)	26.995 (32.539)	32.036 (46.438)	34.692 (44.783)
Change from baseline to Month 18 (n)	467	330	455
Mean (SD)	-0.903 (28.048)	3.179 (44.830)	2.108 (37.665)

NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; SD = standard deviation
Notes: The baseline value is defined as the mean of all available evaluations prior to the first administration of the investigational product.
Source: ISS, Table 3.3.1.2

By baseline diabetes status: Similar trends in glycemic parameters to those of the overall Safety Population were observed in both subjects with and subjects without type 2 diabetes at baseline, although the magnitude of increases was more pronounced in subjects with type 2 diabetes.

By antidiabetic medication use: In subjects who never used antidiabetic medication, no clinically meaningful changes from baseline or trends across treatment groups were observed in fasting plasma glucose, fasting serum insulin, and HbA1c; the results in subjects who never used antidiabetic medication were generally consistent with the results in nondiabetic subjects. In subjects who used antidiabetic medication at baseline, similar trends as for the overall Safety Population were observed for all glycemic parameters. In subjects who initiated antidiabetic medication during the study, treatment with OCA 25 mg was associated with increases in fasting plasma glucose and HbA1c that were sustained through Month 18, whereas there were no clinically meaningful changes from baseline in the OCA 10 mg and placebo groups.

In general, results of glycemic markers over time in the F2/F3 Population (integrated ITT-Safety population (Fibrosis Stages 2 and 3)) were consistent with those of the Safety Population overall, including mean changes from baseline in fasting plasma glucose, HbA1c, and fasting serum insulin.

Serum Markers of Lipid Metabolism: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Serum markers of lipid metabolism included total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Mean observed lipid values and change from baseline to Month 18 are summarized for the pooled population. Based on the pooled analysis, there were increases in mean serum LDL cholesterol concentrations of similar magnitude in the OCA 10 mg and OCA 25 mg groups, which occurred early at Month 3, and diminished in magnitude with continued treatment through Month 18, but remained higher than baseline. In the placebo group, mean LDL cholesterol concentrations decreased modestly throughout the duration of the observation period.

In the pooled analyses, mean serum total cholesterol concentrations were consistent with LDL results in the OCA groups over time.

Based on the pooled analysis, there were dose-dependent decreases in HDL cholesterol concentrations in both OCA groups; these decreases were larger in magnitude at Month 3 in the OCA 25 mg group compared to other treatment groups and sustained through Month 18, as compared to no change in the placebo group. Lastly, a progressive, dose-dependent decrease from baseline in the mean triglyceride concentration was observed in the OCA groups. The decrease in mean triglyceride concentration was observed as early as Month 3 and increased in magnitude with continued treatment until Month 18. In the placebo group, mean triglyceride values fluctuated over time but with a downward trend until Month 18.

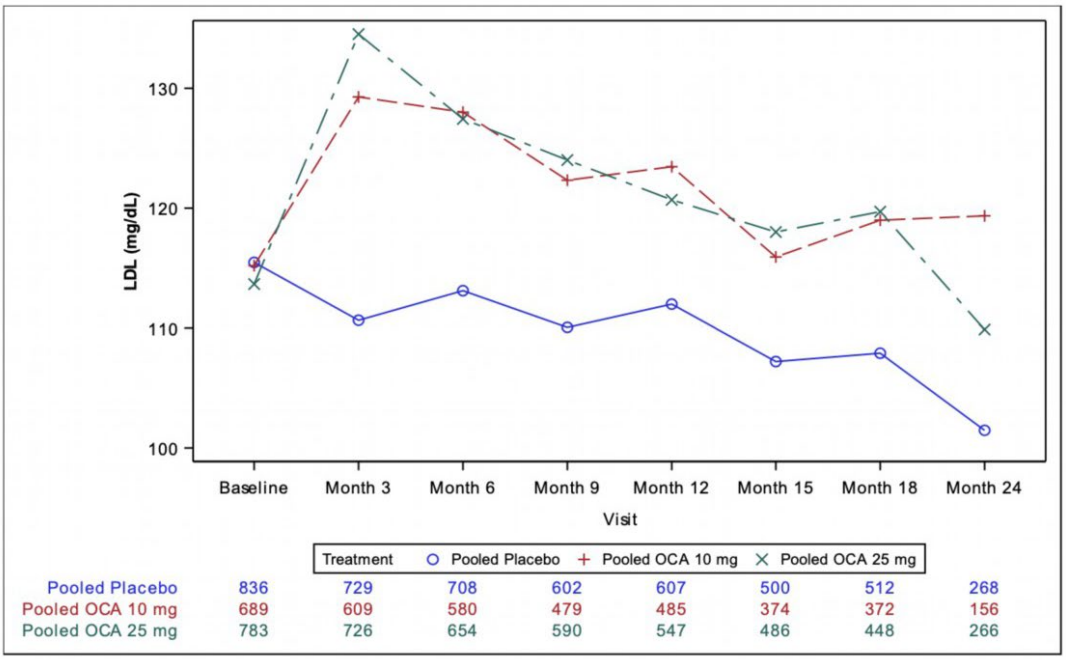
Table 41 Mean Observed and Change from Baseline in LDL, Total Cholesterol, HDL, and Triglycerides at Month 18 - Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

Parameter Visit Statistic	Pooled		
	Placebo N = 849	OCA 10 mg N = 703	OCA 25 mg N = 799
LDL (mg/dL)			
Baseline (n)	836	689	783
Mean (SD)	115.5 (37.94)	115.2 (37.12)	113.7 (37.64)
Month 18, observed (n)	512	372	448
Mean (SD)	107.9 (36.35)	119.0 (37.98)	119.7 (41.04)
Change from baseline to Month 18 (n)	505	363	440
Mean (SD)	-7.1 (30.37)	3.5 (34.46)	4.3 (37.05)
Total cholesterol (mg/dL)			
Baseline (n)	839	689	790
Mean (SD)	185.7 (42.55)	185.8 (46.60)	185.3 (44.28)
Month 18, observed (n)	514	374	455
Mean (SD)	178.2 (41.11)	183.9 (42.07)	184.8 (44.61)

Change from baseline to Month 18 (n)	509	365	450
Mean (SD)	-7.9 (35.00)	-2.3 (47.70)	-3.3 (42.84)
HDL (mg/dL)			
Baseline (n)	838	689	789
Mean (SD)	45.35 (11.516)	45.48 (12.237)	44.34 (10.885)
Month 18, observed (n)	514	373	455
Mean (SD)	45.58 (12.014)	44.33 (11.563)	41.72 (9.931)
Change from baseline to Month 18 (n)	508	364	449
Mean (SD)	0.16 (7.078)	-1.09 (7.501)	-2.29 (7.859)
Triglycerides (mg/dL)			
Baseline (n)	839	688	790
Mean (SD)	172.5 (125.46)	178.7 (167.78)	184.7 (159.98)
Month 18, observed (n)	514	373	455
Mean (SD)	160.4 (104.85)	151.6 (74.00)	156.3 (96.32)
Change from baseline to Month 18 (n)	509	363	450
Mean (SD)	-14.6 (130.24)	-30.5 (166.73)	-38.3 (153.90)
VLDL (mg/dL)			
Baseline (n)	647	638	649
Mean (SD)	32.5 (15.61)	34.5 (29.64)	33.8 (18.65)
Month 18, observed (n)	338	329	329
Mean (SD)	30.8 (14.22)	29.9 (13.62)	28.5 (15.26)
Change from baseline to Month 18 (n)	333	319	324
Mean (SD)	-1.9 (12.77)	-5.4 (32.66)	-6.4 (12.45)

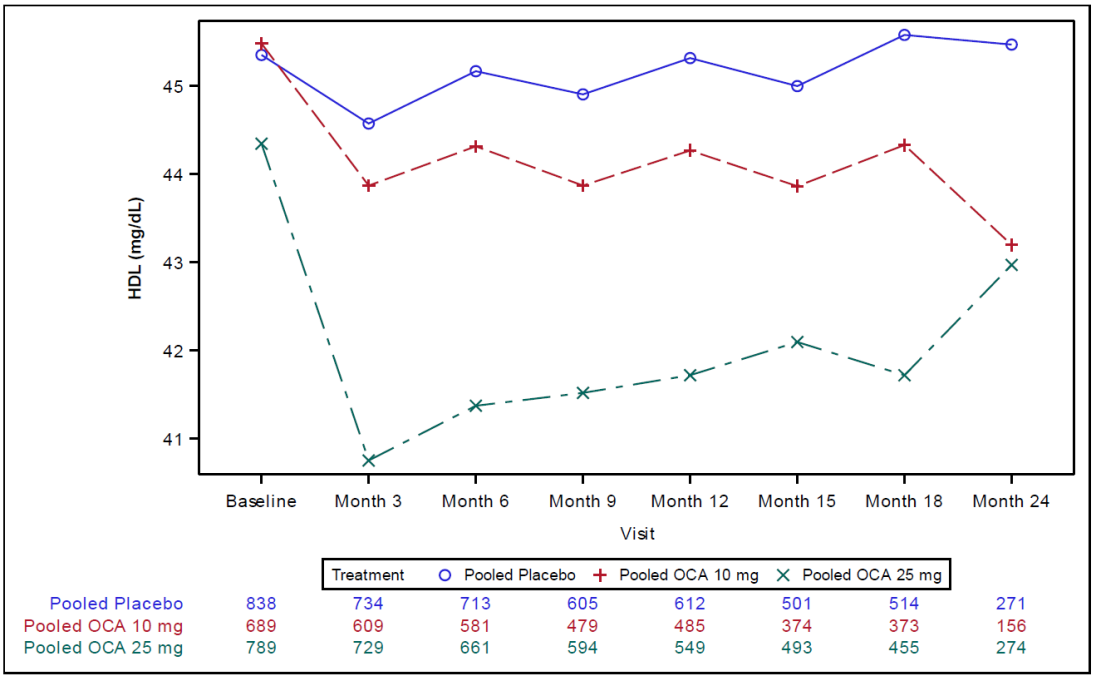
HDL = high-density lipoprotein; LDL = low-density lipoprotein; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; SD = standard deviation; VLDL = very low-density lipoprotein
Notes: The baseline value is defined as the mean of all available evaluations prior to the first administration of the investigational product.
Source: ISS, Table 3.2.1.2

Figure 59 Mean LDL by Visit - Pooled Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)



LDL = low-density lipoprotein; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid
Note: Baseline is defined as the last fasted evaluation prior to the first administration of the investigational product.
Source: ISS, Figure 3.2.1

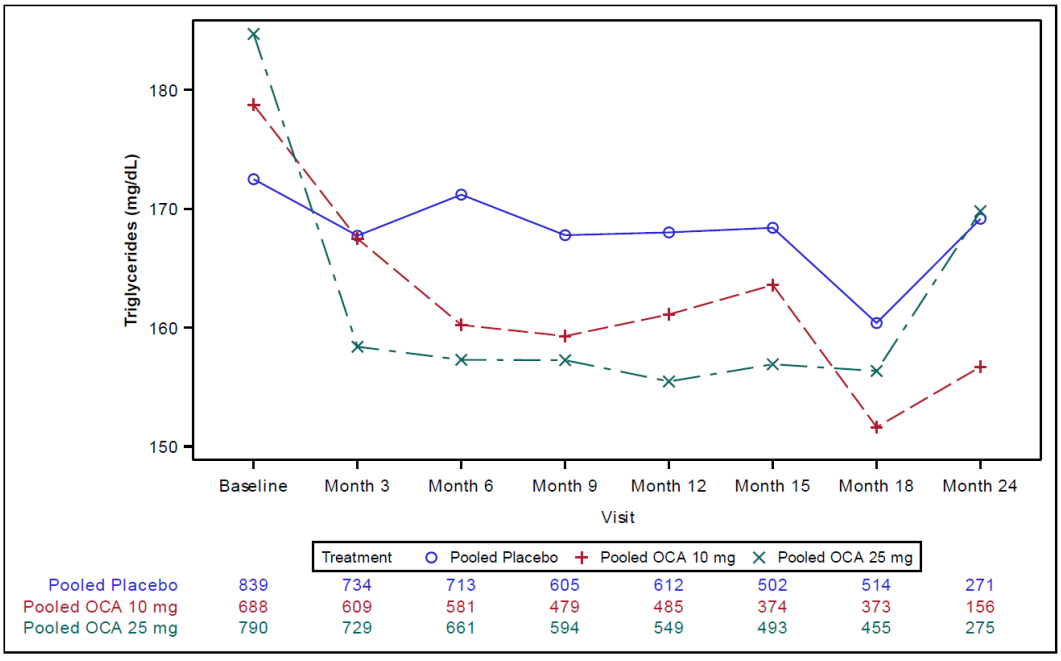
Figure 60 Mean HDL by Visit - Pooled Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)



Pooled Placebo	838	734	713	605	612	501	514	271
Pooled OCA 10 mg	689	609	581	479	485	374	373	156
Pooled OCA 25 mg	789	729	661	594	549	493	455	274

HDL = high-density lipoprotein; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid
Note: Baseline is defined as the last fasted evaluation prior to the first administration of the investigational product.
Source: ISS, Figure 3.2.1

Figure 61 Mean Triglyceride by Visit - Pooled Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)



Pooled Placebo	839	734	713	605	612	502	514	271
Pooled OCA 10 mg	688	609	581	479	485	374	373	156
Pooled OCA 25 mg	790	729	661	594	549	493	455	275

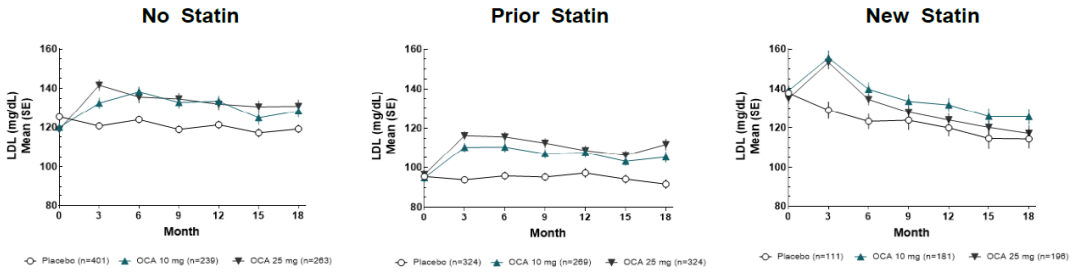
NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid
Note: Baseline is defined as the last fasted evaluation prior to the first administration of the investigational product.
Source: ISS, Figure 3.2.1

Statin Use:

Among subjects with new concomitant statin use, mean LDL cholesterol decreased at Month 18 below baseline to a similar extent in the OCA 25 mg (-17.0 mg/dL), OCA 10 mg (-14.5 mg/dL), and placebo

(-22.3 mg/dL) groups. With respect to HDL cholesterol, slightly greater decreases from baseline to Month 18 were observed in the OCA 25 mg and OCA 10 mg groups, as compared to the placebo group. A greater decrease from baseline to Month 18 in triglycerides was observed in the OCA 25 mg (-59.0 mg/dL) and OCA 10 mg (-30.0 mg/dL) groups, as compared to the placebo group (-24.0 mg/dL). These findings indicate that the increase in LDL cholesterol with OCA treatment can effectively be managed via statin treatment.

Figure 62 Summary of LDL Cholesterol by Visit and Statin Use - Pooled Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)



LDL = low-density lipoprotein; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; SE = standard error
Note: Conventional units are used.
Source: ISS, Table 3.2.3.2

The profile of serum markers of lipid metabolism, according to the administration of a new lipid-lowering agent (excluding statins, in combination with statins, and statins alone) are presented over the 18-month treatment period for the Study 747-303 safety population in table below. Note, "new concomitant use" denotes a start date of Study Day 1 or later (ie, no prior use of any of the lipid-lowering agents in that category).

Table 42 Summary of Serum Chemistry Lipids in Patients with New Concomitant Use of Lipid-Lowering Agents (747-303 Safety Population [N=1968])

Parameter Visit Statistic	Lipid-Lowering Agents (Excluding Statins)			Lipid-Lowering Agents (Including Statins)			Statins Alone		
	Placebo N = 37	OCA 10 mg N = 54	OCA 25 mg N = 88	Placebo N = 76	OCA 10 mg N = 155	OCA 25 mg N = 168	Placebo N = 79	OCA 10 mg N = 164	OCA 25 mg N = 173
LDL (mmol/L)									
Baseline (n)	37	53	87	75	153	167	77	162	170
Mean (SD)	3.0 (1.08)	3.1 (1.06)	3.0 (0.93)	3.7 (0.94)	3.6 (0.93)	3.5 (0.92)	3.7 (0.91)	3.6 (0.91)	3.5 (0.91)
Month 18, observed (n)	24	36	53	45	88	99	49	96	106
Mean (SD)	2.8 (1.03)	3.1 (1.01)	3.1 (1.12)	3.0 (1.02)	3.2 (1.09)	3.1 (1.13)	3.0 (1.06)	3.2 (1.10)	3.1 (1.20)
Change from baseline to Month 18 (n)	24	35	53	44	87	98	48	95	103
Mean (SD)	-0.1 (0.89)	0.0 (1.14)	0.1 (0.93)	-0.6 (1.07)	-0.4 (1.11)	-0.3 (1.07)	-0.7 (1.16)	-0.5 (1.06)	-0.4 (1.15)
Total cholesterol (mmol/L)									
Baseline (n)	37	53	87	75	153	167	77	162	170
Mean (SD)	5.1 (1.36)	5.3 (2.03)	4.8 (1.03)	5.6 (1.14)	5.4 (1.03)	5.3 (1.09)	5.6 (1.09)	5.5 (1.03)	5.4 (1.05)
Month 18, observed (n)	24	36	53	45	88	99	49	96	106
Mean (SD)	4.7 (1.09)	4.7 (1.07)	4.7 (1.13)	4.9 (1.25)	4.9 (1.22)	4.7 (1.20)	4.8 (1.28)	4.9 (1.24)	4.7 (1.27)
Change from baseline to Month 18 (n)	24	35	53	44	87	98	48	95	103
Mean (SD)	-0.2 (1.06)	-0.6 (2.67)	-0.2 (1.06)	-0.7 (1.17)	-0.6 (1.20)	-0.6 (1.25)	-0.8 (1.29)	-0.7 (1.14)	-0.7 (1.30)
HDL (mmol/L)									
Baseline (n)	37	53	87	75	153	167	77	162	170
Mean (SD)	1.11 (0.258)	1.09 (0.319)	1.19 (0.237)	1.23 (0.298)	1.18 (0.320)	1.16 (0.253)	1.23 (0.319)	1.19 (0.317)	1.17 (0.280)
Month 18, observed (n)	24	36	53	45	88	99	49	96	106
Mean (SD)	1.10 (0.303)	1.06 (0.261)	1.12 (0.234)	1.21 (0.314)	1.13 (0.289)	1.11 (0.255)	1.22 (0.300)	1.16 (0.323)	1.09 (0.293)
Change from baseline to Month 18 (n)	24	35	53	44	87	98	48	95	103
Mean (SD)	-0.04	-0.01	-0.08	-0.03	-0.07	-0.07	-0.05	-0.07	-0.07

	(0.182)	(0.210)	(0.217)	(0.194)	(0.235)	(0.210)	(0.213)	(0.232)	(0.204)
Triglycerides (mmol/L)									
Baseline (n)	37	53	87	75	152	167	77	161	170
Mean (SD)	3.4 (4.07)	3.3 (5.41)	1.9 (1.56)	2.6 (2.99)	2.1 (0.97)	2.0 (1.09)	2.1 (1.19)	2.1 (0.97)	2.1 (1.19)
Month 18, observed (n)	24	36	53	45	88	99	49	96	106
Mean (SD)	2.5 (1.49)	1.9 (1.12)	1.6 (0.62)	2.0 (1.10)	1.7 (0.79)	1.6 (0.78)	1.9 (0.94)	1.7 (0.77)	1.6 (0.80)
Change from baseline to Month 18 (n)	24	35	53	44	86	98	48	94	103
Mean (SD)	-1.3 (4.29)	-1.3 (5.04)	-0.4 (0.79)	-0.8 (3.30)	-0.4 (0.95)	-0.5 (0.85)	-0.2 (1.21)	-0.4 (0.93)	-0.5 (0.84)
VLDL (mmol/L)									
Baseline (n)	37	53	87	75	152	167	77	161	170
Mean (SD)	1.2 (0.63)	1.4 (2.17)	0.8 (0.45)	1.0 (0.51)	0.9 (0.40)	0.9 (0.47)	0.9 (0.45)	0.9 (0.39)	0.9 (0.49)
Month 18, observed (n)	24	36	53	45	88	99	49	96	106
Mean (SD)	1.0 (0.51)	0.8 (0.40)	0.7 (0.28)	0.9 (0.45)	0.8 (0.34)	0.7 (0.32)	0.9 (0.42)	0.8 (0.33)	0.7 (0.33)
Change from baseline to Month 18 (n)	24	35	53	44	86	98	48	94	103
Mean (SD)	-0.2 (0.42)	-0.6 (2.37)	-0.1 (0.29)	-0.1 (0.48)	-0.2 (0.36)	-0.2 (0.37)	-0.1 (0.46)	-0.1 (0.35)	-0.2 (0.36)

HDL = high-density lipoprotein; LDL = low-density lipoprotein; OCA = obeticholic acid; SD = standard deviation; VLDL = very low-density lipoprotein
Notes: The baseline value is defined as the last fasted evaluation prior to the first administration of investigational product.
Source: ISS, Tables 3.2.4.1, 3.2.5.1, and 3.2.3.1

Vital signs, Physical findings and other observations related to safety:

Assessment of vital signs included measurements of systolic and diastolic blood pressure, body temperature, and heart rate. Additionally, body weight and BMI are included in the outputs for vital signs. No meaningful trends or differences across treatment groups in vital signs were observed over time. In the pooled analysis, decreases in systolic and diastolic blood pressure across treatment groups were observed at Month 18.

ECG parameters were evaluated using standard 12-lead ECGs and included RR interval, PR interval, QRS complex, QT interval, and QT interval corrected by Fridericia's formula (QTcF). Cardiovascular risk was further classified using the FRS. No pooling of studies will be performed for ECG data because Studies D8602001 and FLINT did not collect the ECG parameters needed for these summaries. There were no clinically meaningful changes over time in ECG parameters across the three treatment groups.

A thorough QT/QTc study (Study 747-108), designed according to the FDA E14 guidance, was performed in healthy subjects to assess the effects of OCA on cardiac repolarization. The primary objective of the study was to assess whether OCA and its conjugates (glyco-OCA and tauro-OCA) at therapeutic and supratherapeutic concentrations differ from placebo in the largest time-matched mean change from baseline in 12-lead ECG corrected QT interval. On Day 5 of dosing, the mean Cmax for

the 100 mg dose was 1116 ng/mL in healthy subjects. This compares to 762 ng/mL observed at steady state with the 25 mg dose in subjects with liver fibrosis due to NASH (747-117).

The primary endpoint of the study was met. The upper limit of the 2-sided 95% CI for the LS mean difference between OCA and placebo in the change in QTc from baseline was well below the +10 msec threshold of regulatory concern for QT prolongation. The results from this study also showed no relationship between OCA exposure and ΔQTc interval. There was no meaningful effect on mean ECG values for QTcF, heart rate, QT interval, RR interval, PR interval, QRS complex, and QRS axis over time. These results confirm that OCA does not cause QT prolongation.

The effect of OCA on cardiac repolarization was also assessed in subjects with liver fibrosis (stages 1 through 4) due to NASH in Study 747-117. In this study, the ECG assessment included evaluations of ECG measures 6.0 hours postdose at steady state (OCA 10 mg and 25 mg), allowing for an evaluation of the exposure-response relationship with OCA and changes in the QT interval. No meaningful effects of OCA on QTcF were observed. Although the sample sizes per group were small (n = 20 in the OCA 25 mg group, n = 20 in the OCA 10 mg group, and n = 11 in the placebo group), the incidence of QTcF intervals >450 msec, >480 msec, and >500 msec, and changes from baseline in QTcF interval >30 msec and >60 msec were similar across the three treatment groups.

A mixed-effects model was used, using data from Study 747-117 (subjects with liver fibrosis due to NASH) and Study 747-108 (healthy subjects), to confirm that there is no relationship between plasma exposure of OCA (unconjugated OCA, glyco-OCA, tauro-OCA, and total OCA) and changes in the QT interval. Based on this analysis, no statistically significant relationship between change in QT interval and plasma exposure of OCA was observed.

These results are consistent with the ECG findings of Study 747-303 and confirm that OCA shows no QT prolongation potential in healthy subjects or subjects with liver fibrosis due to NASH.

Safety in special populations

Age:

An overview of TEAEs by age is provided in table below (<65 years, ≥65 years, or ≥75 years). Trends were generally consistent across the studies, except that subjects in Study D8602001 were all<65 years of age.

Table 43 Overview of Treatment-Emergent Adverse Events by Age Group in the Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

Parameter	Pooled		
	Placebo N=849	OCA 10 mg N=703	OCA 25 mg N=799
Age Group <65 Years			
N	709	578	640
Total Number of TEAEs	3420	3429	3563
Total Number of SAEs	109	98	115
Subjects reporting at least one TEAE, n (%)			
TEAE	571 (80.5)	511 (88.4)	558 (87.2)
TEAE by Severity[a]			
Mild	185 (26.1)	148 (25.6)	132 (20.6)
Moderate	286 (40.3)	282 (48.8)	309 (48.3)

Severe	89 (12.6)	77 (13.3)	109 (17.0)
Life-Threatening	9 (1.3)	4 (0.7)	6 (0.9)
Death	2 (0.3)	0 (0.0)	2 (0.3)
TEAE by Relationship to IP, n (%)[b]			
Not Related	268 (37.8)	180 (31.1)	159 (24.8)
Related	303 (42.7)	331 (57.3)	399 (62.3)
Related TEAE with Severity ≥3, n (%)	12 (1.7)	10 (1.7)	38 (5.9)
AE Leading to Discontinuation of IP, n (%)[c]	NA	NA	NA
SAE, n (%)	77 (10.9)	67 (11.6)	78 (12.2)
Age Group >65 Years			
N	140	125	159
Total Number of TEAEs	638	689	1102
Total Number of SAEs	26	14	64
Subjects reporting at least one TEAE, n (%)			
TEAE	111 (79.3)	112 (89.6)	148 (93.1)
TEAE by Severity[a]			
Mild	36 (25.7)	41 (32.8)	18 (11.3)
Moderate	59 (42.1)	57 (45.6)	83 (52.2)
Severe	13 (9.3)	14 (11.2)	44 (27.7)
Life-Threatening	3 (2.1)	0 (0.0)	2 (1.3)
Death	0 (0.0)	0 (0.0)	1 (0.6)
TEAE by Relationship to IP, n (%)[b]			
Not Related	59 (42.1)	40 (32.0)	25 (15.7)
Related	52 (37.1)	72 (57.6)	123 (77.4)
Related TEAE with Severity ≥3, n (%)	6 (4.3)	2 (1.6)	17 (10.7)
AE Leading to Discontinuation of IP, n (%)[c]	NA	NA	NA
SAE, n (%)	17 (12.1)	11 (8.8)	39 (24.5)
Age group ≥75 years			
N	8	8	8
Total Number of TEAEs	29	32	81
Total Number of SAEs	4	0	2
Subjects reporting at least one TEAE, n (%)			
TEAE	7 (87.5)	7 (87.5)	8 (100.0)
TEAE by Severity[a]			
Mild	1 (12.5)	4 (50.0)	2 (25.0)

Parameter	Pooled		
	Placebo N=849	OCA 10 mg N=703	OCA 25 mg N=799
Moderate	4 (50.0)	3 (37.5)	4 (50.0)
Severe	2 (25.0)	0 (0.0)	2 (25.0)
Life-Threatening	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
TEAE by Relationship to IP, n (%)[b]			
Not Related	5 (62.5)	4 (50.0)	0 (0.0)
Related	2 (25.0)	3 (37.5)	8 (100.0)
Related TEAE with Severity ≥3, n (%)	1 (12.5)	0 (0.0)	0 (0.0)
AE Leading to Discontinuation of IP, n (%)[c]	NA	NA	NA
SAE, n (%)	3 (37.5)	0 (0.0)	2 (25.0)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IP = investigational product; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] Subjects reporting more than one AE are counted only once using the highest severity. AEs are graded for severity using CTCAE Version 4.03.

[b] Subjects reporting more than one AE are counted only once using the closest relationship to investigational product. Not related events include those reported as "Unlikely" or "Not Related" to investigational product; related events include those reported as "Possibly Related," "Probably Related," or "Definitely Related" to investigational product.

[c] AE Leading to IP discontinuation information was not collected in FLINT.

Note: AEs with missing severity are counted in the 'Severe' group. AEs with missing relationship are counted in the 'Related' group.

Note: Denominators for percentages are based on N, the number of subjects in the population.

Source: ISS, Table 2.1.2.1

Table 44 Treatment-Emergent Adverse Events Affecting At Least 10% of Any Group in the Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH by Age Group: Safety Population (All Follow-Up)

Preferred Term, n (%)	Pooled		
	Placebo N = 849	OCA 10 mg N = 703	OCA 25 mg N = 799
Age group <65 years			
N	709	578	640
Number (%) of subjects with Any TEAE	571 (80.5)	511 (88.4)	558 (87.2)
Pruritus	106 (15.0)	152 (26.3)	264 (41.3)
Low density lipoprotein increased	42 (5.9)	90 (15.6)	90 (14.1)
Nausea	70 (9.9)	61 (10.6)	72 (11.3)
Abdominal pain	65 (9.2)	58 (10.0)	61 (9.5)
Fatigue	82 (11.6)	71 (12.3)	57 (8.9)
Diarrhoea	75 (10.6)	35 (6.1)	47 (7.3)
Age group ≥65 years			
N	140	125	159
Number (%) of subjects with any TEAE	111 (79.3)	112 (89.6)	148 (93.1)
Pruritus	21 (15.0)	33 (26.4)	91 (57.2)
Low density lipoprotein increased	5 (3.6)	19 (15.2)	26 (16.4)
Constipation	5 (3.6)	13 (10.4)	22 (13.8)
Nausea	14 (10.0)	11 (8.8)	21 (13.2)
Urinary tract infection	9 (6.4)	15 (12.0)	21 (13.2)
Fatigue	13 (9.3)	9 (7.2)	17 (10.7)
Diarrhoea	15 (10.7)	9 (7.2)	10 (6.3)

MedDRA = Medical Dictionary for Regulatory Activities; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; TEAE = treatment-emergent adverse event

Note: Denominators for percentages are based on N, the number of subjects in the population. Adverse events are coded to MedDRA version 18.1. Subjects may have more than one event per preferred term. At each level of subject summarization, a subject is counted once if he/she reported one or more event at that level.

Source: ISS, Table 2.1.4.1

Hepatic Impairment

Baseline Fibrosis: Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population

An overview of TEAEs by baseline fibrosis stage (stage 0/1, stage 2, and stage 3) is provided in Table below.

Table 45 Overview of Treatment-Emergent Adverse Events by Baseline Fibrosis Stage in the Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-Up)

Parameter	Pooled		
	Placebo N = 849	OCA 10 mg N = 703	OCA 25 mg N = 799
Baseline fibrosis stage: F0/F1			
N	180	122	147
Total number of TEAEs	830	728	836
Total number of SAEs	31	22	25
Number (%) of subjects reporting at least one (n [%])			
TEAE	146 (81.1)	115 (94.3)	130 (88.4)
TEAE by severity[a]			
Mild	50 (27.8)	39 (32.0)	27 (18.4)
Moderate	78 (43.3)	63 (51.6)	81 (55.1)
Severe	13 (7.2)	12 (9.8)	21 (14.3)
Life threatening	4 (2.2)	1 (0.8)	1 (0.7)
Death	1 (0.6)	0 (0.0)	0 (0.0)
TEAE by relationship to IP,[b] n (%)			
Not related	73 (40.6)	45 (36.9)	39 (26.5)
Related	73 (40.6)	70 (57.4)	91 (61.9)
Related TEAE with severity ≥3, n (%)	2 (1.1)	2 (1.6)	11 (7.5)
AE leading to discontinuation of IP[c], n (%)	NA	NA	NA
SAE, n (%)	17 (9.4)	15 (12.3)	16 (10.9)
Baseline fibrosis stage: F2			
N	279	239	283
Total number of TEAEs	1364	1450	1596
Total number of SAEs	41	43	58
Number (%) of subjects reporting at least one (n [%])			
TEAE	227 (81.4)	210 (87.9)	255 (90.1)
TEAE by severity[a]			
Mild	74 (26.5)	56 (23.4)	62 (21.9)
Moderate	113 (40.5)	120 (50.2)	135 (47.7)
Severe	35 (12.5)	32 (13.4)	54 (19.1)
Life threatening	4 (1.4)	2 (0.8)	4 (1.4)
Death	1 (0.4)	0 (0.0)	0 (0.0)
TEAE by relationship to IP[b], n (%)			
Not related	108 (38.7)	76 (31.8)	74 (26.1)

Parameter	Pooled		
	Placebo N = 849	OCA 10 mg N = 703	OCA 25 mg N = 799
Related	119 (42.7)	134 (56.1)	181 (64.0)
Related TEAE with severity ≥3, n (%)	7 (2.5)	6 (2.5)	20 (7.1)
AE leading to discontinuation of IP[c], n (%)	NA	NA	NA
SAE, n (%)	30 (10.8)	26 (10.9)	37 (13.1)
Baseline fibrosis stage: F3			
N	390	342	369
Total number of TEAEs	1864	1940	2233
Total number of SAEs	63	37	96
Number (%) of subjects reporting at least one (n [%])			
TEAE	309 (79.2)	298 (87.1)	321 (87.0)
TEAE by severity[a]			
Mild	97 (24.9)	94 (27.5)	61 (16.5)
Moderate	154 (39.5)	156 (45.6)	176 (47.7)
Severe	54 (13.8)	47 (13.7)	78 (21.1)
Life threatening	4 (1.0)	1 (0.3)	3 (0.8)
Death	0 (0.0)	0 (0.0)	3 (0.8)
TEAE by relationship to IP[b] n (%)			
Not related	146 (37.4)	99 (28.9)	71 (19.2)
Related	163 (41.8)	199 (58.2)	250 (67.8)
Related TEAE with severity ≥3, n (%)	9 (2.3)	4 (1.2)	24 (6.5)
AE leading to discontinuation of IP[c], n (%)	NA	NA	NA
SAE, n (%)	47 (12.1)	37 (10.8)	64 (17.3)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IP = investigational product; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] Subjects reporting more than one AE are counted only once using the highest severity. AEs are graded for severity using CTCAE Version 4.03.

[b] Subjects reporting more than one AE are counted only once using the closest relationship to the IP. Not related events include those reported as "unlikely" or "not related" to the IP; related events include those reported as "possibly related," "probably related," or "definitely related" to the IP.

[c] Information on AE leading to IP discontinuation was not collected in FLINT.

Note: AEs with missing severity are counted in the "severe" group. AEs with missing relationship are counted in the "related" group.

Note: Denominators for percentages are based on N, the number of subjects in the population.

Source: ISS, Table 2.1.2.4

Renal Impairment

Baseline Chronic Kidney Disease Stage: Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population

In the pooled analyses, the majority of subjects had normal eGFR/CKD stage 1 at baseline (67.2%, 67.5%, and 62.6% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively) followed by CKD stage 2 at baseline (29.5%, 30.0%, and 33.1%, respectively). Only a few subjects had CKD stage 3 at baseline (3.3%, 2.5%, and 4.3%, respectively), and none had CKD stage 4 or 5 at baseline.

The overall incidence of TEAEs was similar between subjects with normal renal function/CKD stage 1 and those with CKD stage 2. The incidence of SAEs was slightly higher among subjects with CKD stage 2 compared to those with normal renal function/CKD stage 1. The overall trends between OCA and placebo groups were generally similar to those observed in the overall Safety Population, as well as

between subjects with normal renal function/CKD stage 1 and those with CKD stage 2. There were too few subjects with CKD stage 3 to draw any meaningful conclusions.

Of the three subjects in the OCA 25 mg group who experienced TEAEs leading to death, two (0.8%) subjects had CKD stage 2, and one (0.2%) subject had normal kidney function/CKD stage 1 at baseline. Of the two subjects in the placebo group who experienced TEAEs leading to death, one (0.4%) subject had CKD stage 2, and one (0.2%) subject had normal kidney function/CKD stage 1 at baseline.

Use in Pregnancy and Lactation

The limited available human data on the use of OCA during pregnancy are not sufficient to inform a drug-associated risk. In the NASH studies, there was only one pregnancy reported, which occurred in a subject randomized in Study 747-303. In animal reproduction studies, no developmental abnormalities or direct fetal harm was observed when pregnant rats or rabbits were administered OCA (at the highest tolerated dose) during the period of organogenesis at exposures approximately 13 times and 2 times, respectively, of the human exposures at the 25 mg dose.

No specific nonclinical or clinical studies were conducted to evaluate the presence of OCA or conjugates in breast milk. Tauro-OCA was observed, at low exposures, in rat pups nursing from dams dosed with OCA. The lack of effects in offspring from pre- and postnatal studies at up to 21-fold anticipated human exposure suggests that there are no specific concerns for lactation or breastfeeding of infants (see Module 2.4, Section 4.5). However, the benefits of OCA use during lactation should be weighed against the unknown effects in nursing women.

Paediatric population

The safety and efficacy of OCA in patients <18 years of age have not been established.

Immunological events

Not applicable

Safety related to drug-drug interactions and other interactions

TEAE and SAE data from subjects with NASH treated with OCA or with placebo in the long- term, DB, placebo-controlled studies were evaluated for differences based on the on-study use of the following:

- Bile acid sequestrants
- Warfarin
- Theophylline and tizanidine

TEAEs were reported at similar incidence in subjects concurrently taking a bile acid sequestrant. While the number of subjects taking a bile acid sequestrant was small, the pattern of SOC and PTs reported between the groups was similar.

No clinically significant differences were seen in the 18-month follow-up analysis of TEAEs or SAEs.

The incidence of TEAEs was similar between subjects who were concurrently taking warfarin, theophylline or tizanidine and those who were not.

There were no clinically meaningful trends across treatment groups; however, the small number of subjects prevents from drawing definitive conclusions.

Discontinuation due to AES

Clinical Pharmacology Studies:

In Subjects with Liver Fibrosis due to NASH, TEAEs leading to investigational product withdrawal or study discontinuation were infrequent and occurred only in OCA-treated subjects: one subject with breast cancer stage IV and two subjects with pruritus in the OCA 25 mg group. Of those, both TEAEs of pruritus were considered related to the investigational product; the event of breast cancer stage IV was not considered related to the investigational product.

Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH:

TEAEs leading to investigational product withdrawal or study discontinuation are summarized in Table below. In the Study 747-303 dataset, pruritus was the only TEAE affecting at least 5% of subjects. All other PTs affected only four or fewer subjects.

The median time to permanent discontinuation was not estimable for the Safety Population

Table 46 Treatment-Emergent Adverse Events Leading to Investigational Product Withdrawal or Study Discontinuation in At Least 5% of Subjects by System Organ Class and Preferred Term in Long-Term, Double-Blind, Placebo- Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

System Organ Class Preferred Term, n (%)	747-303		
	Placebo N = 657	OCA 10 mg N = 653	OCA 25 mg N = 658
Number (%) of subjects with any TEAE leading to IP withdrawal or study discontinuation	41 (6.2)	39 (6.0)	86 (13.1)
Skin and subcutaneous tissue disorders	5 (0.8)	10 (1.5)	60 (9.1)
Pruritus	5 (0.8)	5 (0.8)	53 (8.1)

IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; TEAE = treatment-emergent adverse event
Note: Denominators for percentages are based on N, the number of subjects in the population.
Note: Adverse events are coded to MedDRA version 18.1.
Note: Subjects may have more than one event per system organ class and preferred term. At each level of subject summarization, a subject is counted once if he/she reported one or more events at that level.
Source: ISS, Table 2.1.1.32

An analysis of the rate of on-treatment TEAEs leading to investigational product withdrawal is presented in table below.

Table 47 Analysis of On-Treatment Treatment-Emergent Adverse Events Leading to Investigational Product Withdrawal in Long-Term, Double-Blind, Placebo-Controlled Studies in Subjects with Liver Fibrosis due to NASH: Safety Population (All Follow-up)

	Pooled OCA 10 mg vs Placebo[a]		
	Placebo N = 707	OCA 10 mg N = 703	Compare
Subjects with any on-treatment TEAE leading to IP withdrawal	42 (5.9%)	42 (6.0%)	
Crude risk difference (95% CI)[b]			0.03 (-2.44, 2.51)
Total censored at-risk time (years)	867.9	873.9	
EAIR per 100 subject-years (95% CI)[c]	4.84 (3.36, 6.32)	4.81 (3.34, 6.28)	
EAIR difference (95% CI)[d]			-0.03 (-2.10, 2.03)

CI = confidence interval; EAIR = exposure-adjusted incidence rate; IP = investigational product; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; TEAE = treatment-emergent adverse event.
Note: Reason for IP discontinuation was not collected in FLINT.
[a] Based on an integrated analysis of 747-303 and D8602001, stratified by study.
[b] Using the Cochran-Mantel-Haenszel test.
[c] EAIR per 100 subject-years = 100 × (number of subjects with an event) / censored at-risk time.
[d] EAIR difference and 95% CI are derived from a Poisson regression model.
Source: ISS, Table 2.3.5

Post marketing experience

OCA was granted accelerated approval for the treatment of PBC under the tradename Ocaliva by the US FDA on 27 May 2016. Conditional approvals in the EU and by Health Canada were granted on 12 December 2016 and on 24 May 2017, respectively. OCA has also received approval in four additional countries and has been launched in 18 countries as of 31 January 2019. Approvals were granted under the tradename Ocaliva for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. OCA continues to be evaluated in Phase 3 and Phase 4 confirmatory studies in PBC to verify the clinical benefit and safety profile.

PBC Postmarketing Data:

The most recent PSUR/PBRER for OCA (Ocaliva) summarizes available safety data received by Intercept from worldwide sources during the reporting interval from 27 November 2018 to 26 May 2019 (PBRER 2019). Analysis of the safety information received cumulatively through 26 May 2019 did not identify new risks or changes to recognized important or potential risks for OCA, and the benefit-risk balance of OCA remains favorable. The estimated cumulative patient exposure from marketing experience is 7693.7 patient-years.

Pruritus is an identified risk for OCA and is the most frequently reported postmarket AE. In a small proportion of patients, pruritus can be severe and significantly interfere with a patient's daily activities, including sleep. The occurrence and severity of pruritus in an individual patient treated with OCA cannot be reliably predicted or prevented, in part, because pruritus is a frequent clinical feature of the approved indication, PBC. However, pruritus is clinically manageable in most cases and can be mitigated by OCA dose titration or temporary treatment interruption. Fatigue, which accounts for 5% of all reported AEs (cumulative to 31 July 2019), is also an established nonserious clinical feature of PBC and may be exacerbated by treatment- related pruritus.

An important potential risk is liver injury. The characterization of the potential risk of liver injury is difficult to evaluate and distinguish from the hepatic signs and symptoms, often severe, that are associated with the natural progression of the underlying PBC. Risk factors for drug-induced liver-related AEs are, in general, poorly understood in patients with chronic liver disease. Importantly, there is no evidence to suggest that PBC patients with mild hepatic impairment (CP-A) taking OCA consistent with labelled dosing instructions are at risk of hepatic decompensation or failure. However, systemic and hepatic exposure to OCA and its active conjugates can increase significantly in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C cirrhosis). Hence, these patients are advised to start OCA with lower and less frequent dosing and be closely monitored for adverse hepatic effects. A medical safety assessment of reports of potential hepatic injury and/or decompensation during therapy with OCA identified confounders in the majority of reports. Similarly, an analysis of product prescribing medication errors in subjects with hepatic impairment noted that the majority of reports provided alternate etiologies, including comorbid conditions, or described advanced liver disease at baseline, disease progression, and other confounders despite the product prescribing error that was noted. In the interest of patient safety, Intercept undertook significant steps to mitigate product prescribing errors in the postmarket space, resulting in a sustained reduction in the exposure-adjusted medication error incidence rate (cumulative to 26 May 2019). Overall, this risk remains potential, as no evidence is available to establish a causal link between OCA and the occurrence of liver injury in PBC patients.

Atherosclerotic cardiovascular events secondary to changes in lipids is also an important potential risk for Ocaliva. Reduction in HDL cholesterol levels is a feature of PBC disease progression; however, it is unknown whether the changes in HDL are related to increased mortality from CVD in PBC patients when compared with the general population, especially in the context of hyperlipidemia often seen in PBC. Even though CVD can be life-threatening if left untreated, it can be predicted and prevented in PBC patients receiving Ocaliva, by monitoring their lipid levels periodically and by treating lipid changes with dietary intervention or medications such as statins when applicable. A review of cardiovascular events from postmarketing experience provided limited evidence of increased cardiovascular risk secondary to dyslipidemic changes associated with OCA therapy.

Renal events, such as CKD, are associated with hepatic disorders, and severity is positively correlated with hepatic fibrosis stage. A review of the postmarket reports of renal disease associated with OCA therapy did not identify a causal relationship between OCA and drug- induced renal disease due to confounding factors or alternative etiologies and within the context of worsened hepatic function.

No postmarketing data are available for subjects with NASH as OCA is not approved in this indication.

3.3.9. Discussion on clinical safety

The Applicant has provided safety data from healthy volunteers, special populations and subjects treated with up to 500 mg of OCA as well as data from subjects with PBC and other chronic liver diseases. OCA exposure information also includes subjects with compensated Child-Pugh A cirrhosis due to NASH, the majority of whom are from an ongoing randomized, double-blind, placebo-controlled Phase 3 study (Study 747-304) in that population. In addition, data of the already known safety profile of Ocaliva for PBC are available.

The clinical safety database includes data from Clinical pharmacology studies in healthy subjects and special populations, Clinical pharmacology studies conducted in subjects with liver fibrosis due to NASH, Three long-term, double-blind (DB), placebo-controlled studies in subjects with liver fibrosis due to NASH (747-303, FLINT, and D8602001), One open-label (OL) long-term safety extension study in subjects with liver fibrosis due to NASH and Several studies have been evaluated in other chronic liver diseases.

The Pivotal study 747-303 is still on-going at the time of the initial submission.

The clinical safety information submitted includes approximately 3,200 subjects treated with at least one dose of OCA in clinical studies, including over 1700 subjects with liver fibrosis due to NASH. For subjects with liver fibrosis due to NASH, the median number of days on OCA ranged from 269 (clinical pharmacology studies) to 496 days (long-term, double-blind, placebo-controlled studies); a subset of subjects was on investigational product for >2 years.

Pivotal study 747-303

The primary safety population for the Month 18 Interim Analysis, included 1968 subjects with NASH fibrosis stage 1, stage 2 and stage 3 (658 subjects in the OCA 25 mg group, 653 subjects in the OCA 10 mg group and 657 subjects in the placebo group), of whom approximately 1200 subjects were exposed for ≥ 12 months.

Safety analyses for the Month 18Interim Analysis, was also performed for the ITT population (931 subjects) which included subjects with fibrosis stage 2 and 3.

The incidence of TEAEs was slightly higher in subjects who received OCA than in subjects who received placebo. The majority of subjects experienced mild to moderate TEAEs, with a similar incidence across treatment groups. The incidence of severe TEAEs was higher in the OCA 25 mg group (20%) compared with the OCA 10 mg group (14%) and the placebo group (13%). The incidence of life-threatening TEAEs or TEAEs leading to death was low. There were 2 deaths in placebo group and 1 death in OCA 25 mg.

The most frequently reported TEAE was pruritus, which was dose dependent. TEAEs with a higher incidence in the OCA groups than in the placebo group included constipation, low-density lipoprotein increased, blood cholesterol increased, and hyperlipidaemia.

The overall incidence and pattern of TEAEs in subjects <65 years of age, ≥65 years of age, and ≥75 years of age were similar to that in the overall population, but the majority of subjects were <65 years of age. There were too few subjects ≥75 years of age to detect any meaningful trends, this data should be provided separately.

The incidence of SAEs was low for all SOCs except for hepatobiliary disorders (mainly driven by cholelithiasis and cholecystitis/cholecystitis acute), Renal and urinary disorders (mainly driven by nephrolithiasis and acute kidney injury), and Skin and subcutaneous tissue disorders (mainly driven by pruritus). The most commonly reported SAEs (≥5 subjects [<1%]) among OCA-treated subjects included sepsis (7 subjects), nephrolithiasis (6 subjects), acute kidney injury (5 subjects), angina pectoris (5 subjects), atrial fibrillation (5 subjects), and chronic obstructive pulmonary disease (5 subjects). Of these, the SAEs of acute kidney injury, angina pectoris, and chronic obstructive pulmonary disease were reported in subjects in the OCA groups only.

AESIs

Pruritus: Pruritus was the most frequently reported TEAE. This pattern is consistent with previous NASH and PBC studies, as well as postmarketing experience to date with Ocaliva in patients with PBC.

The incidence of treatment-emergent pruritus events was dose dependent, in fact, the incidence was higher in the OCA 25 mg group (51%) than in the OCA 10 mg group (28%) and the placebo group (19%). The majority of adverse events (AEs) of pruritus were assessed as mild to moderate in intensity but moderate and severe pruritus TEAEs were more frequent in the OCA 25 mg group. The Applicant considers that despite the increased incidence of pruritus associated with OCA exposure, there was no significant difference in overall patient-reported quality of life between treatment groups throughout the duration of the study, however pruritus was the main reason for treatment

discontinuation during the study. The occurrence of new or worsening treatment-emergent pruritus events was highest in the first 3 months after starting treatment. After Month 9, the overall incidence of new treatment-emergent pruritus events was <10% in all treatment groups. This leads to a higher treatment discontinuation rate.

Hepatic-related effects: The frequency of hepatic disorder TEAEs was similar across the 3 treatment groups: 11.0%, 12.5% and 10.3% in the placebo, 10 mg OCA and 25 mg OCA arm, respectively. Few cases were severe (no deaths) or led to treatment discontinuation with similar incidences in OCA and PBO groups (1-1.3%).

It seems that the incidence of hepatic disorder TEAEs was generally balanced across treatment groups and serious hepatic disorders TEAEs were rare. 4 of the 6 hepatic SAEs that occurred in the OCA 25 mg group were assessed by the Sponsor and external hepatologists as at least possibly related to the investigational product; however, confounding factors were identified during medical review.

Serious TEAEs of liver injury were few and slightly more frequent with OCA treatment compared to PBO (0.8%; 0.3% and 0.2%, in OCA 25 mg, OCA 10 mg and PBO, respectively). However, considering that in the post-marketing setting, in patients with PBC, a total of 710 liver injury ADRs have been reported, of which 370 (52%) were non-serious and 340 (48%) serious, liver injury is considered to significantly impact on the OCA safety profile. As for PBC, a management strategy and minimization measures for liver-related ADRs have been included in section 4.4 of the SmPC for the NASH indication. This is agreed although some modifications of the wording are proposed (see SmPC).

ALP criterion occurred more frequently with OCA 25 mg, which could be in line with prior observations and an on-target FXR mediated mechanism.

Gallstone disease: There was a higher incidence of gallstone related TEAEs among subjects treated with OCA 25 mg primarily driven by cholelithiasis. The incidence of gallstone-related SAEs was low, but slightly higher in the OCA 25 mg group compared with OCA 10 mg and placebo. In the OCA 25 mg group, 10 subjects had a cholecystectomy during the study.

This information supposes a new and different risk from the known OCA safety profile which has been issued in the RMP and product information. The Applicant proposes to include gallbladder disease in the ADR table of section 4.8 of the SmPC, and a warning on the possible occurrence of cholelithiasis, cholecystitis leading to cholecystectomy with instructions on interruption and possible re-initiation of treatment, which is agreed. Moreover, biliary pancreatitis, is included by the applicant in the warning included on SmPC as Gallbladder disease, however, no information related to this safety concern has been provided. Although a relationship with causality is established, the presentation pattern (signs/symptoms and severity, risk factors) of this TEAE will be better characterized in the long-term. Therefore, cross monitoring in the next PSUR is recommended.

Dyslipidaemia: Changes in LDL, HDL and glycemic parameters were observed.

It is important to highlight that OCA treatment was associated with changes in serum lipids, including an increase in LDL cholesterol and had to be managed by statin therapy; a decrease in HDL cholesterol that occurred early and was sustained throughout the duration of OCA treatment; and a decrease in triglycerides that occurred early and increased in magnitude with continued treatment. The clinical relevance of this issue is due to the fact that NASH is associated with other disorders as obesity, systemic hypertension, dyslipidaemia and diabetes. This aspect should be discussed more deeply.

In the safety population (study 747-303 and FLINT study), treatment with OCA was associated with an increase in LDL-c, a decrease in HDLc, and a decrease in triglycerides. In study 747-303, while in the PBO group a slight constant decline in LDL-c was observed through the 18 week treatment period, in patients treated with OCA 25 mg, mean LDL cholesterol increased from 114 mg/dl baseline to a peak of

138 mg/dl at Month 1, before declining to 119 mg/dl at Month 18. The proportion of patients on statins at baseline was balanced between groups; however, two fold more patients in the OCA groups initiated a statin during the study, or had statin intensification during the study. In order to have clearer picture of how many patients experienced LDL-c increase and, with statin treatment, had their LDL-c plasma concentrations reduced to (or near to) target levels according to their overall cardiovascular risk, the applicant provided spaghetti plots for LDL-c levels across 18 weeks of treatment for groups of patients identified by target LDL-c levels, showing for each patient if and when statin initiation or statin intensification took place. Only a modest number of patients were able to normalize their LDL-c levels in the low-risk and moderate-risk groups, but this appears to be explained by the fact that most of them initiated treatment on moderate/low intensity statins. Few patients shifted from normal to abnormal LDLc from baseline to month 18, in both low risk and moderate risk categories. Patients with low or moderate CV risk who intensified statin use did not consistently demonstrate normalization of LDL-c levels, despite being on high intensity statin. However, in the high and very high-risk segments, the majority of subjects who intensified statin treatment and had abnormal baseline LDL-c levels were able to achieve normal LDL-c levels by month 18 across treatment arms. The overall number of patients who intensified statin treatment is in any case very small.

Mean HDL-c decreased from 45 mg/dl baseline to 40 mg/dl Month 1 and 42 mg/dl Month 18 in the OCA 25 mg group and remained substantially unvaried in the PBO group (46 mg/dl mmol/L baseline). Results on HDL-c were also presented by gender. In both male and female, the HDLc decreased during OCA treatment. However, this reduction was more marked and persistent in men, a category that is often already at slightly increased CV risk and with lower levels of HDL.

Triglycerides were reduced by OCA treatment in a dose-dependent manner; the mean change at Month 18 compared to baseline was: -37.4 mg/dl (81.39 SD) with OCA 25 mg, -29.4 mg/dl (161.61) with OCA 10 mg; -16.5 mg/dl (127.11) with PBO.

The effect of lipid lowering drugs other than statins was not immediately evident by data. The applicant provided a table on effect of lipid-lowering agents on lipoprotein changes (alone and in combination with statins). A lipid-lowering treatment including statin seems the most appropriate to manage LDL-c increases observed following treatment with obeticholic acid.

Changes in plasma lipids with OCA treatment were translated into higher incidences in TEAEs of dyslipidaemia with both OCA 25 mg (31.3%) and OCA 10 mg (31.9%) compared to PBO (13.5%), with no dose dependency. The incidence of dyslipidaemia TEAEs was similar between subjects who experienced cardiovascular TEAEs and those who did not, however the number of observed events is limited and the follow-up too short for any sound conclusion.

Dyslipidaemia is reported as a very common ADR and is an important Potential risk in the current RMP.

A recommendation to monitor lipid levels before initiation of OCA treatment and periodically during treatment is included in SmPC section 4.4.

Cardiovascular (CV) disorders: The frequency of CV TEAEs was low and apparently higher with OCA treatment compared to PBO. CV TEAEs (of any type) were observed in 31 subjects (3.9%) in OCA 25 mg, in 23 (3.3%) in OCA 10 mg, and in 22 (2.6%) in placebo. CV SAEs were also more frequent in OCA 25 mg (n=18, 2.3%), compared to OCA 10 mg (n=9, 1.3%) or PBO (n=10, 1.2%).

CV TEAEs leading to death were observed in 2 subjects (0.3%) in the OCA 25 mg in the FLINT study, and in no subjects in both OCA 10 mg and PBO groups.

Major adverse CV events (MACEs) were prospectively and independently adjudicated in Study 747-303. The number of subjects with MACE TEAEs was similar across treatment arms: 5 pts (<1%) in OCA 25

mg; 0 pt in OCA 10 mg; 4 pts (<1%) in PBO. However, expanded MACE TEAEs were more frequent in the OCA 25 mg group (2%) compared to OCA 10 mg (1%) and PBO (1%).

Among expanded MACEs, hospitalization for unstable angina occurred in 2 subjects treated with OCA 25 mg and 2 with OCA 10 mg but in no one treated with PBO. The small numbers do not allow firm conclusions.

Subgroup analyses, although performed on limited numbers, confirm that MACE occurred preferably in subjects at high risk for atherosclerotic CVD (based on prior history of CVD or Framingham Risk Score), but no clear role seems to have on-study high LDL-c or low HDL-c levels.

The short follow-up (18 months) of MACE events is not considered adequate to fully characterize the cardiovascular safety of OCA in NASH subjects.

Apart from the late stages of NASH (cirrhosis/decompensated cirrhosis), cardiovascular events are a major cause of morbidity and mortality in NAFLD and NASH patients (Metabolism. 2020 Jan 30:154170. doi: 10.1016/j.metabol.2020.154170). Thus, concerns about the cardiovascular safety (increase in dyslipidaemia, possible detrimental effect on glycaemic control and potentially also increased risk of CV events) is particularly worrisome and deserves full scrutiny. In addition, subjects at high with cardiac risk in this population, were excluded from the trial (as OCA was considered unsafe for this population) resulting in a low rate of cardiac events. Thus, based on the protocol-suggested safety risk, a contra-indication in high-risk CV patients, could be even warranted.

Hyperglycemia/Diabetes: Alteration of Glycaemic parameters (plasma glucose and HbA1c) was observed under OCA treatment in the safety population; however, effects were modest. At month 18, OCA 25 mg resulted in a mean increase in glycemia over baseline values of +8.4 (41.04 SD; 0.16%), compared to +3.5 (45.19; +0.20%) observed with OCA 10 mg, and + 4.3 (39.13; + 0.08 %) with PBO. When data were analysed by diabetic status at baseline, changes in HbA1c were observed only in diabetic patients. No apparent difference was observed among study groups in the proportion of subjects with type 2 diabetes who initiated antidiabetic medication or increased the number of antidiabetic medications during the study.

These results, although in contrast with previous evidence generated by hyper insulinemic euglycemic glucose clamp technique, are consistent with clinical data from: i) the FLINT study, indicating possibly greater hepatic insulin resistance with OCA 25 mg treatment compared with placebo at Week 72; and ii) Study 747-209, showing modest increases in fasting plasma glucose, HbA1c, and fasting serum insulin after 16 weeks of treatment with OCA, as compared to PBO.

The average on-study cumulative event rates (including recurring events) with corresponding HRs indicated that the rates of on study hyperglycaemia/diabetes TEAEs were approximately 1.3-fold higher in the OCA 25 mg and OCA 10 mg groups, as compared to PBO.

In view of these results and considering the frequent occurrence of impaired glucose tolerance and type 2 diabetes in patients with NASH, a warning to monitor glycaemic parameters (at initiation of treatment and while on treatment) and provide appropriate anti-diabetic treatment if needed, is included in the 4.4 section of the SmPC.

Renal TEAEs: Acute renal events occurred in 10 (1.5%) subjects in the OCA 25 mg group, 4 (<1%) subjects in the OCA 10 mg group, and 2 (<1%) subjects in the placebo group. Acute renal events were more common in subjects with renal impairment at baseline. Acute kidney injury was the most frequent renal SAE among OCA-treated subjects; the majority of subjects who experienced acute kidney injury had chronic kidney disease (CKD) stage 2 or greater at baseline.

This information supposes a new and different risk from the known OCA safety profile which is addressed in the RMP and product information. A warning before initiating treatment, as acute renal

events were more common in subjects with renal impairment at baseline, is included in the product information.

SAEs were observed in 0.6% of patients treated with OCA 25 mg and 0.4% of patients treated with OCA 10 mg compared with no patient treated with placebo. However, a difference was observed in the number of subjects experiencing acute kidney injury: OCA 25 mg, 1.3%; OCA 10 mg, 0.4%; PBO, 0.2%).

OCA is not eliminated by kidneys (<3% is excreted in urine) and, despite the expression of the FXR receptor in kidney, renal exposure to the drug is considered low. Therefore, the observed difference in acute kidney injury is at present unclear. The applicant argued that advanced NASH fibrosis is associated with a greater incidence and stage of CKD independent of common CKD risk factors and that, therefore, an increased rate of renal disease may be expected within the NASH patient population. The imbalance observed is however not fully justified and this potential event of nephrotoxicity deserves further exploration and is classified as an important potential risk in the RMP.

In general, with the exception of pruritus, no difference in incidence and pattern of TEAEs was observed by CKD stages, although there were very few patients in stage 3.

SAEs and deaths

The incidence of SAEs was low and comparable between the treatment groups, with the exception of Hepatobiliary disorders and Renal and urinary disorders which was higher for OCA groups. Regarding Hepatobiliary disorders, the incidences were higher for OCA25 mg group and were mainly driven by serious events of cholelithiasis and cholecystitis/cholecystitis acute. One of the serious hepatics TEAEs that occurred in the 25 mg group (cholestatic liver injury) resulted in liver transplantation. The Applicant suggest that patients with persistent signs and/or symptoms of impaired health may be at higher risk of liver injury, which is rather reasonable.

The incidence of SAEs in the Renal and urinary disorders SOC was slightly higher in both OCA groups than in the placebo group. The main events were nephrolithiasis and acute kidney injury.

The most commonly reported SAEs among OCA-treated subjects included sepsis (7 subjects), nephrolithiasis (6 subjects), acute kidney injury (5 subjects), angina pectoris (5 subjects), atrial fibrillation (5 subjects), and chronic obstructive pulmonary disease (5 subjects). Of these, the SAEs of acute kidney injury, angina pectoris, and chronic obstructive pulmonary disease were reported in subjects in the OCA groups only, therefore these issues should be discussed in depth.

SAEs were reported with a slightly higher incidence in the OCA higher dose arm (14.6%) than in the OCA lower dose and PLB arms (11.1% each). The Most frequent SAEs in OCA treated subjects were infections (3.0% in OCA 25 mg vs 1.6% in placebo). Diabetes is a known risk factor for infection and these events are not grouped under one/few specific PTs. The overall rate of serious events in the Infections and Infestations SOC was higher across all treatment groups in subjects with type 2 diabetes in comparison to subjects without type 2 diabetes. However, the difference did not reach statistical significance and events are evenly distributed across treatment arms and likely not related to OCA treatment.

A total of 3 deaths were reported (2 subjects in the placebo group [bone cancer and cardiac arrest] and 1 subject in the OCA 25 mg group [glioblastoma]), none of which was considered treatment related. It seems that there was no pattern of concern with respect to the types of events leading to death.

Discontinuations due to AEs

The incidence of TEAEs leading to discontinuation of investigational product was higher in the OCA 25 mg group. The most frequently reported TEAE was pruritus, which was dose dependent

There is a high treatment discontinuation rates due to treatment-emergent pruritus events in OCA groups which was dose dependent, being higher in OCA 25 mg group than in OCA 10 mg group.

The findings in the complete clinical safety database are similar and in line with the pivotal study 747-303.

Safety in special populations (*complete clinical safety database)*

The overall incidence and pattern of TEAEs in subjects <65 years of age, ≥65 years of age, and ≥75 years of age were similar to that in the overall population, but the majority of subjects were <65 years of age. Data in patients ≥ 75 years of age was provided separately but there were too few subjects to detect any meaningful trends.

The safety and efficacy of OCA in patients <18 years of age have not been established as the proposed therapeutic indication is for adults.

Regarding hepatic impairment, the overall pattern of TEAEs, including the higher incidence of pruritus and low-density lipoprotein increased in the OCA groups compared to the placebo group, was generally consistent across baseline fibrosis stages. However, the incidence of SAEs was higher in subjects with baseline fibrosis stage 3.

With respect to renal impairment, the overall incidence of TEAEs was similar between subjects with normal renal function/CKD stage 1 and those with CKD stage 2. The incidence of SAEs was slightly higher among subjects with CKD stage 2 compared to those with normal renal function/CKD stage 1. There were too few subjects with CKD stage 3 to draw any meaningful conclusions.

The limited available human data on the use of OCA during pregnancy are not sufficient to inform a drug-associated risk. Using contraceptives methods was one of the main inclusion criterium in 747-303 Study.

Drug-drug interactions and other interactions (complete safety database)

The interactions with Warfarin, CYP1A2 substrates with narrow therapeutic index (e.g. theophylline and tizanidine) and with bile acid and binding resins have been correctly described in the product information.

The applicant discussed the potential interactions with concomitant medications taking into account the expected comorbidities in NASH patients. OCA has not shown any potential to interfere relevantly with drugs metabolized by CYP3A4, CYP2D6, or CYP2C9 on in vivo metabolism studies conducted in healthy subjects. Moreover, no induction or inhibition of OATP1B1, OATP1B3, OATP2B1, MATE1, MRP2, MRP3, MRP4, OCT1, BCRP, P-gp, or NTCP was observed with OCA. Concomitant medications including lipid-modifying agents, drugs used in diabetes, drugs for acid-related disorders, vitamins, antithrombotic agents, agents acting on the renin-angiotensin system, and thyroid therapy were used in the long-term, double-blind, placebo-controlled studies conducted in subjects with liver fibrosis due to NASH, where interactions where not observed. No clinically meaningful interactions are expected with the main concomitant medications that could be co-administered with OCA.

Additional safety data needed in the context of a conditional MA

Study 747-303 is an ongoing Phase 3, double-blind, randomized, long-term, placebo-controlled, study to support both initial conditional approval based on a Month 18 Interim Analysis of the histologic endpoints and full approval following confirmation of clinical benefit based on an End of Study (EOS) analysis of a composite clinical outcomes endpoint. To date, only safety data from the IA and supportive studies have been submitted. As of Sep 2019, the study was fully enrolled with a total of 2480 subjects randomized (approximately 2190 of whom with fibrosis stage 2 or stage 3). The study is

continuing in a blinded fashion, and subjects will be followed up over an extended period until the EOS analysis. The EOS analysis is planned after the accrual of approximately 291 adjudicated clinical outcome composite events combined in the OCA 25 mg and placebo groups for subjects with fibrosis stage 2 or stage 3 (projected to take approximately 7.5 years in total). Subjects are expected to have a minimum follow-up time of approximately 4 years. Due to the fact that is a chronic treatment, long term exposure in adequate number of patients is needed. Therefore, final safety analysis at the date of EOS should be submitted as part of the requirements of the CMA.

3.3.10. Conclusions on clinical safety

The safety profile is generally consistent with that observed in NASH studies and already established in PBC, the previously approved indication. However, dose-dependent increase in the incidence of liver and gallbladder disorders was observed with NASH patients, together with a more worrisome dose-independent increase in dyslipidaemia and, potentially, in CV events (in particular expanded MACE), that due to the short follow-up cannot be further characterized. Safety data also point towards an increased risk of hyperglycaemia and diabetes events that deserve a cautious approach given that impaired glucose tolerance and type 2 diabetes are frequent in patients with NASH. Acute kidney injury is a new concern that should be addressed. An update on the on-going OCA study in terms of safety should be provided when available.

At the moment, based on the absolute numbers of CV events a definite conclusion on the CV safety of OCA is not possible. However, considering the many signals, all in the same direction, toward an increased CV risk during treatment with OCA in patients with NASH which is per se a metabolic disease with high cardiovascular disease burden, a contraindication for patients at high risk for CV disease is deemed necessary in order to select the target population for which a positive B/R balance might be still expected.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 48

Table SVIII.1: Summary of safety concerns

Summary of safety concerns		
Indication	**PBC**	**NASH**
Important identified risks	Pruritus	Pruritus Gallbladder disease
Important potential risks	Liver injury Atherosclerotic cardiovascular events secondary to changes in lipids	Liver injury Atherosclerotic cardiovascular events secondary to changes in lipids Biliary pancreatitis

Summary of safety concerns		
Missing information	Use in patients with other concomitant liver diseases Use in patients with moderate to severe hepatic impairment (Child-Pugh B and C) Use in patients with HCC Use post liver transplantation Use in elderly and very elderly patients (≥65 years) Use during pregnancy and breast-feeding Long-term safety	Use in patients with other concomitant liver diseases Use in patients with moderate to severe hepatic impairment (Child-Pugh B and C) Use in patients with HCC Use post liver transplantation Use in elderly and very elderly patients (≥65 years) Use during pregnancy and breast-feeding Long-term safety Acute kidney injury

3.4.2. Discussion on safety specification

The applicant has changed the summary of safety concerns included in the obeticholic acid RMP (version 2.1), including in the NASH indication Gallbladder disease as important identified risk, biliary pancreatitis as important potential risk and acute kidney injury as missing information. The mentioned concerns were not identified in the PBC population (OCALIVA).

After the review of the safety data submitted within the current application, it is considered that:

- Gallbladder disease and pruritus are risks sufficiently characterised and included in the Product Information.
- Biliary pancreatitis: This safety concern is described as part of the Gallbladder disease complication in section 4.4 on the SmPC for Zektayos, identified as risk, nevertheless, it is not included in section 4.8 nor described as part of the safety data submitted within this application.
- Acute kidney injury: As part of the responses it has been confirmed that this safety concern has been identified in the clinical trials and even if no dose adjustment is needed an increased risk has been observed in the treatment arms.

Comment PRAC rapporteur:

The applicant included 'Biliary pancreatitis (for NASH indication only)' as important potential risk. If 'Biliary pancreatitis' is causally related to obeticholic acid, it should be reflected in the SmPC in section 4.8. Inclusion in the RMP as an important identified risk may be warranted if CHMP Rapporteur considers that the risk is not sufficiently characterised yet.

'Gallbladder disease' has been re-classified from important potential risk to important identified risk. The applicant found in one of the studies a dose-dependent effect of OCA on the incidence rate of Cholelithiasis / Cholecystitis. In the opinion of the PRAC Rapporteur, that 'Gallbladder disease' has been sufficiently characterised and is sufficiently addressed in the PI (including section 4.8 of the SmPC).

The applicant proposes to add 'Acute kidney injury' as Missing information for the NASH indication.

The applicant proposes to include 'Pruritus' as important identified risk. However, the PRAC Rapporteur is of the opinion that 'Pruritus' is sufficiently characterised and addressed in the SmPC.

In addition, in line with GVP rev 2 special populations 'Use in elderly and very elderly patients (≥65 years)' and 'Use during pregnancy and breast-feeding' should only be included if specific safety concerns are expected in these populations.

3.4.3. Pharmacovigilance plan

Routine pharmacovigilance activities

Specific adverse reaction follow-up questionnaires for hepatic events:

The purpose of the Hepatic Event Follow-up Form is to obtain additional details regarding the event details of hepatic adverse events. More specifically, the form seeks information regarding event details, concomitant medication use, diagnostic activities (including laboratory evaluations and imaging), liver-related medical history, and underlying liver disease severity.

Other forms of routine pharmacovigilance activities:

None

Summary of additional PhV activities

NA

Comment PRAC Rapporteur:

The Applicant proposes routine pharmacovigilance activities, including adverse reaction follow-up questionnaires for hepatic events.

The Applicant has removed additional pharmacovigilance activities for 'Pruritus', 'Liver injury', 'Gallbladder disease (for NASH indication only)', 'Use in elderly and very elderly patients (≥65 years)', and 'Acute kidney injury'. The PRAC Rapporteur however questions if routine PhV is sufficient to further characterise the risk of 'Biliary pancreatitis', and 'Acute kidney injury'.

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is not sufficient to identify and characterise all the risks of the product.

3.4.4. Plans for post-authorisation efficacy studies

Summary of Post authorisation efficacy development plan

Table 49

Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date*
Efficacy studies which are conditions of the marketing authorisation				
Study 747-302, A Phase 4, double blind, randomised, placebo controlled, multicentre study evaluating the	**Primary objectives**: To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical	Clinical outcomes	Final report	Submission expected by end of 2023

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date*
effect of OCA on clinical outcomes in subjects with PBC. On-going	outcomes in subjects with PBC as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint: Death (all-cause), liver transplant, model of end stage liver disease (MELD) score ≥15, hospitalisation for variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, uncontrolled ascites **Secondary objectives**: To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above. To assess the effect of OCA compared to placebo on time to occurrence of liver related death. To assess the effect of OCA compared to placebo on progression to cirrhosis. To assess the effect of OCA compared to placebo on time to occurrence of HCC. To assess the effect of OCA compared to placebo on disease progression via the following: Liver biochemistry and markers of inflammation and fibrosis To assess the effect of OCA compared to historical controls on liver-related clinical outcomes. To characterise the PK of OCA and its conjugates in a subset of subjects. To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo. To assess the safety and tolerability in subjects treated with OCA compared to placebo.			

Study 747-401, A phase 4, DB, randomised, placebo-controlled, study evaluating the efficacy, safety, and PK, of OCA in patients with PBC and moderate to severe hepatic impairment. Ongoing	**Primary objectives**: To evaluate the PK of OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide compared with placebo To evaluate the safety and tolerability of OCA treatment compared with placebo **Secondary objectives**: To evaluate the effect of OCA treatment compared to placebo on: The MELD score and its components, Child-Pugh score and its components, liver biochemistry including total and direct bilirubin, ALP, and aminotransferases (ALT, AST, and GGT), INR, creatinine, albumin, platelets, biomarkers of bile acid synthesis and homeostasis including FGF19, 7α hydroxy-4-cholesten-3-one, and plasma bile acids **Additional Objectives**: To evaluate the effect of OCA treatment compared to placebo on: Noninvasive markers of liver fibrosis (enhanced liver fibrosis [ELF]™ score), noninvasive measurement of liver stiffness (transient elastography [TE]) To assess the PK/PD relationship of OCA with: PK parameters compared to PD parameters and safety and tolerability assessments To assess patient reported outcomes (Pruritus visual analogue scale [VAS], quality of life for primary biliary cirrhosis [PBC-40], Euroqol 5-level EQ-D questionnaire [EQ 5D-5L], chronic liver disease questionnaire [CLDQ]) To assess clinical events consistent with end-stage liver disease: Death (all-cause), liver transplant, MELD score ≥15 (for patients with MELD ≤12 at baseline), hospitalisation (as defined by a stay of 24 hours or greater) for new onset or recurrence of: variceal bleed, hepatic encephalopathy (as defined by a West Haven score of ≥2), spontaneous bacterial peritonitis, uncontrolled ascites (diuretic resistant ascites requiring therapeutic	Clinical outcomes	Final report	Submission expected by end of 2023

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date*
	paracentesis at a frequency of at least twice in a month), HCC.			

Study 747-303: A Phase 3, double-blind, randomized, long-term, placebo-controlled, multicentre study evaluating the safety and efficacy of OCA in subjects with NASH Ongoing	**Primary objectives (at 18 months)**: To evaluate the effect of OCA compared to placebo on histological improvement in NASH by assessing the following primary endpoints using NASH clinical research network (CRN) scoring criteria: ▪ Improvement in fibrosis by at least 1 stage with no worsening of NASH, OR ▪ Resolution of NASH with no worsening of fibrosis **Secondary objectives (at 18 months)**: To evaluate the effect of OCA compared to placebo on histological improvement in NASH by assessing the following using NASH CRN scoring criteria: ▪ Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either ▪ No worsening of fibrosis AND no worsening of NASH ▪ Improvement in each key histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning) ▪ Improvement of fibrosis by at least 2 stages ▪ Improvement in NASH by at least 2 points with no worsening of fibrosis ▪ Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject ▪ Resolution of fibrosis ▪ Histological progression to cirrhosis ▪ To evaluate the effect of OCA compared to placebo on liver biochemistry and markers of liver function **Exploratory objectives (at 18 months)**: To evaluate the effect of OCA compared to placebo on liver histology by assessing the following using alternate scoring methods:	Clinical outcomes	Final report	Submission expected in 2023

	▪ Morphometric assessment of quantitative collagen (assessed as percent collagen area [PCA]) in a subset of subjects ▪ Improvement in fibrosis by at least 1 stage (assessed using modified Ishak scoring criteria) ▪ Improvement in components of steatosis, activity, and fibrosis (SAF) score and total SAF score by at least 2 points To evaluate the effect of OCA compared to placebo on the following additional measures: ▪ Markers of glucose metabolism ▪ Anthropometric measures ▪ Markers of inflammation ▪ Markers of cardiovascular safety (eg, lipoproteins, blood pressure, and cardiovascular risk scores) ▪ Patient-reported outcomes ▪ Cytokeratin-18 and noninvasive scores of liver fibrosis including NAFLD fibrosis score (NFS); Fibrosis 4 (FIB4); ELF; FibroTest/FibroSure; AST to platelet ratio index (APRI), and body mass index (BMI) - AST to ALT ratio - diabetes (BARD) score ▪ PK of OCA in a subset of subjects ▪ Pharmacodynamics (bile acid precursor) of OCA ▪ Non-invasive radiological measurements of liver fibrosis (eg, TE, magnetic resonance elastography [MRE], ultrasound-based shear wave technologies other than TE such as acoustic radiation force impulse [ARFI], or multi-parametric magnetic resonance imaging [MRI]) in a subset of subjects ▪ Incidence of adjudicated cardiovascular events ▪ Safety and tolerability (TEAEs, ECGs, vital signs, clinical laboratory assessments)			

	Primary Objective (at end of study): To evaluate the effect of OCA compared to placebo on all-cause mortality and liver-related clinical outcomes as measured by the time to first occurrence of any of the following adjudicated events (clinical outcomes composite endpoint): ▪ Death (all cause) ▪ MELD score ≥15 ▪ Liver transplant ▪ Hospitalization (as defined by a stay of ≥24 hours) for onset of: o Variceal bleed o Hepatic encephalopathy (as defined by a West Haven score of ≥2) o Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) ▪ Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis) ▪ Histological progression to cirrhosis **Secondary Objectives (at end of study)**: To evaluate the effect of OCA compared to placebo on histological improvement in NASH by assessing the following endpoints using NASH CRN scoring criteria: ▪ Improvement in fibrosis by at least 1 stage with no worsening of NASH ▪ NASH resolution with no worsening of fibrosis ▪ Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either ▪ No worsening of fibrosis AND no worsening of NASH ▪ Improvement in each key histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning)			

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date*
	▪ Improvement of fibrosis by at least 2 stages ▪ Improvement in NASH by at least 2 points with no worsening of fibrosis ▪ Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject ▪ Resolution of fibrosis To evaluate the effect of OCA compared to placebo on liver biochemistry and markers of liver function **Exploratory Objectives (at end of study)**: To evaluate the effect of OCA compared to placebo on: ▪ Time to first occurrence of each individual component of the clinical outcomes composite endpoint as listed above ▪ Time to occurrence of liver related death ▪ Time to occurrence of HCC ▪ Patient-reported outcomes ▪ Non-invasive scores of liver fibrosis including NFS, FIB4, ELF, FibroTest/FibroSure, APRI, and BARD score ▪ Noninvasive radiological measurements of liver fibrosis (eg, TE) in a subset of subjects ▪ Incidence of adjudicated cardiovascular events ▪ Long-term safety and tolerability (TEAEs, ECGs, vital signs, clinical laboratory assessments) To evaluate the correlation between histology and non-invasive scores of liver fibrosis with clinical outcomes at the end of the study			

*Dates correct at time of submission

3.4.5. Risk minimisation measures

Routine Risk Minimisation Measures

Changes are highlighted in yellow.

Table 50

Part V.1: Description of routine risk minimisation measures by safety concern

Routine risk minimisation activities		
Safety concern	**OCALIVA**	**ZEKTAYOS**
Important Identified Risks		
Pruritus	**Routine risk communication**: SmPC section 4.2 and 4.4. Patient leaflet (PL) section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Management and dose adjustment for severe pruritus are included in SmPC section 4.2. Management strategies like addition of bile acid binding resins or antihistamines, dose reduction, reduced dosing frequency, and/or temporary dose interruption are included in SmPC section 4.4. **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine	**Routine risk communication:** SmPC section 4.2, 4.4, 4.8, 4.9. PL section 2, 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Advice regarding management and dose adjustment is included in SmPC section 4.2 and 4.4. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine
Gallbladder disease (for NASH indication only)	Not applicable	**Routine risk communication**: SmPC section 4.2, 4.4, 4.8. PL section 2, 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Advice regarding management and dose adjustment is included in SmPC section 4.2 and 4.4. **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine
Important Potential Risks		
Liver injury	**Routine risk communication**: SmPC section 4.2 PL section 2 & 3 **Routine risk minimisation activities recommending specific**	**Routine risk communication:** SmPC section 4.2, 4.4, 4.8, 4.9. PL section 2, 4 **Routine risk minimisation activities recommending specific**

	clinical measures to address the risk: Management and dose adjustment are included in SmPC section 4.2. **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine	**clinical measures to address the risk:** Advice regarding management and dose adjustments is included in SmPC section 4.2. Advice regarding liver tests, monitoring of symptoms and treatment management is included in SmPC section 4.4. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine
Atherosclerotic cardiovascular events secondary to changes in lipids	**Routine risk communication**: SmPC section 4.8 PL section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine	**Routine risk communication:** SmPC section 4.4, 4.8. PL section 2, 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Advice regarding treatment management is included in SmPC section 4.4. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine
Biliary pancreatitis (for NASH indication only)	Not applicable	**Routine risk communication**: SmPC section 4.2, 4.4. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Advice regarding treatment management is included in SmPC section 4.2 and 4.4. **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine
Missing Information		
Use in patients with other concomitant liver diseases	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**:	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**:

	Legal status: Prescription only medicine	Legal status: Prescription only medicine
Use in patients with moderate (Child-Pugh Class B) and severe (Child Pugh Class C) hepatic impairment	**Routine risk communication**: SmPC section 4.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Management and dose adjustment are included in SmPC section 4.2. **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine	**Routine risk communication**: SmPC section 4.2, 4.4. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Advice regarding monitoring is included in SmPC section 4.2. Advice regarding treatment management is included in SmPC section 4.4. **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine
Use in patients with HCC	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine
Use post-liver transplantation	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine
Use in elderly and very elderly patients (≥65 years)	**Routine risk communication**: SmPC section 4.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine	**Routine risk communication**: SmPC section 4.2, 5.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine

Use during pregnancy and breast-feeding	**Routine risk communication**: SmPC section 4.6 PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine	**Routine risk communication:** SmPC section 4.6 PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine
Long term safety	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine
Acute kidney injury (for NASH indication only)	Not applicable	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine

Comment PRAC Rapporteur:

The applicant made some adjustments to the routine risk communication. For 'Pruritus' and 'Liver injury' wording is included in section 4.9 of the SmPC. For the newly included 'Biliary pancreatitis (for NASH indication only)', the applicant proposed routine risk minimisation in section 4.2 and 4.4.

Additional risk minimisation measures

The applicant states that routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Summary of risk minimisation measures

Changes are highlighted in yellow.

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures (PBC)	Risk minimisation measures (NASH)	Pharmacovigilance activities
Important identified risks			
Pruritus	**Routine risk minimisation measures**: SmPC section 4.2 and 4.4 PL section 2 Management and dose adjustment for severe pruritus are included in SmPC section 4.2. Management strategies like addition of bile acid binding resins or antihistamines, dose reduction, reduced dosing frequency, and/or temporary dose interruption are included in SmPC section 4.4. Prescription only medicine **Additional risk minimisation measures**: None	**Routine risk minimisation measures**: SmPC section 4.2, 4.4, 4.8, 4.9. PL section 2, 4 Advice regarding management and dose adjustment is included in SmPC sections 4.2 and 4.4. **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Gallbladder disease (for NASH indication only)	Not applicable	**Routine risk minimisation measures**: SmPC section 4.2, 4.4, 4.8. PL section 2, 4 Advice regarding treatment management is included in SmPC section 4.2 and 4.4. Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

Safety concern	Risk minimisation measures (PBC)	Risk minimisation measures (NASH)	Pharmacovigilance activities
Important potential risks			
Liver injury	**Routine risk minimisation measures**: SmPC section 4.2 PL section 2 & 3 Management and dose adjustment are included in SmPC section 4.2. Prescription only medicine **Additional risk minimisation measures**: None	**Routine risk minimisation measures**: SmPC section 4.2, 4.4, 4.8, 4.9. PL section 2, 4 Advice regarding management and dose adjustments is included in SmPC section 4.2. Advice regarding liver tests, monitoring of symptoms and treatment management is included in SmPC section 4.4. Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: AE follow-up form for hepatic events **Additional pharmacovigilance activities**: None
Atherosclerotic cardiovascular events secondary to changes in lipids	**Routine risk minimisation measures**: SmPC section 4.8 PL section 4 Prescription only medicine **Additional risk minimisation measures**: None	**Routine risk minimisation measures**: SmPC section 4.4, 4.8. PL section 2, 4 Advice regarding treatment management is included in SmPC section 4.4. Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

Safety concern	Risk minimisation measures (PBC)	Risk minimisation measures (NASH)	Pharmacovigilance activities
Biliary pancreatitis (for NASH indication only)	Not applicable	**Routine risk communication**: SmPC section 4.2, 4.4. Advice regarding treatment management is included in SmPC section 4.2 and 4.4. Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

Missing information			
Use in patients with other concomitant liver diseases	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Use in patients with moderate to severe hepatic impairment (ie, Child-Pugh B and C)	**Routine risk minimisation measures**: SmPC section 4.2 Management and dose adjustment are included in SmPC section 4.2. Prescription only medicine **Additional risk minimisation measures**: None	**Routine risk minimisation measures**: SmPC section 4.2, 4.4. Advice regarding monitoring is included in SmPC section 4.2. Advice regarding treatment management is included in SmPC section 4.4. Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

Use in patients with HCC	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Use post liver transplantation	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Use in elderly and very elderly patients (≥65 years)	**Routine risk minimisation measures**: SmPC section 4.2 Prescription only medicine **Additional risk minimisation measures**: None	**Routine risk minimisation measures**: SmPC section 4.2, 5.2. Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Use during pregnancy and breast-feeding	**Routine risk minimisation measures**: SmPC section 4.6 PL section 2 Prescription only medicine **Additional risk minimisation measures**: None	**Routine risk minimisation measures**: SmPC section 4.6 PL section 2 Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

Long-term safety	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Acute kidney injury (for NASH indication only)	Not applicable	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

Comment PRAC Rapporteur:

Changes have been made to the summary table of pharmacovigilance activities and risk minimisation activities by safety concern. The additional risk minimisation measures for 'liver injury' has been removed upon PRAC request.

The proposed routine risk minimisation activities are deemed sufficient.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.4.6. Summary of the risk management plan

The applicant proposed a combined summary of risk management plan for the PBC and NASH indication. For both indications risk minimisation measures were included in the table II.B Summary of important risks separately for all risks. Studies Study 747-302, Study 747-401, Study 747-303 are included in table II.C.1 Studies which are conditions of the marketing authorisation in the RMP.

The public summary of the RMP may require revision.

PRAC Outcome

The PRAC fully supported the assessment of the pharmacovigilance plan and risk minimisation measures as detailed in the assessment report as well as the following suggestions made on the summary of safety concerns:

- "Biliary pancreatitis" should be included in the RMP as an important identified risk if it is considered that the risk needs to be further characterised in the post-marketing setting.

- "Gallbladder disease" should be removed from the RMP as it has been sufficiently characterised and is sufficiently addressed in the PI including section 4.8 of the SmPC

- 'Acute kidney injury' should be classified as an important potential risk in the RMP based on the clinical trials findings.

- 'Pruritus' should be removed from the RMP as it is sufficiently characterised and addressed in the SmPC.

In addition, in line with GVP V, revision 2, special populations such as 'Use in elderly and very elderly patients (≥65 years)' and 'Use during pregnancy and breast-feeding' should only be included if the safety profile in these populations is expected to differ from the know safety profile.

The PRAC agreed that the RMP Zektayos-Hepjuvo (OBETICHOLIC ACID) in the proposed indication is could be acceptable provided that an update to RMP version 2.1 and satisfactory responses to the questions detailed in the joint CHMP-PRAC D150 overview assessment report (AR) are submitted.

3.4.7. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 2.1 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report.

3.5. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

4. Significance of paediatric studies

Not applicable

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The Applicant is seeking the conditional marketing authorisation of obeticholic acid (OCA) for improvement of liver fibrosis and resolution of steatohepatitis in adult patients with significant liver fibrosis due to nonalcoholic steatohepatitis (NASH), without clinical signs or symptoms of cirrhosis.

Non-alcoholic steatohepatitis (NASH) is considered the progressive phenotype of non-alcoholic fatty liver disease (NAFLD), which itself is the most prevalent chronic liver disease worldwide with an estimated prevalence in the Western world of around 25%, and it is estimated that about 20% of these suffer from NASH. The progression is related to the development of liver cell stress, subsequent inflammation, and fibrosis with the potential development of cirrhosis, and end-stage liver disease. NASH is also a relevant risk factor for the occurrence of hepatocellular carcinoma.

From a diagnostic point of view, the diagnosis of NASH is one of exclusion (involving the exclusion of relevant alcohol intake, and infectious and non-infectious liver disease) as well as positive confirmation

of the features by liver biopsy and histology, the latter relating to the pathognomonic features of steatosis, hepatocellular ballooning, lobular inflammation, and fibrosis. The progression of fibrosis is estimated to be slow, and progression of 1 fibrosis stage is estimated to occur at a mean of more than 7 years (7.7 years; 95% CI 5.5-14.8 y).

5.1.2. Available therapies and unmet medical need

NASH is a chronic, progressive disease with no available therapy and, as such, is recognized as a condition with unmet medical need. At present, potential pharmacologic therapies (e.g. Vitamin E or some insulin sensitizers) are limited and it is not possible to use them in all patients.

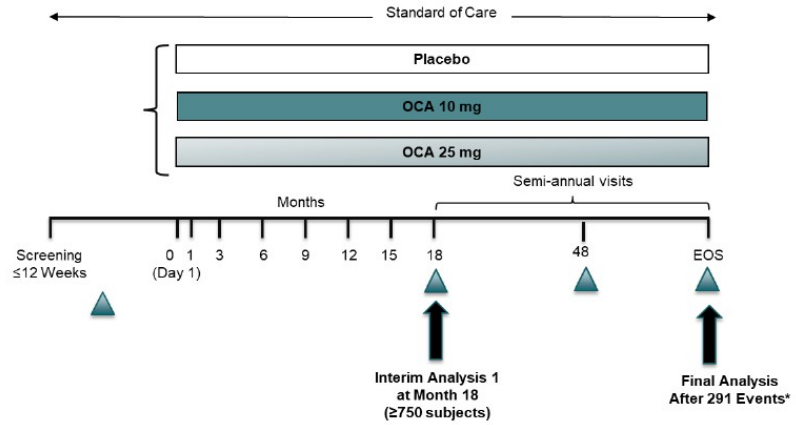
5.1.3. Main clinical studies

Study 747-303 is an ongoing Phase 3, double-blind, randomized, long-term, placebo-controlled, study to support both initial CMA based on a Month 18 Interim Analysis of the histologic endpoints and full approval following confirmation of clinical benefit based on an End of Study (EOS) analysis of a composite clinical outcomes endpoint. The primary efficacy endpoint at the EOS will be the time from randomization to the first occurrence of one of the following post-randomization: Death (all-cause); MELD score ≥15; Liver transplant; Hospitalization; Ascites secondary to cirrhosis and requiring medical intervention; Histological progression to cirrhosis.

The Month 18 Interim Analysis cohort includes all randomized subjects who received ≥1 dose of OCA (10mg or 25 mg) or placebo by the pre-specified data cut-off (DCO) of 26 Oct 2018.The primary efficacy endpoints at the IA were the improvement of fibrosis by ≥1 stage with no worsening of NASH and the resolution of NASH with no worsening of fibrosis

The study is continuing in a blinded fashion, and subjects will be followed up over an extended period until the EOS analysis. The EOS analysis is planned after the accrual of approximately 291 adjudicated clinical outcome composite events combined in the OCA 25 mg and placebo groups for subjects with fibrosis stage 2 or stage 3 (projected to take approximately 7.5 years in total). Subjects are expected to have a minimum follow-up time of approximately 4 years

Figure 63



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

Additional supportive data are from a Phase IIb, double-blind, placebo-controlled study, FLINT, in subjects with biopsy evidence of NASH. The trial was stopped early for efficacy based on a planned interim analysis. An integrated analysis of data from the ITT population of the pivotal trial with matched

population of the FLINT study has been performed and submitted. However, due to the apparent heterogeneity in the pooled data, results from the integrated analysis are not considered reliable and a random effects meta-analysis assessing the degree of heterogeneity has been requested

5.2. Favourable effects

Study 747-303 (results from the Interim Analysis at 18 moths)

- Improvement in liver fibrosis ≥ to 1 stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis)
    - The percentage of subjects achieving improvement of fibrosis by ≥1 stage with no worsening of NASH was 17.6% in the OCA 10 mg group versus 11.9% in the placebo group (p = 0.0446), with an OCA 10 mg:placebo response ratio of 1.48 (95% CI: 1.01, 2.18).
    - The percentage of subjects achieving improvement of fibrosis by ≥1 stage with no worsening of NASH was 23.1% in the OCA 25 mg group versus 11.9% in the placebo group (p = 0.0002). The OCA 25 mg:placebo response ratio was 1.94 (95% CI: 1.35, 2.78)
- 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 NAS score of 0 to 1 for inflammation, 0 for ballooning, and any value for steatosis.
    - The percentage of subjects achieving resolution of NASH with no worsening of fibrosis was11.2% in the OCA 10 mg group versus 8.0% in the placebo group (p = 0.1814), with an OCA10 mg:placebo response ratio of 1.39 (95% CI: 0.86, 2.25)
    - The percentage of subjects achieving resolution of NASH with no worsening of fibrosis was11.7% in the OCA 25 mg group versus 8.0% in the placebo group (p = 0.1268), with an OCA 25 mg:placebo response ratio of 1.45 (95% CI: 0.90, 2.35)

The histologic benefit of OCA was consistent across analysis populations and subgroups of interest and was further confirmed by several sensitivity analyses. The beneficial effect on histologic endpoints was accompanied by consistent improvements in other markers of liver health including liver biochemistry and non-invasive markers of fibrosis and NASH, as well as in cardiometabolic parameters.

A post hoc analysis of the second primary endpoint (Resolution of NASH with no worsening of fibrosis) using a different definition of NASH resolution, by a pathologist's overall assessment, showed statistically significant results for the 25 mg OCA dose, with 23.1% of responders, a gain over placebo of 10.8%, and an OCA/placebo response ratio of 1.89 (95% CI: 1.32-2.70; p=0.0004). The reliability of results obtained with the post-hoc analysis, is supported by the higher concordance (intra- and inter-observer) in central biopsy reads obtained with the second definition of NASH compared to the original one.

When OCA effect was assessed simultaneously on the two primary endpoints (key secondary endpoint: and/or), including only subjects without worsening of either component, treatment responders to the 24 mg dose were 27.3% of patients, with a gain over placebo of 11.5% (p nominal 0.0005), and RR 1.73. Results were largely driven by OCA effect on fibrosis

For the Key Secondary Endpoint, "*Improvement of Fibrosis by ≥1 Stage and/or Resolution of NASH Without Worsening of Either",* OCA 25 mg showed improvement in nearly twice as many subjects (27.3%; p= 0.0005). The responder rates in the post-hoc analysis using the second definition of resolution of NASH were also higher.

The results were favourable for secondary histologic endpoints showing the effect of OCA 25 mg treatment on a number of fibrosis-related endpoints as % of subjects with no worsening of fibrosis and no worsening of NASH, % of subjects with improvement of fibrosis by ≥2 stages, % of subjects with improvement of NAS by ≥2 points with no worsening of fibrosis

5.3. Uncertainties and limitations about favourable effects

The study changed from the initial co-primary endpoints design to a two primary endpoints approach after a FDA interaction meeting. This fact, even if reflected in the protocol after the implementation of the amendment 6, does not follow the recommendations given by the CHMP SA (EMA/CHMP/SAWP/775188/2018) and the reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH).Efficacy in these two composites was expected to be demonstrated in a co-primary fashion, meaning that both have to independently demonstrate a statistically significant and clinically relevant difference to placebo.

A statistical significant treatment effect on steatohepatitis has not been shown.

Indication of treatment effect on NASH relies on a post-hoc analysis based on a different definition of NASH resolution and not on overall histopathologic interpretation AND NAS score. In this post-hoc analysis, a treatment responder is considered a subject with "absence of definite NASH". However as defined by the applicant the meaning of "absence of definite NASH" can be very different from "NASH resolution" in terms of improvement of NASH.

For an indication targeting only fibrosis in NASH a strong effect in improvement of fibrosis is expected (e.g. fibrosis regression of at least 2 stages without worsening of NASH). In study 747-303 only when the effect on NASH worsening is not considered as part of the definition the endpoint for fibrosis ≥ 2 stages achieved statistically significant results. This was in addition a secondary endpoint and the proportion of responders was low.

Reduction in liver fibrosis is generally considered a prognostic factor of long-term clinical benefit. However, the surrogacy of the primary endpoint, reduction in liver fibrosis, for liver-related outcomes (e.g. progression toward cirrhosis) and mortality is based on retrospective observations and has not been formally demonstrated.

There is the risk that long-term treatment efficacy on hard endpoints will not be assessable if a CMA is granted and a high drop-out rate occurs in the placebo arm of the 747-303 trial.

5.4. Unfavourable effects

The Applicant has provided safety data from healthy volunteers, special populations and subjects treated with up to 500 mg of OCA as well as data from subjects with PBC and other chronic liver diseases. OCA exposure information also includes subjects with compensated Child-Pugh A cirrhosis due to NASH, the majority of whom are from an ongoing randomized, double-blind, placebo-controlled Phase 3 study (Study 747-304) in that population. In addition, data of the already known safety profile of Ocaliva for PBC are available.

The primary safety population for Month 18 Interim Analysis, included 1968 subjects with NASH fibrosis stage 1, stage 2 and stage 3 (658 subjects in the OCA 25 mg group, 653 subjects in the OCA 10 mg group and 657 subjects in the placebo group), of whom approximately 1200 subjects were exposed for ≥ 12 months.

The incidence of TEAEs was slightly higher in subjects who received OCA than in subjects who received placebo. The majority of subjects experienced mild to moderate TEAEs, with a similar incidence across

treatment groups. The incidence of severe TEAEs was higher in the OCA 25 mg group (20%) compared with the OCA 10 mg group (14%) and the placebo group (13%). The incidence of life-threatening TEAEs or TEAEs leading to death was low. There were 2 deaths in placebo group and 1 death in OCA 25 mg.

The most frequently reported TEAE was pruritus, which was dose dependent. TEAEs with a higher incidence in the OCA groups than in the placebo group included constipation, low-density lipoprotein increased, blood cholesterol increased, and hyperlipidaemia.

Dyslipidaemia. In the safety population (study 747-303 and FLINT study), treatment with OCA was associated with an increase in LDL-c, a decrease in HDLc, and a decrease in triglycerides. In study 747-303, while in the PBO group a slight constant decline in LDL-c was observed through the 18 week treatment period, in patients treated with OCA 25 mg, mean LDL cholesterol increased from 114 mg/dl baseline to a peak of 138 mg/dl at Month 1, before declining to 119 mg/dl at Month 18. Changes in plasma lipids with OCA treatment were translated into higher incidences (31%) in TEAEs of dyslipidaemia compared to PBO (13.5%). The incidence of dyslipidaemia TEAEs was similar between subjects who experienced cardiovascular TEAEs and those who did not. Dyslipidaemia is reported as a very common ADR and is an important Potential risk in the current RMP.

Cardiovascular (CV) disorders. The frequency of CV TEAEs was low and apparently higher (3.9%) with OCA treatment compared to PBO (2.6%). CV SAEs were also more frequent in OCA 25 mg (n=18, 2.3%, including 2 deaths), compared to PBO (n=10, 1.2%). The number of subjects with MACE TEAEs was similar across treatment arms (<1), however, expanded MACE TEAEs were more frequent in the OCA 25 mg group (2%) compared to PBO (1%).

Alteration of glycaemic parameters, plasma glucose and HbA1c, was observed under OCA treatment; however effects were modest. At month 18, OCA 25 mg resulted in a mean increase in glycemia over baseline values of +8.4 (41.04 SD; 0.16%), compared to + 4.3 (39.13; + 0.08 %) with PBO. When data were analysed by diabetic status at baseline, changes in HbA1c were observed only in diabetic patients. No apparent difference was observed among study groups in the proportion of subjects with type 2 diabetes who initiated antidiabetic medication or increased the number of antidiabetic medications during the study.

The average on-study cumulative event rates (including recurring events) with corresponding HRs indicated that the rates of on study hyperglycaemia/diabetes TEAEs were approximately 1.3-fold higher in the OCA 25 mg and OCA 10 mg groups, as compared to PBO.

The incidence of SAEs was low for all SOCs except for hepatobiliary disorders (mainly driven by cholelithiasis and cholecystitis/cholecystitis acute), Renal and urinary disorders (mainly driven by nephrolithiasis and acute kidney injury), and Skin and subcutaneous tissue disorders (mainly driven by pruritus). The most commonly reported SAEs (≥5 subjects [<1%]) among OCA-treated subjects included sepsis (7 subjects), nephrolithiasis (6 subjects), acute kidney injury (5 subjects), angina pectoris (5 subjects), atrial fibrillation (5 subjects), and chronic obstructive pulmonary disease (5 subjects). Of these, the SAEs of acute kidney injury, angina pectoris, and chronic obstructive pulmonary disease were reported in subjects in the OCA groups only.

A total of 3 deaths were reported (2 subjects in the placebo group [bone cancer and cardiac arrest] and 1 subject in the OCA 25 mg group [glioblastoma]), none of which was considered related treatment.

The safety profile is in line with the Ocaliva known safety profile. However, new safety concerns have been found, including changes in metabolic laboratory parameters (lipids and blood glucose), gallbladder disease and acute kidney injury.

5.5. Uncertainties and limitations about unfavourable effects

The majority of subjects in the Safety Population had at least 15 months of exposure, and approximately 200 subjects in total received OCA at 10 or 25 mg dose (100 pts each dose) for 2 to 3 years. This exposure could be acceptable in the frame of CMA, but it is not adequate to evaluate long term safety in the setting of a slow developing disease.

The overall incidence and pattern of TEAEs in subjects <65 years of age, ≥65 years of age, and ≥75 years of age were similar to that in the overall population, but the majority of subjects were <65 years of age. There were too few subjects ≥75 years of age to detect any meaningful trends.

The follow-up (18 months) of MACE events is too short to fully characterize the cardiovascular safety of OCA in NASH subjects.

Based on the absolute numbers of CV events a definite conclusion on the CV safety of OCA is not possible. However, many signals, all in the same direction, point towards an increased CV risk during treatment with OCA in patients with NASH which is per se a metabolic disease with high cardiovascular disease burden.

It is at present not clear why cases of acute kidney injury were observed with OCA. OCA is not eliminated by kidneys (<3% is excreted in urine) and, despite the expression of the FXR receptor in kidney, renal exposure to the drug is considered low. The imbalance observed is however not fully justified and this potential event of nephrotoxicity deserves further exploration and is classified as an important potential risk in the RMP.

Long-term safety is uncertain as the pivotal study 747-303 is still on-going at the time of the initial submission. The Applicant is requested to provide an update on this on-going OCA study in terms of safety.

5.6. Effects Table

Effects Table for OCA in improvement of liver fibrosis and resolution of steatohepatitis in adult patients with significant liver fibrosis due to nonalcoholic steatohepatitis (NASH), without clinical signs or symptoms of cirrhosis (data cut-off: 26 Oct 2018).

Effect	Short Description	Unit	OCA 25 mg	OCA 10 mg	Placebo	Uncertainties/ Strength of evidence
Favourable Effects						
Improvement of Fibrosis by ≥1 Stage with No Worsening of NASH	Primary composite Endpoint	% RR	23.1	17.6	11.9	Unknown results patients treated with concomitant medication with potential NASH-modifying properties.

Effect	Short Description	Unit	OCA 25 mg	OCA 10 mg	Placebo	Uncertainties/ Strength of evidence
Resolution of NASH with No Worsening of Fibrosis	Primary composite Endpoint	% RR	11.7	11.2	8.0	The number of responders was not statistically significant for each group compared to placebo. In a post-hoc analysis the Applicant changed the initial definition of *"Resolution of NASH"* (based on a more comprehensive assessment of the pattern of injury (pathologist's overall assessment)) resulting in a significantly greater proportion of responders in the OCA 25 mg group (23.1%; p= 0.0004). Unknown results patients treated with concomitant medication with potential NASH-modifying properties.
Improvement of Fibrosis by ≥1 Stage and/or Resolution of NASH Without Worsening of Either	key secondary endpoint	% RR	27.3	21.5	15.8	Unknown results patients treated with concomitant medication with potential NASH-modifying properties.
Unfavourable Effects						
Pruritus	TEAE in≥5 subjects in either OCA group presented by PT	%	48	27	17	
LDL increased	TEAE in≥5 subjects in either OCA group presented by PT	%	17	17	7	
Blood cholesterol increased	TEAE in≥5 subjects in either OCA group presented by PT	%	6	5	2	
Nephrolithiasis	Incidence SEAEs in≤2subjects by PT	n (%)	3 (<1)	3 (<1)	1 (<1)	
Acute kidney injury	Incidence SEAEs in≤2subjects by PT	n (%)	4 (<1)	1(<1)	0	

Effect	Short Description	Unit	OCA 25 mg	OCA 10 mg	Placebo	Uncertainties/ Strength of evidence
Cholelithiasis	Incidence SEAEs in≤2subjects by PT	n (%)	3 (<1)	0	1 (<1)	
Angina pectoris	Incidence SEAEs in≤2subjects by PT	n (%)	3 (<1)	2 (<1)	0	
Diabetes mellitus inadequate control	Incidence SEAEs in≤2subjects by PT	n (%)	2 (<1)	2 (<1)	0	
Cardiovascular TEAE		n (%)	31 (3.9)	23 (3.3)	22 (2.6)	
Serious cardiovascular TEAE		n (%)	18 (2.3)	9 (1.3)	10 (1.2)	
Core MACE		n (%)	5 (<1)	0	4 (<1)	
Expanded MACE		n (%)	13 (2)	7 (1)	9 (1)	

MACE = major adverse cardiovascular events; MI = myocardial infarction; OCA = obeticholic acid

[a] Core MACE: Cardiovascular death, nonfatal MI, nonfatal stroke.

[b] Expanded MACE components: Death from any cause, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, transient ischemic attack, coronary revascularization procedures, peripheral revascularization procedures, or hospitalization/urgent visit for heart failure.

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

From a methodological perspective the interim analysis of the study 747-303 could be declared as a success, since the final protocol clearly establishes that either of the two primary endpoints could be positive. However, the latest version of the protocol was modified after the introduction of an amendment which implemented a relevant modification, the change from the original planned analysis with two co-primary endpoints to the above-mentioned final version. This substantial alteration of the initial protocol was supported by the FDA, since according to this regulatory agency, histologic improvement in any of the two endpoints could reasonably predict clinical benefit to support accelerated approval in the USA. However, the same strategy was not supported by the CHMP, and the SA given by the committee in Europe, clearly did not agree with that proposal.

A statistical significant improvement was observed in liver fibrosis in patients with NASH treated with OCA 25 mg for 18 months. Currently there is no marketed drug in EU that has demonstrated a clinically relevant effect on liver fibrosis in NASH.

Long-term follow-up studies have showed that fibrosis stage is the most important determinant of the risk of liver-related death in patients with NAFLD, and that discrete fibrosis categories influence future outcomes. It is possible thus to infer that liver fibrosis regression may correspond to a significant benefit in terms of reduction of liver-related deaths at patient level. However, surrogacy of liver fibrosis for long-

term liver-related outcomes (e.g. progression toward cirrhosis) and mortality in NASH is based on retrospective observations and has not been formally demonstrated.

On the other hand, statistical significant effect of OCA 25 mg on NASH resolution was not demonstrated. The role of NASH in NAFLD progression is unclear. Neither NASH presence nor its different grades measured by NAS have shown per se long-term prognostic value in NAFLD patients, in long-term follow-up studies. However, it is also obvious that a combined effect of treatment on both fibrosis and steatohepatitis would have increased the confidence that the effect on fibrosis could translate into a clinically relevant change in patient outcomes.

A statistically significant effect of OCA on steatohepatitis is indeed observed when the definition of NASH resolution is changed, post hoc, with an alternative one, based on pathologists' assessment of "the overall pattern of injury". The change is justified by the Applicant as a more reproducible and clinically relevant approach to determine presence or absence of definite NASH. However as defined by the applicant the meaning of "absence of definite NASH" can be very different from "NASH resolution" in terms of improvement of NASH.

In addition, the new method of evaluating the NASH resolution, even carried out by central pathological review, has not been accepted by any regulatory agencies so far. Therefore, such a strategy does not alleviate the absence of a statistically significant outcome.

Overall, all secondary endpoints support treatment effect on fibrosis and some components of liver damage as inflammation and hepatocellular ballooning, but not on steatosis.

For an indication targeting only fibrosis in NASH a strong effect in improvement of fibrosis is expected (e.g. fibrosis regression of at least 2 stages without worsening of NASH). In study 747-303 only when the effect on NASH worsening is not considered as part of the definition the endpoint for fibrosis ≥ 2 stages achieved statistically significant results. This was in addition a secondary endpoint and the proportion of responders was low.

The safety profile was generally consistent with that observed in NASH studies and already established in PBC, the previously approved indication. An update on the on-going OCA study in terms of safety should be provided when available. There are numerous adverse reactions which are dose dependent and, in this case, OCA 25 mg once day is a highest dose. As a matter of fact, a dose-dependent increase in the incidence of liver and gallbladder disorders was observed with NASH patients, together with a more worrisome dose-independent increase in dyslipidaemia and, potentially, in CV events. Both liver injury and gallbladder disease are considered manageable. On the other hand, the short follow-up is not considered adequate to fully characterize the cardiovascular safety of OCA in NASH Patients. Subjects with a history of significant cardiovascular or cerebrovascular disorders, within one year from study initiation, were excluded from the pivotal study, which needs to be reflected in the SmPC. MACE occurred preferably in NASH subjects at high risk for atherosclerotic CVD. It is also of concern, for the potential negative impact on CV risk, the observed increase in fasting glycemia and in the rates of cumulative hyperglycaemia/diabetes events. Impaired glucose tolerance and type 2 diabetes are frequent in patients with NASH, and the increase in frequency with OCA treatment is clinically relevant and requires that regular monitoring of glycaemic parameters is specifically recommended in the SmPC. At the moment, based on the absolute numbers of CV events a definite conclusion on the CV safety of OCA is not possible. However, considering the many signals, all in the same direction, towards an increased CV risk during treatment with OCA in patients with NASH which is per se a metabolic disease with high cardiovascular disease burden, a contraindication for patients at high risk for CV disease is deemed necessary in order to select the target population for which a positive B/R balance might be still expected.

An increase in the number of subjects experiencing acute kidney injury was observed with OCA 25 mg, although the drug is not eliminated by kidneys and, despite the expression of the FXR receptor in kidney, renal exposure to the drug is considered low. Further investigation is required before a sound evaluation of its impact on OCA treatment and patient management may be performed. This adds uncertainties to the evaluation of the unfavourable effects of OCA in NASH.

5.7.2. Balance of benefits and risks

Eventually, the clinical consequences of a progression in the disease is related to the development of cirrhosis, and end-stage liver disease. NASH is also a relevant risk factor for the occurrence of hepatocellular carcinoma. Hard clinical endpoints showing delay of these consequences are therefore clinically relevant. However, due to the slow progression of the disease, conditional approval has been proposed as a reasonable approach to obtain treatments that in the end could offer clinical improvements.

The way of getting conditional approval relies on the fact of having variables able to predict in a quantitative manner a positive benefit in the long run (surrogacy).

In the main study of this application (for CMA) the two (co-)primary endpoints of the interim analysis are histologic variables. Fibrosis improvement and NASH resolution have been correlated at patient level with a better prognosis. However, no surrogacy has been demonstrated so far. It cannot be assumed that patients experiencing the reverse event (decrease of fibrosis stage by one), experience the same level of reduction of this overall risk (as stated in the CHMP advice).

The fact that only one of the two primary variables has been unequivocally met, does not precisely clarify the true benefit of this medicinal product for the claimed indication (improvement fibrosis and resolution of steatohepatitis). In addition, for an indication targeting only fibrosis in NASH a strong effect in improvement of fibrosis is expected i.e. of such a relevant magnitude that it could be reasonably expected to translate in/predict clinical benefit in the long-term (and to also compensate for the safety profile of a treatment intended to be given chronically to patients who are most suffering from several comorbidities mainly metabolic and CV). However, evidence of efficacy currently available is considered limited as the proportion of responders is low (particularly when focusing in more stringent definitions of response in fibrosis, i.e. $\geq$ 2 stages) and the reported gain over placebo small.

Despite the safety profile is not prohibitive considering the many signals, all in the same direction, towards an increased CV risk during treatment with OCA, a contraindication for patients at high risk for CV disease is deemed necessary in order to select the target population for which a positive B/R balance might be still expected.

Last but not least, even if finally, a CMA could be achieved, the requirements of such a condition should be met. Even if obeticholic may be able to address an unmet need in the treatment of NASH with fibrosis, at the moment the benefit/ risk balance is considered negative. In addition the risk remains high that even if the applicant has put in place prospective measures to ensure retention of subjects and study completion that the submission of the final analysis of the study 747-303 could be seriously jeopardised if an approval of obeticholic acid were granted.

5.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating disease.

The product is not considered to fulfil the requirements for a conditional marketing authorisation at the moment since the benefit-risk balance is not considered positive, as discussed. Further, even if it is agreed that NASH poses an unmet need, the limited magnitude of the effect fails to address this unmet medical need. In addition, there are still some concerns that even if the applicant has put in place prospective measures to ensure retention of subjects and study completion, that that the submission of the final analysis of the study 747-303 could be seriously jeopardised if an approval of obeticholic acid were granted.

The benefits to public health of the immediate availability would outweigh the risks inherent in the fact that additional data are still required if the previous requirement were fulfilled.

5.8. Conclusions

The overall B/R of Zektayos-Hepjuvo is currently negative.