13 October 2016
EMA/725757/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OCALIVA

International non-proprietary name: obeticholic acid

Procedure No. EMEA/H/C/004093/0000

Note

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

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Administrative information

Name of the medicinal product:	OCALIVA
Applicant:	Intercept Pharma Ltd. 2 Pancras Square London N1C 4AG UNITED KINGDOM
Active substance:	obeticholic acid
International Non-proprietary Name:	obeticholic acid
Pharmaco-therapeutic group (ATC Code):	bile therapy, bile acid preparations (A05AA04)
Therapeutic indication(s):	OCALIVA is 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.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	5 mg and 10 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	30 tablets

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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	adverse event
AMA	antimitochondrial antibody
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AMA	antimitochondrial antibodies
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical/Therapeutic/Chemical
AUC	area under the curve
BA	bioavailability
BAS	bile acid sequestrants
BE	bioequivalence
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
CA	cholic acid
CDCA	chenodeoxycholic acid
Clcr	creatinine clearance
Cmax	Maximum observed concentration
CRA	clinical research associate
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
DB	double-blind
DCA	deoxycholic acid
DDI	drug-drug interaction
DEXA	dual-emission x-ray absorptiometry
DSMC	Data Safety Monitoring Committee
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form
EE	Efficacy Evaluable
ELF	enhanced liver fibrosis (markers)
EOT	end of treatment
EU	European Union
FGF-19	fibroblast growth factor-19
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HA	hyaluronic acid
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDLc	high-density lipoprotein cholesterol
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL-6	interleukin-6
INR	international normalized ratio
IRB	institutional review board
ITT	Intent-to-Treat
IWRS	interactive web response system
LA	lysophosphatidic acid
LCA	lithocholic acid
LDL	low-density lipoprotein
LDLc	low-density lipoprotein cholesterol

LLN	lower limit of normal
LTSE	long-term safety extension
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End Stage Liver Disease
MMRM	repeated measures linear mixed model
MRS	Mayo Risk Score
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NF	National Formulary
OCA	obeticholic acid
P3NP	procollagen-3 N-terminal peptide
PBC	primary biliary cirrhosis
PK	pharmacokinetic(s)
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SE	standard error
SI	International System of Units
SUSAR(s)	suspected unexpected serious adverse reaction(s)
TE	transient elastography
TEAE(s)	treatment-emergent adverse event(s)
TIMP-1	tissue inhibitor of metalloproteinase 1
TIPS	transjugular intrahepatic portosystemic shunt
TNF-α	tumor necrosis factor-alpha
TNF-β	tumor necrosis factor-beta
UDCA	ursodeoxycholic acid
ULN	upper limit(s) of normal
VAS	visual analog scale
VLDL	very low-density lipoprotein
VLDLc	very low-density lipoprotein cholesterol
WHO	World Health Organization
WHODDE	World Health Organization Drug Dictionary Enhanced

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Intercept Italia s.r.l. submitted on 8 June 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for OCALIVA, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 September 2014.

On 15 August 2016, the applicant was changed from Intercept Italia s.r.l. to Intercept Pharma Ltd.

OCALIVA was designated as an orphan medicinal product EU/3/10/753 on 27 July 2010. OCALIVA was designated as an orphan medicinal product in the following indication: treatment of primary biliary cirrhosis.

The applicant applied for the following indication: *treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA*.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ocaliva as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, complete and independent application. The applicant indicated that obeticholic acid was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance obeticholic acid contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decision

P/0310/2015 on the granting of a (product-specific) waiver for the condition “treatment of primary biliary cirrhosis”.

Protocol Assistance

The applicant received Protocol Assistance (PA) from the CHMP on 17 February 2011, 25 July 2013, 22 May 2014 and 22 January 2015. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aranzazu Sancho-Lopez Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 8 June 2015.
- The procedure started on 25 June 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 September 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 September 2015. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 28 September 2015.
- During the meeting on 8 October 2015, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 22 October 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 October 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2016.
- The following GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  GCP inspections were conducted at three clinical investigator sites, one in Belgium and two in the USA (routine inspections) and also at the sponsor site and CRO site in the USA (triggered inspection) on dates between October 2015 and January 2016. The outcome of the inspections carried out was issued on 8 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 29 June 2016.
- During the PRAC meeting on 7 July 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 21 July 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 2 September 2016.
- During the meeting on 15 September 2016, the CHMP, the CHMP agreed on a second list of

outstanding issues to be addressed in writing by the applicant.

- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 20 September 2016.
- The Rapporteurs circulated the second Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 29 September 2016.
- During the meeting on 13 October 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ocaliva on 13 October 2016.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Primary biliary cirrhosis (PBC) is a rare, serious, life-threatening liver disease characterized by cholestasis with progressive impairment of bile flow in the liver that results in increased hepatocellular bile acid concentrations. Bile acids at elevated hepatocellular concentrations can be toxic to the liver. Such hepatocellular injury results in a local inflammatory response and is signalled early on by the secretion of alkaline phosphatase (ALP). In patients with an inadequate response to therapy, the disease frequently progresses to hepatic fibrosis and eventual cirrhosis, hepatic decompensation, and death unless a patient receives a liver transplant (Kuiper 2010).

2.1.2. Epidemiology and risk factors

Given that most epidemiological studies are performed in the Western world, in addition to the rarity of the disease, true population-based studies in PBC are scarce. Based on well-defined and rigorous case ascertainment, the incidence and prevalence rates for PBC in Europe, North America, Asia, and Australia are reported ranging from 0.33 to 5.8 per 100,000 inhabitants and 1.91 to 40.2 per 100,000 inhabitants, respectively (Boonstra 2012).

PBC disproportionately affects women versus men (approximately 10:1) and is typically diagnosed in patients between 40 years to 60 years of age. It is estimated that 1 in 1000 women over the age of 40 are affected. Recent data suggest that those who are young at onset (diagnosed before 50 years of age) or male have a worse prognosis (Carbone 2013). Racial or ethnic differences in PBC patients have not been consistently identified (Al-Harthy 2012, Boonstra 2012).

2.1.3. Aetiology and pathogenesis

While the cause of the disease is unclear, genetic predispositions have been described (Hirschfield 2009, Mells 2011). It is believed that the disease may be 'triggered' by a response to a number of factors, such as infection or chemicals, followed by an autoimmune response (Pratt 2005).

2.1.4. Clinical presentation, diagnosis and stage / prognosis

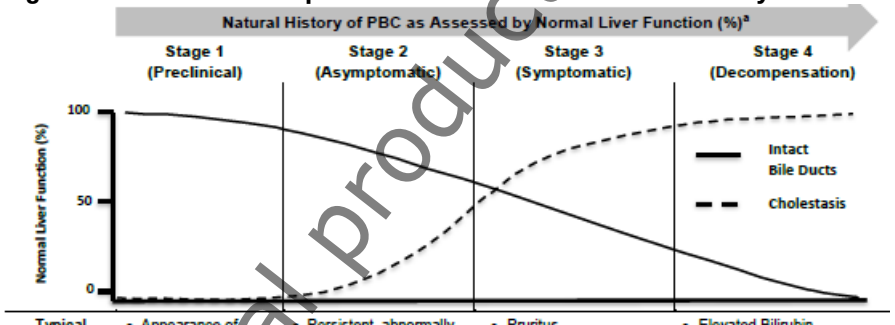
The presence of antimitochondrial antibodies (AMA) is a specific immunological hallmark of PBC and is an early diagnostic of the disease (Hirschfield 2013). ALP is the predominant biochemical marker used in the diagnosis and treatment for cholestatic conditions. Gamma-glutamyl transferase (GGT) lacks specificity as it is seen in many clinical conditions; however, elevation of this enzyme in the presence of elevated ALP levels is confirmatory of a hepatic etiology and in particular cholestatic condition such as PBC (Giannini 2005). In the later stage of PBC, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may also be elevated due to hepatocellular damage as a secondary effect of cholestasis. Thus, in PBC, especially in the earlier stages, aminotransferase levels are usually within normal limits, and if elevated, only minimally (approximately 1x upper limit of normal [ULN] to 3x ULN) (Lindor 2009) (EASL 2009).

PBC disease progression can vary widely across patients, with some patients progressing to decompensation over a period of years and others remaining asymptomatic for more than a decade. In the early stages of disease, PBC patients do not manifest the signs and symptoms of illness.

As shown in Figure 1, liver function begins to deteriorate prior to onset of symptoms. ALP levels correlate with disease progression, and over the first year, with and without treatment, are highly predictive of long-term clinical outcomes, e.g. transplant-free survival (Beuers 2011, Lammers 2014, Carbone 2013).

Changes in ALP and bilirubin correlate with and fully capture the net effects of OCA on the primary pathophysiology of PBC. Persistent hepatocellular damage eventually leads to increased circulating bilirubin once hepatic excretory function has been significantly damaged; therefore, elevated circulating bilirubin is a direct result of significant liver damage. Furthermore, literature suggests that increased levels of circulating ALP, when occurring in patients with a concurrent rise in GGT, occurs in parallel with decreased expression in the canalicular space. This results in dysregulation of adenosine triphosphate and pH triggering continued heightened inflammatory response, and in turn results in persistent, cholestasis-induced, hepatocellular damage and ultimately liver failure.

Figure 1: Schematic representation of the natural history of PBC



[a] PBC disease progression can vary widely across patients, with some patients progressing to decompensation over a period of years and others remaining asymptomatic for more than a decade. This schematic is a qualitative representation of the typical stage of the onset of antibodies, biomarkers, symptoms, and outcomes.

[b] Lipid abnormalities among PBC patients change based upon the stage of PBC disease. With PBC disease progression, levels of total and HDL cholesterol are reduced. Elevated lipoprotein X typically observed in last stage (Loria 2014).

[c] Given the underlying autoimmunity etiology, PBC can recur in a significant percentage of patients receiving liver transplants, with increasing likelihood over time (Silveira 2010, Lindor 2009).

Adapted from Selmi 2011.

Lipid abnormalities, including triglycerides, low density lipoprotein cholesterol (LDLc), and high density lipoprotein cholesterol (HDLc), are observed at all stages of the disease but elevated HDLc is frequently observed early. With PBC disease progression, levels of total and HDLc are reduced, while levels of lipoprotein X increase (Loria 2014). There is no consensus that these lipid abnormalities in PBC patients correlate with an increased risk for developing cardiovascular disease (Crippin 1992, Longo 2002, Allocca 2006, Ungprasert 2014).

Pruritus and fatigue are the most commonly reported symptoms in PBC (Mayo 2008, Crosignani 2008). Neither the exact pruritogen nor the underlying mechanisms for the cause of cholestatic pruritus have been completely elucidated, although the autotaxin pathway has been implicated (Bolier 2012, Beuers 2014). Pruritus may subside spontaneously when patients decompensate and develop hepatic failure, suggesting the pruritogen is synthetized in the liver (Jones 2012, Jones 1999). Fatigue is reported in up to 78% of PBC patients. Although fatigue is not well understood, it known that it is not specific to PBC, and it does not correlate with disease severity (Crosignani 2008). Fatigue is related to autonomic dysfunction in the brainstem and can be severe. Decrements in mental and physical functions can be observed.

Osteoporosis is the bone disorder seen most often in PBC and occurs in up to one-third of patients. The cause of osteoporosis in PBC is uncertain. Patients with PBC appear to have “low-turnover” osteoporosis in which bone formation is inhibited and bone resorption is low or normal (Adorini 2009). Vitamin D metabolism is normal in patients with PBC except for those with jaundice and clinically advanced disease (Lindor 2009).

Portal hypertension often develops in the advanced stages of PBC when patients have well-established cirrhosis; however, in contrast to other liver diseases, it may develop prior to cirrhosis (Crosignani 2008, Lindor 2009). Patients with cirrhosis may haemorrhage from oesophageal or gastric varices, or portal gastropathy despite having normal or near normal synthetic liver synthetic function (Lindor 2009).

The final stage of PBC is decompensation marked by progressive liver insufficiency. Total bilirubin generally remains within normal limits until the onset of extensive hepatic failure and loss of functional liver tissue. Studies of patients with partial hepatectomy (up to 75% resection) have shown that bilirubin levels remain relatively normal (Helling 2006). Scleral jaundice may start to appear at a bilirubin level of approximately 50 µmol/L and indicates, in a cholestatic patient, that the net excretory capacity of the remaining functional liver tissue is failing.

2.1.5. Management

There are limited therapeutic options for PBC patients. Liver transplantation can significantly improve survival and pruritus in patients (Corpechot 2008, Lindor 2009). However, it is a complex, time-consuming operation with identified risks suitable only for patients with advanced liver disease, including perioperative and surgical complications, immunologic and infectious disorders, and various medical complications. Complications of liver transplant include bleeding, rejection, infection, and side effects from medications such as immunosuppressants. Furthermore, given the underlying autoimmunity that causes PBC, the disease can recur in a significant percentage of patients receiving liver transplants, with increasing likelihood over time (Silveira 2010, Lindor 2009).

Ursodeoxycholic acid (UDCA), a bile acid constituent, is the only medicine currently approved to treat PBC. UDCA improves biochemical indices such as ALP and bilirubin and delays histological progression (Poupon 1997, Corpechot 2008). The results of clinical trials of appropriate dose and length of treatment, in combination with well-controlled epidemiologic analyses, provide strong evidence that treatment with UDCA increases progression-free survival, with significantly greater benefit for patients who demonstrate greater response as measured by decreases in ALP, bilirubin and ALT. Accordingly, UDCA treatment has

been recommended as first line therapy for patients with PBC in both European (European Association for the Study of the Liver [EASL]) and American (American Association for the Study of Liver Diseases [AASLD]) treatment guidelines (Lindor 2009, EASL 2009).

While UDCA has a marked impact on clinical outcomes in PBC, up to 50% of UDCA-treated patients either fail to respond or have a suboptimal response as defined based on various liver biochemistry algorithms. These criteria included a decrease >40% in ALP from the baseline value or decrease to a normal level (Parés 2006); ALP <3x ULN, AST<2x ULN, and bilirubin <ULN (Corpechot 2008, Corpechot 2011); and normalization of abnormal concentrations of bilirubin, albumin, or both. (Kuiper 2009).

The risk associated with non-response to UDCA is substantial. A cross-sectional study using the United Kingdom PBC patient cohort (UK-PBC) data indicates that this lack of response is significantly more common in patients who are young at disease onset or who are male, presumably reflecting an accelerated disease course (Carbone 2013). Fifty percent of patients in the UK-PBC study who had presented with PBC below the age of 50 were either in a state of UDCA non-response or had already undergone liver transplantation. There is an increased impact in those patients with a non-response to UDCA (in population terms) who develop the disease when younger given their expectations of normal lifespan. These patients are at significantly increased risk of an adverse outcome such as a liver transplant or end stage liver disease (Parés 2006, Kuiper 2009, Corpechot 2008, Kumagi 2010b, Corepchot 2011, Momah 2012). These findings have recently been confirmed by both the nationwide UK-PBC group (Mells 2011) and the Global PBC Study Group (Lammers 2014).

Furthermore, while UDCA at the recommended dosage (13 mg/kg/day to 15 mg/kg day) is generally well tolerated (Hempfling 2003, Axcan Pharma US, Inc.), there is a small subset of PBC patients who are unable to tolerate UDCA (primarily due to gastrointestinal symptoms) and thus are at an even greater risk of adverse outcome if unable to remain on therapy.

While research has been conducted on a number of other drugs (azathioprine, methotrexate, colchicine, D-penicillamine, cyclosporine A, chlorambucil, glucocorticosteroids), little to no consistent research supports the benefit of these compounds on PBC (Rudic 2012).

Based on the totality of evidence, there is a clear ongoing unmet medical need for second-line therapies in this serious, life-threatening disease, as well as other alternative therapies for the small percentage of patients with PBC who are unable to tolerate UDCA.

About the product

OCA is a selective and potent agonist for the farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine. The endogenous bile acid chenodeoxycholic acid (CDCA) is the natural ligand for FXR; OCA is approximately 100-fold more potent than CDCA at the FXR due to the addition of a single α-ethyl group in the 6-carbon position.

UDCA is an epimer of CDCA without significant FXR agonist effects acting rather through post-translational mechanisms (Beuers 2010, Hohenester 2012). UDCA needs to be administered in large doses (13 mg/kg to 15 mg/kg). OCA induces transcriptional effects, thus augmenting the properties of UDCA.

While several downstream aspects of FXR activation are important, the regulation of bile acid homeostasis primarily underlies the therapeutic rationale for FXR agonists in PBC. Activation of FXR in the intestine and liver leads to the following:

1. Increased synthesis of fibroblast growth factor-19 (FGF-19);

2. Induction of transcription factor heterodimer protein (SHP); and

3. Repression of cholesterol 7-alpha-hydroxylase (CYP7A1) expression and bile acid synthesis (Rizzo 2010).

This reduction of bile acid synthesis is complemented by the effects of OCA to increase expression of bile acid transporters thus promoting choleresis (Rizzo 2010). Induction of the bile salt excretory pump (BSEP) leads to transport of conjugated bile acids from the liver in to bile, while induction of the heterodimer protein organic solute transporter α/β (OST α/β) leads to transport of conjugated bile acids from the liver to the systemic circulation. The unique combination of decreased bile acid synthesis and increased transport of bile acids out of the hepatocyte serves to combat the toxic burden of hepatic bile acid accumulation in cholestasis.

FXR activation also leads to anti-fibrotic and anti-inflammatory effects (Pellicciari 2002, Albanis 2005, Wang 2008). The description of bile acid signaling pathways, the identification of endogenous activators, and the recognition that certain signaling pathways are deficient or defective in hepatic disease, have led to the development of OCA for the treatment of patients with PBC.

The proposed indication is as follows:

"Obeticholic Acid (OCA) is indicated for the treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA."

As major hepatology societies and advocacy groups have recognized the name change for this disease to "Primary Biliary Cholangitis" instead of cirrhosis the indication was adapted during the procedure as follows:

"OCALIVA is 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."

Type of Application and aspects on development

The application is submitted under the Centralized Procedure (according to Regulation (EC) No 726/2004, of mandatory scope of said Regulation (Article 3(1)) as an orphan designated product.

With the responses to the D120 LOQ, the Applicant applied for a Conditional Marketing Authorisation. The requirements of Regulation (EC) No 507/2006 on the Conditional Marketing Authorization for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 are met (see chapter 3.7.3 of this report for discussion).

There are no EU specific guidelines for this condition. The Sponsor received Protocol Assistance (PA) from the CHMP dated 17 Feb 2011 on the clinical development program and the quality registration package.

During this CHMP PAs, several key clinical issues were discussed at length, such as chosen endpoint, planned inclusion criteria, length of study (6 month in the original design), and their partial character as dose-finding studies, as the phase 3 studies were originally planned. At that time, the CHMP expressed concerns whether the change in laboratory values (chosen primary endpoint) seen under the treatment with UDCA would lead to the same long-term outcome after treatment with obeticholic acid. The unfeasibility of a hard clinical endpoint such as "transplant free survival" at preapproval was acknowledged and it was stated that the acceptance of the proposed endpoint would also be based on the assessment of (historical) data demonstrating an UDCA treatment effect vs. placebo on hard clinical

endpoints. In addition, the Applicant was made aware of the fact that the acceptance of this endpoint would also be subject to the obligation of the Applicant to collect as much data as possible regarding harder clinical endpoints, such as biochemical progress based on different published algorithms, histology, cirrhosis related events and transplantation, along with data regarding symptomatic changes, evaluation of Quality of Life, and the evaluation of the fibrosis serum markers and elastography.

Following this initial PA, the Sponsor conducted 2 follow-up Protocol Assistance procedures in 2013 and 2014.The first focused on pharmaceutical development of OCA including GMP starting material and stability to support the MAA filing. The second addressed issues noted in the prior meeting with the EMA, mainly related to the clinical pharmacology program.

In October 2014, a final follow-up Protocol Assistance procedure was initiated to seek advice regarding design of the Phase 3bclinical outcomes study (Study 747-302). In addition, the statistical analysis plan for the study was also addressed during this procedure, with the final advice received in January 2015.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 5 mg or 10 mg of obeticholic acid (OCA) as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, sodium starch glycollate (Type IA) and magnesium stearate.

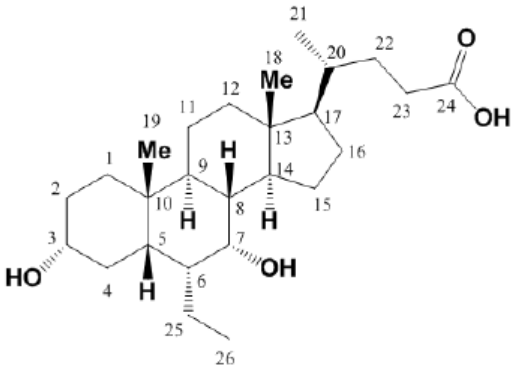
Coating: polyvinyl alcohol, partially hydrolyzed (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b) and iron oxide yellow (E172).

The product is available in high-density polyethylene (HDPE) bottles with a child resistant polypropylene closure and an aluminium foil induction seal as described in section 6.5 of the SmPC

2.2.2. Active Substance

General information

The chemical name of obeticholic acid is 3α,7α-dihydroxy-6α-ethyl-5β-cholan-24-oic acid corresponding to the molecular formula $C_{26}H_{44}O_4$. It has a relative molecular mass of 420.63 g/mol and the following structure:



The structure of the active substance has been demonstrated by several common techniques in organic chemistry: ^{1}H and ^{13}C Nuclear Magnetic Resonance, Fourier Transformed Infrared Spectrometry, UV Absorption, Mass Spectrometry and Single Crystal X-ray Powder Diffraction.

The active substance is a white to off-white powder, moderately hygroscopic, and freely soluble in water at pH ≥7. It is a stable amorphous solid. Obeticholic acid has cohesive properties that help during tablet compression. Other physicochemical characteristics of the active substance that impact the quality of the finished product are particle size distribution which plays a critical role in the content uniformity and dissolution of the tablets.

Obeticholic acid exhibits stereoisomerism due to the presence of 11 chiral centres. Nine of them are defined by the raw material and are maintained during the active substance synthesis. The manufacturing process defines the stereochemistry and physico-chemical properties of the active substance. The absolute stereochemistry of the molecule was determined by X-ray diffraction.

Manufacture, characterisation and process controls

Obeticholic acid is synthesized in 6 synthetic steps using a commercially available well-defined starting material with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in low density polyethylene (LDPE) double bag, a secondary polyethylene terephthalate/aluminium (PET/Al) bag containing a desiccant (both bags closed with cable straps). The bags are stored inside a fibreboard drum. The materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identification (FTIR, HPLC), assay (HPLC), related substances (HPLC), residual solvents (Ph. Eur.), water content (Ph. Eur.), sulphated ash (Ph. Eur.), heavy metals, palladium (Ph. Eur.), particle size distribution, solid state form (XRPD), and microbial limits (Ph. Eur.)

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data of active substance from the proposed manufacturer stored in the intended commercial package for 12 months under long term conditions at 5 °C ± 3 °C and for up to 6 months under accelerated conditions at 25 °C/60% RH according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch.

Forced degradation studies were carried out on under the following conditions: acid stress (1M nitic acid), base stress (1M ammonia solution), oxidative (5% H_2O_2), oxidative with alkaline media (5% H_2O_2 in 1M ammonia solution), thermal stress (50°C, 60°C, and 70°C) and thermal stress with water (50°C, 60°C, and 70°C in aqueous solution).

Supporting non-milled pilot stability batches were stored under long term and accelerated conditions described above.

The analytical methods used were the same as for release and were stability indicating.

All available results at the long term and accelerated condition meet specifications. It was considered that the proposed limits can be accepted and do not pose any safety risk.

The stress studies demonstrate that the active substance assay method and related substance methods are stability indicating and specific for quantifying obeticholic acid and related substances, respectively. The results of the forced degradation studies demonstrated that the active substance is stable in the solid state but is sensitive to alkaline, acidic and oxidative conditions in solution. This is in line with stability results under accelerated conditions. The results of the photostability study confirm that the active substance is not photosensitive.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored at 5 °C ± 3 °C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Ocaliva film coated tablets are formulated as an immediate release solid dosage form available in 2 strengths containing 5 mg and 10 mg of OCA active substance per tablet. The 5 mg and 10 mg OCA tablets are both yellow, but differ in their shape and debossing for dose differentiation. The 5 mg OCA tablet is round and debossed with INT on one side and 5 on the other side. The 10 mg OCA tablet is triangular and debossed with INT on one side and 10 on the other side.

The tablet was selected as a safe and convenient dosage form for commercial product.

The active substance has cohesive properties that help during tablet compression. Other physicochemical characteristics of the active substance that impact the quality of the finished product were considered during development. Chemical compatibility studies between the active substance and the excipients used in the finished product formulation were performed. The results are in agreement with long-term finished product stability data.

Each excipient used in the finished product was chosen based on its ability to impart characteristics desired for a robust manufacturing process capable of producing a compressed tablet dosage form. The excipients are standard pharmaceutical inactive ingredients that are commonly used in solid oral dosage forms and are compatible with the active substance. The level of each excipient is at levels typically found in non-sterile solid dosage forms. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

The finished product was initially formulated as a hard gelatin capsule for phase 1 and 2 clinical trials. As the development continued, a tablet formulation was developed to support pivotal clinical trials

During development, the manufacturing site of tablets was changed to the proposed commercial manufacturing site. No change was made in the quantitative composition of the finished product. The pivotal clinical studies were conducted with tablets manufactured at the earlier manufacturing site using the previous manufacturing process. An *in vivo* comparison study was conducted using the 10 mg tablets, along with a series of *in vitro* dissolution studies to investigate bioequivalence. An *in vivo* study was also conducted to compare the phase 2 capsule formulation with the proposed commercial product. *In vitro* dissolution data was also generated for the capsule formulations. The studies demonstrated that the clinical formulations and the proposed commercial formulation are bioequivalent.

The dissolution method was developed for routine quality control purposes, as well as for making comparisons between products during development. The experiments performed to establish the suitability of the method as a discriminatory procedure were provided.

Over the course of development, the manufacturing process has been optimized with initial prototype batches being manufactured and subsequently transferred to the manufacturing sites to support clinical manufacture and commercialization. The main process steps used to manufacture the finished product have remained consistent throughout development. However, they have been refined as the process has evolved.

The primary packaging is 40 cc HDPE bottles with child resistant polypropylene closures and induction seals. The components selected for the commercial primary container closure system were evaluated for performance, compatibility of components, and environmental protection to assess their suitability for

commercial use with the finished product. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

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.

No validation data were provided in the marketing authorisation application as the validation of the manufacturing process will be conducted post-approval according to the protocol provided. This is acceptable being an immediate release dosage form manufactured with a standard process. The in-process controls are adequate for this type of manufacturing process

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC, TLC), assay (HPLC), degradation products (HPLC), total specified and unspecified impurities (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), microbial limits (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. However, the CHMP recommended that a second identification method for OCA be developed and validated as TLC is an outdated and inaccurate method. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released onto the market based on the -approved release specifications, through traditional final product release testing.

Stability of the product

Stability data to support the proposed shelf-life in the commercial packaging have been generated using 5 mg and 10 mg white OCA tablets) and yellow commercial image OCA tablets packaged in 40 cc and 85 cc HDPE bottles. The use of white OCA tablets is appropriate as the change of colour has no impact on the stability of the tablets. Stability data from the finished product stored under long term conditions for up to 24 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. All data collected to date have met the commercial specification. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products, total specified and unspecified impurities, dissolution, water content, and microbial limits. The analytical procedures used are stability indicating. All stability data provided under long term and accelerated conditions met the specification. No significant changes have been observed.

In addition, forced degradation studies were performed to understand major degradation products arising from the active substance, when exposed to stress conditions. Stress testing involving forced degradation with acid, base, oxidation, and heat/thermal conditions in solution was conducted on one batch of each

strength. The results of the forced degradation studies demonstrate that the finished product is stable when exposed to alkaline conditions but are sensitive to acidic, oxidative and thermal conditions in solution.

Photostability was evaluated in accordance with ICH guideline Q1B "Stability Testing: Photostability Testing of New Drug Substances and Products" using 1 batch of each strength. No significant changes were observed in any test attribute. The finished product, therefore, is not photosensitive and does not require any special protection from light during storage.

The proposed hold period for bulk tablets is 12 months in double LDPE bags, sealed with bag ties, inside an HDPE container. The hold period is supported by stability data of bulk tablets held in simulated bulk tablet storage conditions. Stability data has been collected up to 12 months stored in double LDPE bags, sealed with bag ties, inside a fibreboard box that was held in the warehouse at controlled ambient temperature (15°C to 25°C). Stability data demonstrate that bulk OCA tablets remain stable throughout the proposed 12 month hold time period. A minor increase in one of the impurities is observed that is consistent with that observed for OCA tablets in long-term (25 °C/60% RH) stability studies in the commercial container closure system. A 12-month hold time period for bulk OCA tablets is therefore justified.

The stability studies have demonstrated that the dissolution profiles of both the 5 mg and 10 mg OCA tablets have not changed during storage at both 25 ºC / 60% RH and 40 ºC / 75% RH and as such, no test for polymorphic form is included in the finished product specification.

Based on available stability data, the proposed shelf-life of 36 months without any special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Cholic acid is the only substance of human or animal origin used. A valid TSE CEP from the suppliers of cholic acid used in manufacturing process is provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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 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 clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

A second identification method for OCA should be developed and validated as TLC is an outdated and inaccurate method.

Non-clinical aspects

2.2.7. Introduction

OCA has been tested in in vitro and in vivo nonclinical studies to evaluate its pharmacological activity and efficacy in liver and metabolic diseases. The nonclinical pharmacology profile indicated that OCA is a potent and selective FXR agonist that acts as an anticholestatic, antifibrotic, and anti-inflammatory agent with hepatoprotective properties and that lacks untoward pharmacology effects in nonclinical safety models.

Secondary pharmacology studies (non-GLP) demonstrated other potential beneficial effects of OCA on the liver, and supported extra-hepatic antifibrotic and anti-inflammatory activities.

Safety pharmacology studies evaluated the potential for OCA to cause safety-related, unintended pharmacologic effects. In vitro studies assessed the effects of OCA on hERG channel currents and hERG binding to tracer ligand. In vivo safety pharmacology studies assessed neurological, respiratory, and gastrointestinal (GI) effects in rats, and cardiovascular effects in beagle dogs.

2.2.8. Pharmacology

Primary pharmacodynamic studies

The nonclinical pharmacology profile indicated that OCA is a potent agonist for FXR and was approximately 100-fold more potent than CDCA, with EC50 values from 44 to 100 nM.

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 (EC50 = 20 µM).

The glyco- and tauro-conjugated derivatives of OCA are able to activate FXR, with an activity similar to the parental compound OCA, and do not show any activity for 14 different nuclear receptors tested.

Upon oral administration, OCA functions as a bile acid and signaling molecule in several pathways modulated by FXR. Also, OCA treatment modulated the expression of genes regulating lipid and glucose metabolism. Direct anti-inflammatory, anti-fibrotic and immune-modulatory effects of OCA were demonstrated in test systems such as cultured human hepatic stellate cells, mouse primary hepatocytes and human immune cells.

In a rat model of acute cholestasis, co-infusion of OCA with LCA fully reversed impairment of bile flow and protected against acute liver cell necrosis. In a rat model of liver fibrosis, co-administration of OCA and TAA significantly inhibited the progression of fibrosis and therapeutic administration of OCA reversed established fibrosis and cirrhosis. OCA improves portal hypertension in two different rat models of cirrhosis by decreasing intrahepatic vascular resistance. This hemodynamic effect relates to increased intrahepatic endothelial nitric oxide synthase activity by pathways that differ depending on the aetiology of cirrhosis.

Secondary pharmacodynamic studies

Secondary pharmacology studies were conducted in animal models of diet-induced metabolic syndrome and in mouse models of inflammatory bowel disease. It has been shown that OCA not only regulates endogenous bile acid synthesis but also activates protective pathways in hepatocytes challenged with toxic xenobiotics. Thus, secondary pharmacodynamic studies demonstrated that OCA had beneficial effects on glucose and lipid metabolism, liver steatosis and inflammation, visceral fat, bladder alterations, diabetes- and obesity-related renal disease, and vascular tone in animal models of disease.

Safety pharmacology programme

Several safety pharmacology studies have evaluated the neurological, cardiovascular, pulmonary and gastrointestinal effects of OCA. In study 070927.JPQ to assess the effects of OCA on the hERG channel current, the concentration of 300 µM caused a disruption of the cell/patch recordings. At 82.8 µM OCA, hERG channel currents were slightly reduced. At 8.3 µM, a small difference in the magnitude of the hERG current was noted when compared to vehicle, but this is not clearly a test substance-related effect. Therefore, it is considered that OCA does not block hERG channels. Also, in patients treated with 50 mg of OCA, the plasma concentrations were around 160 ng/ml or 380 nM. This means that the safety margin between therapeutic plasma concentration and hERG channel block is greater than 218 fold. Indeed, in a cardiovascular safety study in dogs, the no-observable-effect level (NOEL) for OCA occurred at the highest dose tested (20 mg/kg), and no noteworthy effects were found.

Oral administration of OCA, up to 120 mg/kg, did not produce any apparent neuro-pharmacological or toxicological effects, changes in pulmonary function or GI propulsion, or biologically relevant effects on body temperature in Sprague-Dawley rats.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted which was considered acceptable by the CHMP.

2.2.9. Pharmacokinetics

The synthesis, conjugation, secretion, enterohepatic circulation/distribution and excretion of bile acids has been reviewed (Lefebvre et al., 2009 Hofmann and Hagey, 2014). The pharmacokinetic studies to assess the OCA employed validated methods of analysis using either liquid-liquid or protein precipitation-based extraction methods, C18 reverse-phase HPLC and triple quadrupole LC-MS/MS with ion transitions appropriate for OCA, glyco-OCA and tauro-OCA.

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.

The absorption of OCA in oral administration studies was rapid, with a Tmax ranging from 0.25 hour to 1 hour in mice, 0.25 hour to 2 hours in rats, 1 hour to 2 hours in rabbits and 0.5 hour 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 and OCA exposure was higher in females than in males while exposure to tauro-OCA was similar in male and female mice. 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.

Pharmacokinetic studies in rats include 2 absorption/metabolism studies, unlabeled and radiolabeled, 4 studies ranging in duration from 14 days to 24 months and one study during embryo-fetal development in pregnant rats. 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.

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.

In dogs, the pharmacokinetics of OCA was evaluated in 3 GLP studies lasting 7 days to 9 months and 1 non-GLP crossover study lasting 7 days in each period. Systemic exposure of dogs to OCA were 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, OCA was recovered in the liver, but not detected in bile or plasma. The concentrations of OCA and tauro-OCA in the liver were similar to those of the endogenous bile acids. In bile, the accumulation of tauro-OCA was less than 10% of total bile acids. These data suggest that tauro-OCA is still absorbed by active mechanisms like naturally occurring taurine conjugated bile acids, but the mechanism could be less efficient and some tauro-OCA is lost in the stools.

At 24 h after dosing, approximately 96.5% of the administered dose of OCA could be accounted for in the feces, urine, plasma and the organs of the gastrointestinal tract and liver.

These results suggest that distribution of [14C]-OCA is largely restricted to tissues of the enterohepatic circulation, with relatively little distribution to, or accumulation in, peripheral tissues. Radiolabel remaining in the carcass at 168 h following administration was 1.4% of the dose.

In in vitro experimental conditions, [14C]-OCA was stable in mouse, rat and monkey intestine S9, and rat and dog kidney S9 fractions, and relatively less stable in kidney and intestine S9 fractions from humans. [14C]-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 observed in plasma (7.3%). This epimer 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. Also it's confirmed 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 rabbit, equivalent concentrations of OCA and glyco-OCA in plasma were found. Only glyco-OCA was tested in bile and liver.

The major route of elimination of OCA is in the feces via biliary excretion with no elimination via the kidneys and urine.

Results from the SCHH indicate that OCA, tauro-OCA and glyco-OCA has the potential to down-regulate of CYP1A2, CYP3A4 and OCT1 gene expression by ≥ 2-fold, in line with the EMA guideline on the investigation of drug interactions (2012). Conversely, no induction or suppression of drug metabolizing enzymes (CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19, UGT1A3) and drug transporters (OATP1B1, OATP1B3, OATP2B1, MATE1, MRP2, MRP3, MRP4, BCRP, P-gp, and NTCP) were observed, thus suggesting low potential for DDIs between OCA and both CYP isoforms and drug transporters studied.

2.2.10. Toxicology

Single dose toxicity

In single-dose toxicity studies in rats and dogs, no deaths were reported. In dogs, findings considered OCA-related, as decrease in body weight and decrease in serum liver function enzymes, were found. The single dose of OCA -that resulted in no adverse effects- is high in both studies, up to 300 mg/kg in rats while the MTD in dogs was 750 mg/kg.

Repeat dose toxicity

In repeat-dose studies, several OCA-related deaths have been reported in mice and rats treated at high doses, ≥120/80 mg/kg/day and 150 mg/kg/day, respectively. The cause of death is liver injury in both species, and also GI injury in rats. No deaths have been reported in studies performed in dogs.

In study 019958 performed in rat during 13 or 26 week, one male, treated with 6 mg/kg/day of OCA, was terminated for humane reasons at Day 47. Necropsy findings in this male 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 this death is not considered to be test-article related, this finding had to be mentioned in the toxicology written summary.

The primary toxicologic effect of OCA in mice, rats and dogs is on the hepatobiliary system. Findings included increased liver weights, alterations in serum chemistry parameters indicative of hepatic (ALT, AST, LDH) and biliary (ALP, GGT, and/or bilirubin) toxicity. The relationship to dose of these findings varied across species. In the mouse and dog, increased liver weights and elevated serum chemistry parameters generally only occurred at the highest doses tested. In the rat, alterations in liver weights and liver enzymes occurred at lower doses than liver histopathology changes, ie, ≥25 mg/kg/day (6.5-fold maximum human exposure).

In mice, single cell necrosis has been reported after 3 months of dosing at low margins of human exposure, ≥4 mg/kg/day and ≥12 mg/kg/day (0.9-fold and 2.3-fold maximum human exposure, respectively). This effect was not associated with lethality since was not reported at doses of up to 25 mg/kg/day (12-fold maximum human exposure) in the 2-year carcinogenicity study. Thus, it is suggested that this lesion might resolve spontaneously with long-term exposure.

In rats and dogs histopathology lesions only occurred at high multiples of human exposures. Macroscopic/microscopic alterations in rats include cholangiohepatitis, bile duct hyperplasia and individual hepatocyte degeneration/necrosis at 60 mg/kg/day (29-fold maximum human exposure). In dogs, cystic hyperplasia and/or secretion in the gallbladder, hepatocellular atrophy, and centrilobular hepatocellular degeneration occurred at 50 mg/kg/day (107-fold maximum human exposure).

In these studies performed in rats and dogs, a full recovery for histopathology changes and partial recovery of serum chemistry changes were observed after a 14-day treatment free period. The histological changes in the livers of both species observed at termination of the studies were not considered adverse and were consistent with the hepatobiliary toxicity observed in other general toxicity studies suggesting that hepatobiliary injury is ongoing and fully reversible with longer periods.

Histopathology changes in the GI tract of rat at high doses (150 mg/kg/day) were also reported. These changes were not seen in mice or dogs, and have been considered to be a species-specific toxicity.

Genotoxicity

OCA, tauro-OCA and glyco-OCA were not mutagenic in a bacterial reverse mutation assay and no clastogenic 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 taurine and glycine conjugates, have been tested for carcinogenic potential in 2-year bioassays using rats and mice. OCA was not carcinogenic at doses of up to 20 mg/kg/day (12-fold MHE) and 25 mg/kg/day (12-fold MHE) in rats and mice, respectively.

Carcinogenicity

OCA, and its taurine and glycine conjugates, have been tested for carcinogenic potential in 2-year bioassays using rats and mice. OCA was not carcinogenic at doses of up to 20 mg/kg/day (12-fold MHE) and 25 mg/kg/day (12-fold MHE) in rats and mice, respectively. OCA was not considered carcinogenic in mice and rats under the conditions of those studies.

Reproduction Toxicity

The reproductive toxicity of OCA was evaluated in fertility and early embryonic development study in rats, embryo-fetal development studies in rats and rabbits, and a pre-postnatal study in rats. Two studies are non-pivotal, study WIL661001 and study WIL661002, but all reproductive toxicity studies are GLP.

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 (13-fold maximum human exposure) no maternal toxicity or developmental effects were found.

There were no teratogenic effects of OCA at doses up to 75 mg/kg/day (40-fold MHE) in rats and 20 mg/kg/day (6-fold maximum human exposure) in rabbits.

Toxicokinetic data

Toxicokinetic results from the pivotal repeat dose toxicity, Carcinogenicity and reproductive toxicity studies are summarized in the respective Sections.

Local Tolerance

No local tolerance, antigenicity and immunotoxicity studies, and studies in dependence, have been submitted this was considered acceptable by the CHMP.

2.2.11. Ecotoxicity / environmental risk assessment

Substance (INN / Invented Name): Obeticholic acid (OCA)			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	log D = 2.98 (pH =7.4), log D = 4.3 to 1.7 (pH = 6 to 9)	No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log D = 2.98 (pH =7.4), log D = 4.3 to 1.7 (pH = 6 to 9)	(N)
	BCF	ND	(N)
Persistence	DT50 or ready biodegradability	ND	(N)
Toxicity	NOEC or CMR	ND	(N)
PBT-statement :	See assessor´s comments		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)		0.002010 μg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

Obeticholic acid PEC $_{surfacewater}$ value is below the action limit of 0.01 μg/L. and is not a PBT substance as log K_{ow} does not exceed 4.5.

Therefore obeticholic acid is not expected to pose a risk to the environment.

2.2.12. Discussion on non-clinical aspects

The pharmacological properties of bile acids including that of obeticholic acid are well documented in numerous scientific publications.

No pharmacodynamic drug interaction studies have been conducted although OCA is also intended to be administered together with UDCA. The applicant clarified during the procedure that the ability of OCA to decrease bile acid synthesis and increase bile acids secretion is mainly driven by transcriptional

mechanisms mediated by FXR. Instead, post-transcriptional mechanisms (e.g. decrease of the concentration of hydrophobic bile acids, stimulation of hepatobiliary secretion, putatively via Ca(2+)- and protein kinase C-alpha-dependent mechanisms) would be responsible for UDCA effects. Both substances may share "ancillary" overlapping actions i.e. NF-kB transcription, BSEP, for which however a clear understanding is not yet reached. Published data are inconclusive in unequivocally confirm/exclude the potential in vivo target (FXR) interaction between OCA and UDCA. However, based on clinical results from 2 Phase IIa studies co-administration of OCA and UDCA is not expected to produce any relevant interference. Finally, the different mechanism of action between OCA and UDCA reflects into some clinically relevant differences (e.g., different dosages, different behaviour on circulating bile acids).

In the toxicology studies, the target organs were on the hepatobiliary system (liver, bile duct and gall bladder), similar to the 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. All changes were reversible with discontinued dosing, and are consistent with and predict the dose-limiting toxicity in humans. Similar to nonclinical species, signs of toxicity occur in patients with PBC at doses that are 5-fold higher than the proposed maximum dose of 10 mg, and toxicity would not be expected at therapeutic doses. Thus, the main toxicity finding (hepatobiliary effects) in nonclinical species is predictive of toxicity in human populations at similar therapeutic margins.

In rats treated with high dose of OCA, effects in GI system were also found but can be considered to be a species-specific toxicity.

Obeticholic acid, and its conjugate glyco-OCA, were found no genotoxic and they have not mutagenic potential. No statistically significant increases in numerical aberrations were observed in any test-article treated cultures.

There were no teratogenic effects of OCA at doses up to 75 mg/kg/day (40-fold MHE) in rats and 20 mg/kg/day (6-fold maximum human exposure) in rabbits.

On the other hand, in the submitted study WIL661004 in rabbits, the Company set the NOAEL at 20 mg/kg/day. However this cannot be considered correct since an abortion occurs in a female in the 9 mg/kg/day treatment group, and although the applicant states that is not related with treatment, the NOAEL must be established at 3 mg/kg/day.

Although no specific studies have been done to assess the presence of OCA or conjugates in breast milk, tauro-OCA exposure was measured in nursing rat pups on postnatal Day 10. This suggests the transfer of OCA or tauro-OCA during lactation. Appropriate statements have been included into the SmPC.

No potential carcinogenicity and no effects in reproduction and development have been reported for OCA.

Based on the environmental risk assessment OCA is not expected to pose a risk to the environment

2.2.13. Conclusion on the non-clinical aspects

The non-clinical data submitted on obeticholic acid are considered to be sufficient in the context of this marketing authorisation application. Relevant information such as the observed toxicity on the hepatobiliary system at supra-therapeutic doses in repeat dose toxicity studies are outlined in the SmPC.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical 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 DSP-1747 (OCA) after single and multiple oral administration of DSP-1747 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, and fecal 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 (glyco-OCA and tauro-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 (glyco-OCA and tauro-OCA) concentrations in healthy subjects in preparation for a thorough QT study
747-109	To assess DDI of OCA on the single dose PK of CYP3A4 [sensitive substrate: midazolam] and CYP1A2 [sensitive substrate: caffeine])
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, glyco-OCA, and tauro-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
Patient PK and initial tolerability study reports	
747-103	To assess the PK of OCA and its conjugates (glycol-OCA and tauro-OCA) in subjects with mild to severe hepatic impairment compared with healthy volunteers with normal hepatic function
Healthy subject PD and PK/PD study reports	
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

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

Phase II and III clinical studies

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
747-201 Double-Blind Phase	Primary Assess the effects OCA in subjects with proven or likely PBC on the following: • Serum ALP levels • Safety Secondary Assess the effects of OCA in subjects with proven or likely PBC on the following: • Hepatocellular injury and liver function • Disease-specific and general health symptoms • Biomarkers of hepatic inflammation and fibrosis • Plasma trough concentrations of OCA and its major, known conjugates	Phase 2 International, multicenter, randomized, double-blind, placebo-controlled, multidose, parallel group Note: OCA monotherapy study in the context of determining the properties of OCA without concomitant UDCA during the double-blind phase of the study	OCA 10-mg capsules OCA 50-mg capsules Placebo capsules Treatment Groups: a) Placebo b) OCA 10 mg c) OCA 50 mg Each dose made up of 1 capsule was to be administered once daily from Day 1 through Day 85 Oral	59 subjects enrolled; 48 subjects completed the study	Subjects with a proven or likely diagnosis of PBC	85 days	Completed Full

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
747-201 LTSE Phase	Primary Safety Secondary • ALP levels, as an assessment of efficacy • Hepatocellular injury and liver function • Disease-specific and general health symptoms	Phase 2 Open-label (optional combination with UDCA was allowed if recommended by the Investigator)	OCA 10-mg capsules OCA 25-mg capsules OCA 50-mg capsules OCA 10-mg tablets OCA 25-mg tablets Starting dose based on the dose of OCA or placebo received in the double-blind phase, or on the timing of entry into the LTSE phase (OCA 10 mg for placebo subjects). The dosing titration was 10 mg to 25 mg to 50 mg once daily. Note: The titration schedule was to be modified for safety and tolerability issues. Oral	28 subjects enrolled (ongoing study)	Subjects with a proven or likely diagnosis of PBC	For up to 6 years, or discontinuation of the LTSE phase by the Sponsor	Ongoing study

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
747-202 Double-Blind Phase	Primary Assess the effects of OCA in subjects with PBC on the following: • ALP levels • Safety Secondary Assess the effects of OCA in subjects with PBC on the following: • Hepatocellular injury and liver function • Disease-specific and general health symptoms • Biomarkers of hepatic inflammation and fibrosis • Plasma trough concentrations of OCA and its major, known conjugates	Phase 2 International, multicenter, randomized, double-blind, placebo-controlled, multidose, parallel-group Subjects were randomized in a 1:1:1:1 ratio to placebo, OCA 10 mg, OCA 25 mg, or OCA 50 mg groups	OCA 10-mg capsules OCA 25-mg capsules OCA 50-mg capsules Placebo Capsules Each dose made up of 1 capsule was administered once daily from Day 1 through Day 85 Oral	165 randomized subjects; 136 subjects completed the study	Subjects with a proven or likely diagnosis of PBC	85 days	Completed Full

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
747-202 LTSE Phase	Primary • Safety Secondary • ALP levels, as an assessment of efficacy • Hepatocellular injury and liver function • Disease-specific and general health symptoms	Phase 2 Multicenter, open-label	OCA 10-mg capsules OCA 25-mg capsules OCA 50-mg capsules Starting dose was based on the dose of OCA or placebo received in the double-blind phase, or on the timing of entry into the LTSE (OCA 10 mg for placebo subjects). The dosing titration was 10 mg to 25 mg to 50 mg once daily. Note: The titration schedule was to be modified for safety and tolerability issues. Oral	78 subjects enrolled; 59 still participating upon Sponsor's closing study for administrative reasons	Subjects with a proven or likely diagnosis of PBC	Planned: Up to 18 months or until the Sponsor discontinued the study Actual: For administrative reasons the Sponsor discontinued the study after approximately 20 months	Completed Full

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
747-301 Double-Blind Phase	Primary Assess the effects of OCA in subjects with PBC on the following: • Serum ALP and total bilirubin, together as a composite endpoint • Safety Secondary Assess the effects of OCA in subjects with PBC on the following: • Hepatocellular injury and liver function, including histology • Disease-specific symptoms • Biomarkers and noninvasive assessments of liver fibrosis • Bile acids • Other exploratory evaluations	Phase 3 Randomized, double-blind, placebo-controlled, parallel group Randomization (1:1:1) was stratified by: 1.Pretreatment ALP>3x upper limit of normal (ULN) and/or AST >2x ULN and/or total bilirubin >ULN, intolerant to UDCA 2.Pretreatment ALP ≤3x ULN and/or AST ≤2x ULN and/or total bilirubin ≤ULN, intolerant to UDCA 3.Pretreatment ALP>3x ULN and/or AST >2x ULN and/or total bilirubin >ULN, currently taking UDCA 4.retreatment ALP ≤3x ULN and/or AST ≤2x ULN and/or total bilirubin <ULN, currently taking UDCA	OCA 5-mg tablets OCA 10-mg tablets Placebo tablets Treatment Groups: Placebo: Subjects received placebo tablets for 12 months OCA 10 mg: Subjects received OCA 10 mg for 12 months OCA Titration: Subjects received OCA 5 mg for the initial 6 month period. Subjects not meeting the composite endpoint at 6 months with no evidence of tolerability issues were titrated from OCA 5 mg to OCA 10 mg for the remaining 6 months All OCA doses were administered orally, once daily |	217 subjects randomized; 198 subjects completed the study	Subjects with definite or probable PBC diagnosis Note: For subjects either taking UDCA or, who were unable to tolerate UDCA	12 months	Completed Full

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
747-301 LTSE Phase	To assess the long-term safety and efficacy of OCA in subjects with PBC, including durability of response, the primary and secondary objectives of the double-blind phase out to maximum exposure of OCA	Phase 3 Open-label	OCA 5-mg tablets OCA 10-mg tablets Subjects receiving placebo started OCA 5 mg. Subjects already on 5 mg continued on the same dose. Subjects receiving 10 mg at the end of the double-blind phase were titrated down to 5 mg. All OCA doses were administered orally, once daily	193 subjects enrolled into the LTSE phase	Subjects with definite or probable PBC diagnosis	Up to 5 years	Ongoing study

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
747-205	To assess the effects of OCA in subjects with primary biliary cirrhosis (PBC) on the following: safety, tolerability, and high density lipoprotein (HDL) metabolism	Phase 2 Open-label, multicenter	OCA 10-mg tablets OCA dose administered orally once daily for 8 weeks	27 subjects enrolled; 25 subjects completed the study	Subjects with a definite or probably diagnosis of PBC	8 weeks	Completed Full

2.3.2. Pharmacokinetics

OCA clinical pharmacology program includes: characterization of the PK through single- and multiple-dose studies, bridging bioequivalence studies, ADME study, investigation of extrinsic (drug-drug interaction and food effect studies) and intrinsic factors (hepatic impairment) in healthy subjects. A thorough QT study was also performed. Limited data in the target population derive from PK samples collected in patients enrolled in phase 2 and 3 studies. The Applicant had developed i) a physiological PK model of exposure of OCA both in plasma (systemic) and in the liver; and ii) a model to investigate relationships between OCA exposure and PD endpoints.

Absorption

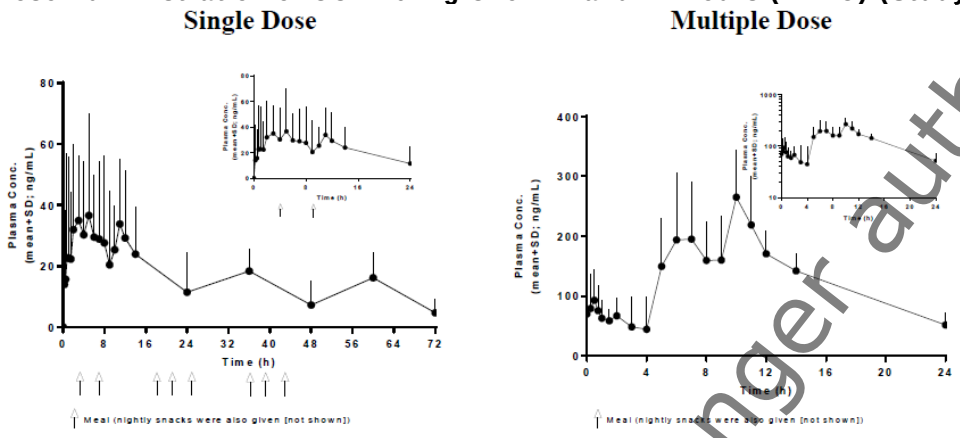
Bioavailability

A wide range of OCA doses were assessed in the clinical development program: single dose (5 mg to 500 mg) and multi-dose (5 mg to 250 mg).

Following single-dose administration, OCA was rapidly absorbed followed by extensive conjugation to glycine and taurine to form glyco-OCA and tauro-OCA, consistent with the endogenous primary bile acid, CDCA.

PK exposure of OCA and its conjugates generally increased dose proportionally based on AUC_{0-24} and Cmax up to 100 mg.

Figure 2: Mean (SD) Pharmacokinetic Profile of Total OCA Following Single Dose and Multiple Dose Administration of OCA 10 mg Over 72 and 24 hours (N = 8) (Study 747-105)



Conc. = concentration; h = hour. Note: Time is relative to the last dose of the Multiple-Dose Phase.

Summary statistics of single-dose plasma OCA, glyco-OCA, tauro-OCA, and total OCA PK parameters by dose are summarized in Table 2 below.

Table 1: Mean (CV%) Single-Dose Pharmacokinetic Parameters for OCA, Glyco-OCA, Tauro-OCA, and Total OCA by Dose

Analyte PK Parameter	n	5-mg OCA (N = 8)	n	10-mg OCA (N = 8)	n	25-mg OCA (N = 8)
OCA						
C_{max} (ng/mL)	8	18.6 (51.1)	8	29.7 (69.9)	8	78.6 (56.7)
t_{max} (h)[a]	8	0.5 (0.3-1.5)	8	1.8 (0.3-3.0)	8	0.9 (0.3-4.0)
AUC_t (ng·h/mL)	8	36.5 (70.7)	8	68.5 (54.7)	8	263 (33.7)
AUC_{0-24} (ng·h/mL)	6	33.2 (45.5)	7	61.1 (39.5)	8	162 (34.5)
Glyco-OCA						
C_{max} (ng/mL)	8	19.3 (48.2)	8	37.5 (86.9)	8	81.9 (55.9)
t_{max} (h)[a]	8	5.5 (1.5-60)	8	4.5 (2.0-10)	8	10 (1.5-36)
AUC_t (ng·h/mL)	8	371 (58.4)	8	734 (81.0)	8	1641 (53.6)
AUC_{0-24} (ng·h/mL)	8	173 (59.2)	8	412 (88.8)	8	935 (69.4)
MRC_{max}	8	1.1 (52.4)	8	1.3 (90.3)	8	0.9 (13.5)
$MRAUC_{0-24}$	6	5.3 (35.9)	7	6.4 (59.9)	8	4.7 (33.9)
Tauro-OCA						
C_{max} (ng/mL)	8	10.8 (82.5)	8	19.8 (54.5)	8	42.5 (50.5)
t_{max} (h)[a]	8	5 (2-60)	8	8 (3-36)	8	10 (5-36)
AUC_t (ng·h/mL)	8	232 (78.3)	8	428 (44.8)	8	827 (33.1)
AUC_{0-24} (ng·h/mL)	8	80.1 (82.0)	8	197 (53.5)	8	352 (25.1)
MRC_{max}	8	0.5 (65.1)	8	0.7 (58.9)	8	0.6 (77.8)
$MRAUC_{0-24}$	6	2.2 (40.0)	7	2.9 (52.4)	8	1.9 (40.7)
Total OCA						
C_{max} (ng-eq/mL)	8	28.8 (47.9)	8	53.7 (68.7)	8	126 (42.8)
t_{max} (h)[a]	8	4.5 (0.3-60)	8	4.5 (0.3-11)	8	1.8 (1.5-36)
AUC_t (ng-eq·h/mL)	8	534 (64.7)	8	1040 (66.6)	8	2357 (37.4)
AUC_{0-24} (ng-eq·h/mL)	8	237 (63.5)	8	568 (72.1)	8	1260 (51.2)

AUC = area under the plasma concentration-time curve; AUC_t = AUC from time 0 to the last sampling time with measurable analyte concentration; AUC_{0-24} = AUC from time 0 to 24 hours; C_{max} = maximum concentration (observed); CV% = percent coefficient of variation; glyco-OCA = glycine 6α-ethyl-chenodeoxycholic acid; $MRAUC_{0-24}$ = ratio of conjugate to OCA for AUC_{0-24}; MRC_{max} = ratio of conjugate to OCA for C_{max}; ng-eq = nanogram equivalents; OCA = obeticholic acid; tauro-OCA = taurine 6α-ethyl-chenodeoxycholic acid; t_{max} = time to C_{max}

[a] Median and range

Convergent observations suggest that the PK profile(s) of OCA are consistent with those of endogenous bile acids:

- The PK profile is consistent to the natural endogenous bile acid CDCA and includes extensive conjugation to glycine and taurine along with significant enterohepatic recirculation.
- Following single-dose administration of OCA at 25 mg, 50 mg, 100 mg (study 747-102) and at 5 mg, 10 mg, and 25 mg (study747-105), PK exposure of OCA and its conjugates generally increased dose proportionally based on AUC0-24 and Cmax.
- OCA was shown to be rapidly absorbed and typically reached maximum concentrations between 1 to 4 hours after the administration.
- Steady-state concentrations of OCA and its conjugates were achieved by Day 13 (9 days after starting daily administration of OCA in the multiple-dose phase [study747-105]).
- There was significant accumulation of glyco-OCA (3- to 7-fold) and tauro-OCA (4- to 18-fold) with minimal accumulation of OCA (approximately 2-fold) after daily administration.

- The exposure of total OCA after daily administration was primarily made up of glyco-OCA and tauro-OCA with minimal contribution of OCA, indicating that the majority of total OCA plasma exposure with repeat dosing is primarily due to the conjugates.
- Exposure levels of total OCA were on average less than 20% of the steady-state concentration 2 weeks after cessation of dosing.

Maximum plasma exposure and overall exposure (AUC) of OCA and total OCA were generally consistent across studies in healthy subjects, albeit a high degree of variability within each study was observed. The high degree of variability is consistent with the low bioavailability of endogenous bile acids.

Bioequivalence

Two bioequivalence (BE) studies were performed: Study 747-115 (conducted to assess the BE of the OCA 10 mg clinical tablet relative to the OCA 10 mg commercial image tablet) and Study 747-116 (conducted to assess the BE of the OCA 10 mg capsule relative to the OCA 10 mg commercial image tablet). The obtained results were within the CI, thus demonstration BE of both formulations.

Influence of food

A preliminary assessment of the effect of a meal on the PK of OCA and its conjugates was performed in Japanese healthy volunteers in Study D8601002. This study showed that OCA was rapidly absorbed and reached median maximum plasma OCA concentrations within 0.75 to 1.5 hours. There was significant enterohepatic recirculation of OCA and its conjugates with secondary absorption peaks observed after a meal and AUC increased minimally with food.

The effect of food (high-fat meal) on rate and extent of OCA absorption was further examined in Study 747-104, whereby single doses of 10 mg and 25 mg OCA were administered to healthy subjects under fasting and fed conditions.

Thirty two healthy subjects were given a single 10 mg dose of OCA under fasting and fed conditions in a crossover manner. Extensive PK plasma samples were collected up to 216 hours (10 days) after the administration of OCA (10 mg) to characterize the PK of OCA and its conjugates under fasted and fed conditions

Results and Conclusions:

Table 2: Summary of Statistical Comparisons of Plasma OCA, Glyco-OCA, and Tauro-OCA Pharmacokinetic Parameters AUCt and Cmax Following 10-mg or 25-mg OCA Tablet Under Fed Versus Fasted Conditions

PK Parameters	OCA		Glyco-OCA		Tauro-OCA	
	Geometric LS Mean Ratio (%)	90% Confidence Interval	Geometric LS Mean Ratio (%)	90% Confidence Interval	Geometric LS Mean Ratio (%)	90% Confidence Interval
10 mg OCA Tablet Fed (Test) Versus Fasted (Reference)						
N	14		14		14	
AUC_t	111.1	88.0 – 140.2	101.2	88.2 – 116.2	98.4	84.2 – 115.1
C_{max}	104.0	74.2 – 145.9	107.1	91.4 – 125.5	93.6	81.3 – 107.7
25 mg OCA Tablet Fed (Test) Versus Fasted (Reference)						
	16		15		13	
AUC_t	112.3	96.7 – 130.4	108.5	95.6 – 123.3	99.5	89.2 – 110.9
C_{max}	110.5	76.9 – 158.6	103.7	84.9 – 126.8	91.1	73.1 – 113.5

- Plasma exposure of OCA and glyco-OCA was marginally higher under fed conditions (approximately 15% higher) and is not expected to be clinically meaningful
- Plasma exposure of tauro-OCA was slightly lower under fed conditions (approximately less than 5%) and is not expected to be clinically meaningful
- OCA was found to be safe and well tolerated
- OCA may be administered without regard to meals

Due to the drug's physiochemical properties and high plasma protein binding, the tissue distribution of OCA and its conjugates are limited to blood except for organs (eg, kidney) that are capable of transporting OCA.

Distribution

OCA, glyco-OCA, and tauro-OCA are all highly protein bound (>99%). Results from the ADME study showed that there was minimal distribution of radioactivity into whole blood. Therefore, OCA and its metabolites are mainly confined in the plasma. The volume of distribution of obeticholic acid is 618L. The volume of distributions of glyco- and tauro-obeticholic acid has not been determined.

Elimination

Mass balance data confirmed that the primary route of elimination is through the feces, while a minor percentage was recovered from the urine.

Following a single oral dose of 25 mg [14C]-OCA, a mean of 75.1% (range 28.30% to 97.5%), of the radioactivity administered was recovered by the end of the sampling period (504 hours post-dose). 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. An average of 72.3% (range 25.2% to 95.9%) was recovered from faeces by 504 hours post-dose; 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 post-dose (7/8 subjects until 816 hours, 3/8 subjects until 888 hours post-dose and 2/8 subjects until 1152 hours post-dose). Across the entire collection period (up to 1152 hours post-dose), between 73.2% and 107% of the administered radioactivity was recovered in feces. The majority of drug-related material in the feces was recovered within 552 hours of dosing with investigational product.

Total recovery (urine and feces combined) from each of the subjects ranged from 76.31% to 111.28% of the administered radioactivity.

In Study 747-113, the presence of the primary metabolites, glyco-OCA and tauro-OCA was confirmed using LC/MS/MS technique (XBL 14830). In addition, two glucuronide metabolites were also identified in the 3-position (OCA-3 glucuronide) and 24-position (OCA-24-glucuronide). The presence of the two glucuronide metabolites appeared to be less than 10% based on radioactivity; however, since glyco-OCA and tauro-OCA accumulate after daily administration, the relevant exposure levels of the two glucuronides were assessed in plasma from Study 747-105 (XBL 14830) after daily administration of OCA 10 mg. The relative exposure of the OCA-3 glucuronide was approximately 20% and therefore required toxicological qualification. However, activity of OCA-3 glucuronide on FXR is low suggesting that its clinical significance is minimal. The relative exposure of OCA-24-glucuonide is less than 5% and not

clinically relevant. Of note, glucuronides are not generally of safety concern as glucuronidation renders drugs more polar and water soluble, which enhances elimination from the body.

Dose proportionality and time dependencies

Dose proportionality

The dose proportionality of concentration-dependent parameters (Cmax and AUC) following single-dose and multiple-dose administration of OCA was assessed using a power model. Dose proportionality was concluded if the 90% CI of β included the value 1 and was statistically different from 0.

Following single-dose administration, dose-proportionality was concluded for all parameters and all analytes with the exception of AUCt for OCA (likely due to higher variability in the 5-mg dose group). Following multiple-dose administration, dose-proportionality was concluded for the parent drug only. For the conjugates and total OCA, peak and total systemic exposure increased more than proportionally with dose.

Table 3: Results of Dose-Proportionality Assessment

Phase	Analyte	Parameter	β	90% CI
Single Dose	OCA	C_{max}	0.91	0.60, 1.22
		AUC_t	1.35	1.04, 1.66
		AUC_{0-24}	1.02	0.79, 1.25
	Glyco-OCA	C_{max}	0.88	0.57, 1.20
		AUC_t	0.94	0.64, 1.25
		AUC_{0-24}	1.03	0.70, 1.36
	Tauro-OCA	C_{max}	0.96	0.65, 1.26
		AUC_t	0.93	0.63, 1.23
		AUC_{0-24}	1.02	0.75, 1.28
	Total OCA	C_{max}	0.93	0.64, 1.22
		AUC_t	1.00	0.72, 1.28
		AUC_{0-24}	1.06	0.79, 1.34
Multiple Dose	OCA	C_{max}	1.00	0.74, 1.25
		AUC_{0-24}	1.10	0.93, 1.26
	Glyco-OCA	C_{max}	1.26	1.01, 1.51
		AUC_{0-24}	1.29	1.01, 1.57
	Tauro-OCA	C_{max}	1.65	1.28, 2.02
		AUC_{0-24}	1.75	1.36, 2.13
	Total OCA	C_{max}	1.41	1.16, 1.67
		AUC_{0-24}	1.45	1.18, 1.72

AUC_{0-24} = AUC from time 0 to 24 hours; CI = confidence interval; C_{max} = maximum plasma concentration (observed); glyco-OCA = glycine conjugate of OCA; tauro-OCA = taurine conjugate of OCA

Time dependency

Single Dose

Following single-dose administration of OCA at 5 mg, 10 mg, and 25 mg, PK exposure of OCA and its conjugates increased dose proportionally based on AUC0-24 and Cmax.

OCA was rapidly absorbed and conjugated to glycine and taurine to form glyco-OCA and tauro-OCA, respectively. Overall exposure (AUC) for glyco-OCA and tauro-OCA was 5- and 2-fold higher, respectively, relative to OCA.

Multiple Dose

Steady-state concentrations of OCA and its conjugates were achieved by Day 13 (9 days after starting daily administration of OCA in the Multiple-Dose Phase).

There was significant accumulation of glyco-OCA (4- to 7-fold) and tauro-OCA (4- to 14-fold) with minimal accumulation of OCA (approximately 2-fold).

The exposure of total OCA was primarily made up of glyco-OCA and tauro-OCA with minimal contribution of OCA, indicating that the majority of total OCA plasma exposure with repeat dosing is primarily due to the conjugates. Exposure levels of OCA and its conjugates were on average less than 20% of the steady-state concentration of OCA (Day 14 of daily administration) 2 weeks after cessation of dosing. Urinary excretion of OCA and its conjugates was minimal (<1%).

A comparison of the pharmacokinetics of OCA and total OCA in healthy subjects after a single dose of OCA was studied in the following studies: 747-102, D8601002, 747-104, 747-105, 747-115, and 747-116. OCA was shown to be rapidly absorbed and typically reached maximum concentrations between 1 to 4 hours after the administration of OCA. Maximum plasma exposure and overall exposure (AUC) of OCA and total OCA were generally consistent across studies in healthy subjects albeit a high degree of variability within each study was observed.

Pharmacokinetics in target population

The pharmacokinetics of OCA and total OCA were studied in a subgroup of patients with PBC in Study 747-205 after a 10 mg dose of OCA. The PK profile of OCA and its conjugates were evaluated over the first 6 hours after the last dose administration of OCA (Week 8). A comparison of the steady-state PK profile of total OCA from Study 747-205, patients with PBC, versus healthy subjects (Study 747-105, 14 days of daily administration) showed a similar profile overall but modestly higher systemic exposure for patients with PBC (Figure 3). However, the limited number of subjects and the high variability in the systemic exposures limits the interpretation of these results.

A summary of the PK parameters for OCA, glyco-OCA, tauro-OCA, and total OCA from Study 747-205 are presented in Table 5.

Figure 3: Mean (SD) Steady-State Plasma Concentration-Time Profile of Total OCA in Subjects with Primary Biliary Cirrhosis (Study 747-205) and Healthy Subjects (Study 747-105) After Daily Administration of 10 mg OCA

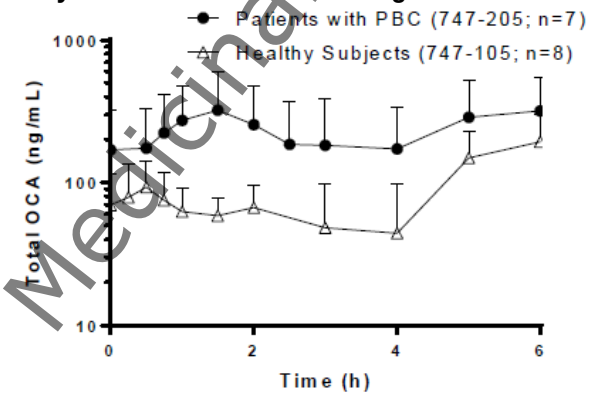


Table 4: Mean (SD) PK Parameters of OCA, Glyco-OCA, Tauro-OCA, and Total OCA after Daily Administration in Subjects with PBC (Study 747-205)

	10-mg OCA (N = 8[a])			
	OCA (ng/mL)	Glyco-OCA (ng/mL)	Tauro-OCA (ng/mL)	Total-OCA (ng/mL)
C_{max} (ng/mL)				
n	7	7	7	7
Mean (SD)	107 (112)	212 (144)	219 (208)	409 (299)
T_{max} (h)				
N	7	7	7	7
Median (Min, Max)	1.00 (0.750, 4.00)	5.00 (1.50, 6.00)	5.98 (5.00, 6.00)	5.00 (1.00, 6.00)
AUC_{0-6} (ng·h/mL)				
N	7	7	7	7
Mean (SD)	189 (185)	702 (644)	698 (653)	1360 (1150)

AUC = area under the plasma concentration-time curve; AUC_{0-6} = AUC from time 0 to 6 hours; C_{max} = maximum concentration (observed); glyco-OCA = glycine 6α-ethyl-chenodeoxycholic acid, h = hour; OCA = obeticholic acid; tauro-OCA = taurine 6α-ethyl-chenodeoxycholic acid; SD = standard deviation; t_{max} = time to C_{max};

[a] Note that one subject (Subject 146-001) had a medical history of cirrhosis and therefore was excluded. The PK estimates are presented separately for this subject in CSR 747-205.

Note: The PK results for Total OCA are presented in nanogram equivalents (ng-eq)

The PK of OCA was also characterized in Study 747-301 using trough concentrations after daily administration of OCA at Month 6 and Month 12 of therapy (Table 6). Although there is limited PK data from Study 747-301, higher systemic exposure of total OCA was observed for the 10 mg dose relative to the 5 mg dose. Trough concentrations appeared to be approximately dose proportional at Month 12 but slightly less than dose proportional at Month 6 which is most likely due to significant variability in the PK of OCA (due to high extraction and enterohepatic recirculation).

Table 5: Mean (SD) Trough Concentrations of OCA, Glyco-OCA, Tauro-OCA, and Total OCA After Daily Administration of OCA (5 mg and 10 mg) at Month 6 and Month 12 in Subjects with PBC (Study 747-301)

Dose		OCA (ng/mL)	Glyco-OCA (ng/mL)	Tauro-OCA (ng/mL)	Total-OCA (ng/mL)
	Month 6				
5 mg OCA	n	63	63	63	63
	Mean (SD)	3.73 (4.62)	39.2 (43.0)	31.8 (44.7)	63.6 (70.1)
10 mg OCA	n	57	57	57	57
	Mean (SD)	4.90 (4.96)	50.7 (60.9)	42.5 (103)	83.4 (114)
	Month 12				
5 mg OCA	n	61	61	61	61
	Mean (SD)	5.71 (8.79)	49.9 (56.6)	34.5 (48.9)	77.2 (86.4)
10 mg OCA	n	60	60	60	60
	Mean (SD)	5.98 (6.82)	79.8 (122)	57.7 (92.5)	122 (166)

glyco-OCA = glycine 6α-ethyl-chenodeoxycholic acid, OCA = obeticholic acid; SD = standard deviation; tauro-OCA = taurine 6α-ethyl-chenodeoxycholic acid

Note: The PK results for Total OCA are presented in nanogram equivalents (ng-eq).

Special populations

Impaired renal function

The effects of renal impairment in patients with severe or end-stage renal disease have not been studied; however, OCA is not eliminated by the kidneys and is not expected to influence the PK of OCA.

In Study 747-113 using radiolabelled OCA, less than 3% of the dose was excreted in urine. These results are consistent to results observed in Studies 747-102, 747-103, and 747-105.

A population PK model was developed to characterize the plasma PK of OCA and its conjugates in healthy volunteers, patients with PBC, and special populations using population PK modeling. This model was used to identify relevant covariates (ie, age, sex, race, body weight, markers of liver and renal function as well as daily doses). Renal function was not found to be a significant predictor of OCA exposure.

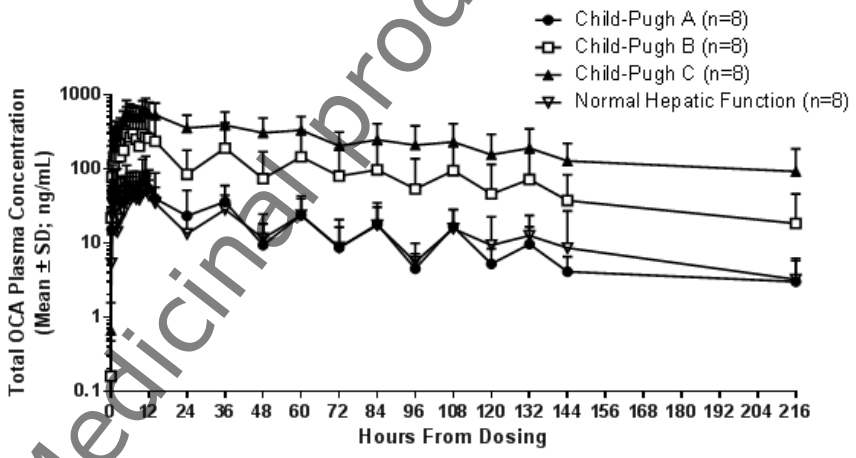
Impaired hepatic function

The systemic (plasma) concentrations of OCA have been studied in subjects with hepatic impairment after a single dose of OCA (10 mg) (747-103) and after daily administration (10 mg and 25 mg) in patients with portal hypertension (cirrhosis) in 747-204.

As expected with a bile acid analog, significantly higher systemic exposure (AUC) of total OCA was observed in subjects with moderate and severe hepatic impairment (4-fold and 17-fold greater exposure with moderate and severe hepatic impairment, respectively) (Figure 4). The least square mean (LSM) ratio of OCA and total OCA for subjects with mild, moderate, and severe hepatic impairment from Study 747-103 are presented in Table 7. Of note, the plasma exposure of total endogenous bile acids were approximately 1.6-, 6.4-, and 12.7-fold greater in subjects with mild, moderate, and severe hepatic impairment relative to subjects with normal liver function in Study 747-103.

Consistent with these findings, systemic exposure of total OCA was higher in patients with liver cirrhosis (portal hypertension) in Study 747-204 relative to healthy subjects (747-105) which is consistent with what was observed in Study 747-103.

Figure 4: Mean Plasma Concentration Versus Time Curves of Total OCA Following a Single Oral 10 mg OCA Tablet Dose – Evaluable PK Population – Study 747-103 (Semi-Log Scale)



glyco-OCA = glycine 6α-ethyl-chenodeoxycholic acid, OCA = obeticholic acid; SD = standard deviation; tauro-OCA = taurine 6α-ethyl-chenodeoxycholic acid.

Table 6: Summary of the Statistical Comparisons (ANOVA) of Plasma PK Parameters AUCt, AUC24, and Cmax of OCA, and Total OCA (Evaluable PK Population) – Study 747-103

Comparison[a]	PK Parameters	OCA		Total OCA	
		Geometric LS Mean Ratio[c] (%)	90% Confidence Interval	Geometric LS Mean Ratio[c] (%)	90% Confidence Interval
Mild (A; test) vs Normal (reference)	AUC_t (ng·h/mL)	138	72.8-261	113	56.5-225
	AUC_{24} (ng·h/mL)	146	79.7-268	123	64.7- 234
	C_{max} (ng/mL)	135	79.8-228	149	86.3-256
Moderate (B; test) vs Normal (reference)	AUC_t (ng·h/mL)	241	127-456	420	211-838
	AUC_{24} (ng·h/mL)	315	172-578	440	232-837
	C_{max} (ng/mL)	191	113-323	376	218-647
Severe (C; test) vs Normal (reference)	AUC_t (ng·h/mL)	703	372-1330	1730	867-3440
	AUC_{24} (ng·h/mL)	830	462-1490	1530	804-2900
	C_{max} (ng/mL)	470	278-796	975	566-1680

ANOVA = analysis of variance; AUC = area under the plasma concentration versus time curve; AUC_{0-24} = AUC from time 0 to 24 hours postdose; AUC_{0-t} = AUC from time 0 to the time of the last measurable concentration; C_{max} = maximum observed plasma concentration; LS = least-squares; PK = pharmacokinetic

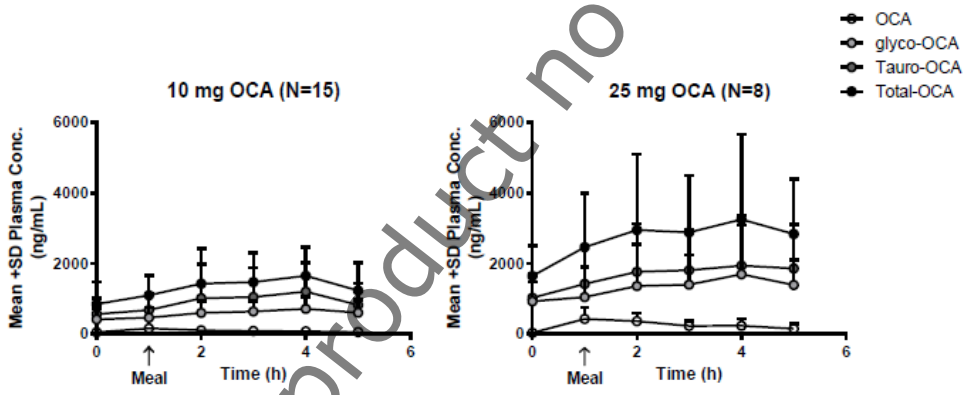
[a] Mild hepatic impairment (Child-Pugh A); moderate hepatic impairment (Child-Pugh B); severe hepatic impairment (Child-Pugh C); normal hepatic function.

[b] Geometric LS means, mean ratios, and confidence intervals were calculated by exponentiating the LS means from the ANOVA.

[c] Geometric LS Mean Ratio (%) = 100 × (Test/Reference).

Note: Parameters were ln-transformed prior to analysis.

Figure 5: Mean (SD) Plasma Concentrations of OCA, Glyco-OCA, Tauro-OCA, and Total OCA Versus Time Following a Single Oral 10 mg or 25 mg OCA Tablet Dose (Linear Scale) – Study 747-204



Conc = concentration; glyco-OCA = glycine 6α-ethyl- chenodeoxycholic acid; OCA = obeticholic acid; SD = standard deviation; tauro-OCA = taurine 6α-ethyl-chenodeoxycholic acid. Note: Day 7/EOT dosing included all Day 7/EOT dosing between Days 6 and 12.

The mean plasma concentration versus time curves for OCA and total OCA plotted on semi-logarithmic scale were approximately parallel, indicating that elimination was not affected by hepatic impairment. No differences in Tmax of OCA were found in subjects with varying degrees of hepatic impairment relative to subjects with normal hepatic function, suggesting no changes in the rate of absorption of OCA. Furthermore, no clinically relevant differences in tmax of glyco-OCA or tauro-OCA were found suggesting that the rate of formation and reabsorption of the conjugates during enterohepatic recirculation is not altered in subjects with hepatic impairment (Table 8).

Table 7: Mean (SD) PK Parameters of Total OCA After Single and/or Multiple OCA Doses Under Fasting Conditions (Studies with Hepatically Impaired Population)

PK Parameter	Study 747-103 (Day 1/Single Dose)				Study 747-204[a] (Day 7/Steady State)	
	OCA 10 mg				OCA 10 mg QD (n=15)	OCA 25 mg QD (n=8)
	Hepatic Impairment (Child-Pugh Class)					
	Normal Hepatic Function (n=8)	Mild (A) (n=8)	Moderate (B) (n=8)	Severe (C) (n=8)		
C_{max} (ng/mL)/	68.3 (27.6)	107 (65.1)	348 (377)	674 (281)	1773 (942)	3723 (2299)
AUC_{0-24} (ng·h/mL)	747 (426)	1020 (955)	4710 (5370)	10900 (4580)	NA	NA
AUC_{0-t} (ng·h/mL)	2480 (1810)	2770 (2060)	15700 (19100)	41000 (21900)	5822 (3363)	13652 (7712)

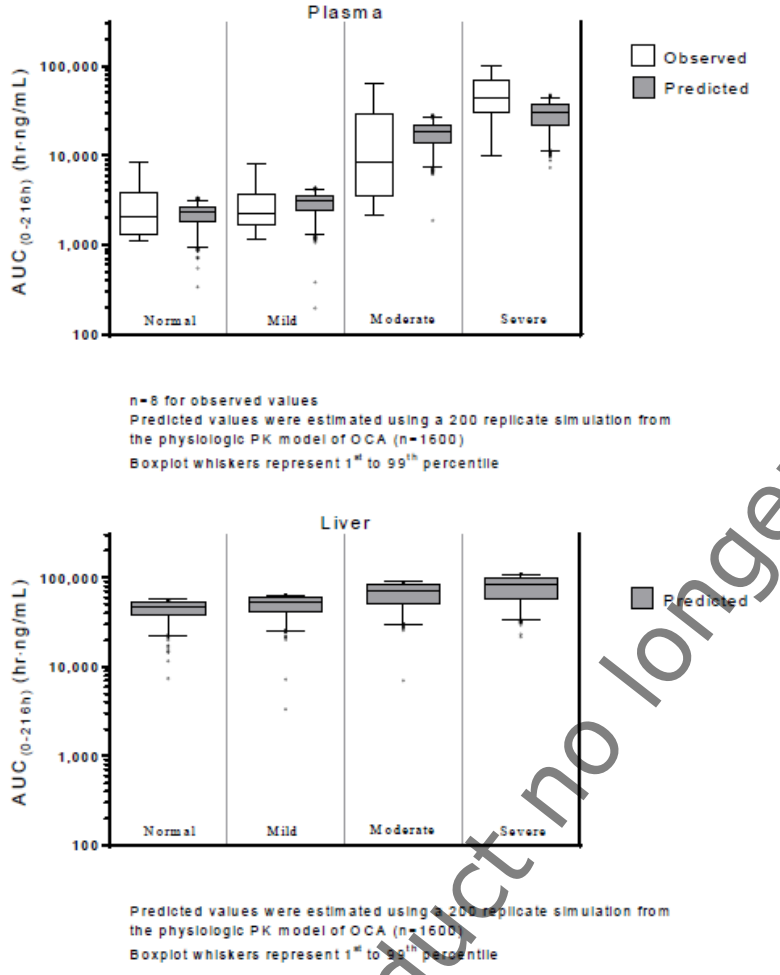
AUC = area under the plasma concentration versus time curve; AUC_{0-24} = AUC from time 0 to 24 hours postdose; AUC_{0-t} = AUC from time 0 to the time of the last measurable concentration; C_{max} = maximum observed plasma concentration, NA = not available; OCA = obeticholic acid; PK = pharmacokinetic; SD = standard deviation
Note: The PK results for Total OCA are presented in nanogram equivalents (ng-eq)

Mean peak (Cmax) and overall (AU0-t and AUC0-24) plasma exposures increased with increasing severity of hepatic impairment for OCA and total OCA. While, the higher peak and overall exposure was not considered significant in subjects with mild hepatic impairment compared with subjects with normal hepatic function, there were substantially higher exposures in subjects with moderate and severe hepatic impairment.

Simulations for Prediction of Liver Exposure

The pharmacokinetic model was used to simulate the overall mean concentration-time profile of total OCA in plasma and liver in subjects from Study 747-103 (single 10 mg dose of OCA). The observed and predicted plasma (systemic) exposure and the predicted liver exposure of total OCA are presented in Figure 6.

Figure 6: Observed and Predicted Systemic and Predicted Liver Exposure of Total OCA for Subjects with Mild, Moderate, and Severe Hepatic Impairment and Healthy Subjects (Study 747-103))



AUC = area under the curve; C_{max} = maximum concentration; HEPIMP = hepatic impairment; n = number of subjects; OCA = obeticholic acid
Observed data values are based on n =8 subjects by group of hepatic impairment; Predicted data values are based on 200 iterations Monte-Carlo simulations in 8 subjects by group of hepatic impairment; Boxplot whiskers represent 1st and 99th percentile.

The physiologic PK model adequately predicted the systemic exposure of OCA for healthy subjects and subjects with hepatic impairment highlighting the predictability of the model and the suitability to predict exposures in physiologic compartments including the liver. It is of note that based on the model, liver exposure of OCA in patients with hepatic impairment was similar to that in healthy subjects. This is likely due to the decreased hepatic uptake of OCA and its conjugates, portal systemic shunting, decreased anatomical/functional liver volume, and an increase in taurine conjugation. Based on the above predictions, the marked increase in systemic exposure to OCA in subjects with hepatic impairment is not likely to result in liver toxicity.

- **Other Intrinsic Predictors of OCA Exposure**

To identify other covariates that are the predictors of OCA exposure, a population PK model was developed to characterize the plasma PK of OCA and its conjugates in healthy volunteers, patients with PBC, and special populations using population PK modeling. The population PK model of OCA and its

conjugates was used to identify relevant covariates (ie, age, sex, race, body weight, markers of liver and renal function as well as daily doses).

The empirical population PK model was developed based on concentration-time profiles of OCA, glyco-OCA and tauro-OCA collected in 16 clinical studies in which OCA was orally administered to healthy volunteers, patients with PBC, as well as special populations (747-101, 747-102, 747-103, 747-104, 747-105, 747-107, 747-108, 747-109, 747-110, 747-111, 747-112, 747-114, 747-115, 747-116, 747-204, and 747-205).

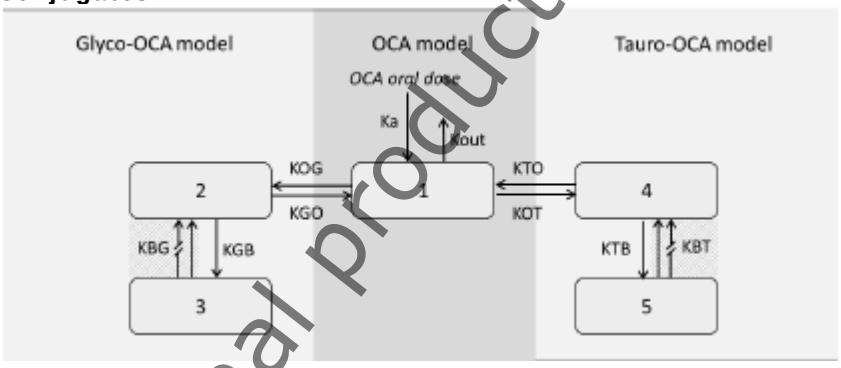
A schematic representation of the empirical population PK model is presented in Figure 7. This model included a central compartment for OCA, tauro-OCA, and glyco-OCA and an enterohepatic recirculation "gallbladder" compartment for glyco-OCA and tauro-OCA. Between-subject variability was estimated for all parameters except the rates from the 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. For OCA, tauro-OCA and glyco-OCA, predictions from the model compared well with the observed data.

The structural population PK model of OCA and its conjugates was used to evaluate the most relevant covariates (ie, age, sex, race, body weight, markers of liver and renal function as well as daily doses) using a full model approach (ie, multivariate).

The final model included the following covariates for OCA and its conjugates:

- Hepatic impairment on volumes of distribution, rates of conjugation/deconjugation and rates of gallbladder emptying
- Body weight on volume of distribution of OCA and its conjugates, as well as rate of gall bladder emptying (for glyco-OCA and tauro-OCA only) during gallbladder contraction

Figure 7: Schematic Representation of Empirical Population PK Model of OCA and its Conjugates



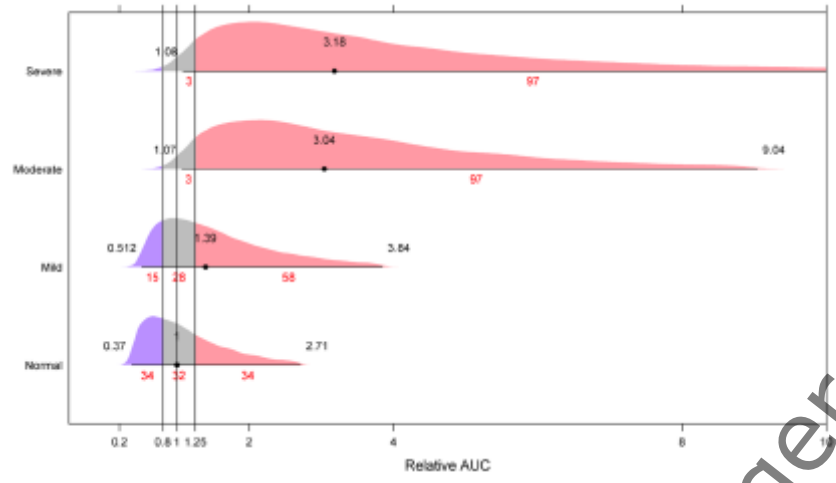
Compartments #1, 2, 4 represent the central compartment of OCA, glyco-OCA and tauro-OCA concentrations (ie, observed) in the plasma, respectively and compartments #3 and 5 represent the gallbladder compartments for glyco- and tauro-OCA, respectively; arrows with breaks correspond to intermittent gallbladder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

glyco-OCA = glycine conjugate of OCA; 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; tauro-OCA = taurine conjugate of OCA.

A Forest plot was generated to represent the effect of hepatic impairment on total OCA (the sum of exposure of OCA, glyco-OCA and tauro-OCA) (Figure 8).

Figure 8: Forest Plot: Relationship Between Degree of Liver Impairment and AUC of Total OCA



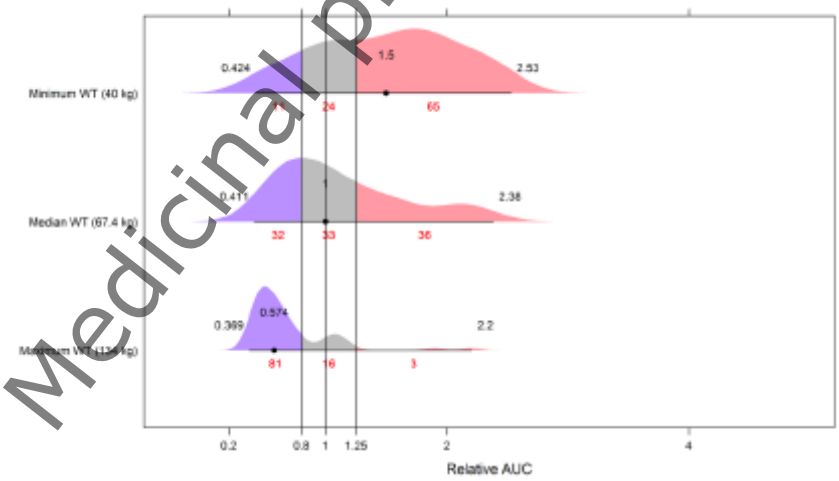
AUC= area under the curve

Note: The above figure assumed after daily dose of 10 mg of OCA at 8 AM and meals taken at 8 AM, 12 PM and 6 PM with a dosing at 8 AM; 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.

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

A Forest plot was generated to represent the effect of body weight on total OCA. Individual body weight values from Study 747-301 were considered for the simulations. Prediction of AUC for minimum (40 kg), median (66.5 kg) and maximum (134 kg) weight values are presented in Figure 9.

Figure 9: Forest Plot: Relationship Between Body Weight and AUC of Total OCA



AUC = area under the curve; n = number of subjects; OCA = obeticholic acid; WT = body weight

Note: the above figure assumed after daily dose of 10 mg of OCA at 8 AM and meals taken at 8 AM, 12 PM and 6 PM with a dosing at 8 AM; 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 for 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 for a typical 67.4-kg subject.

Elderly

The exposure of OCA in elderly patients (≥65 years of age) appeared similar to that in adult patients less than 65 years of age. In clinical Study 747-301, trough PK samples were collected from subjects with PBC after 6 months and 12 months of dosing. The PK population included 20 patients (16% of population) aged 65 years or older. Trough OCA and total OCA concentrations (sum of OCA, glyco-OCA and tauro-OCA) in the older patient populations (ages 65 to 74 and ages 75 to 84) were similar to those in younger populations (under 65). There were no patients >85 years of age. Plots of the trough OCA and total OCA data showed substantial variability in exposures and the relative sparsity of data from patients ≥65 years.

Pharmacokinetic interaction studies

Results from the human sandwich cultured hepatocytes indicate that OCA has the potential for weak suppression of CYP1A2 and CYP3A4 which is consistent with the results for the clinical drug-drug interaction Study 747-109. Because FXR activation has been shown to suppress metabolizing enzymes and transporters involved in bile acid homeostasis, the potential of OCA to induce or suppress drug metabolizing enzymes (CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19, UGT1A3) and drug transporters OATP1B1, OATP1B3, OATP2B1, MATE1, MRP2, MRP3, MRP4, OCT1, BCRP, P-gp, and NTCP were assessed in SCHH (ICPT-1002-3). No induction or suppression of the previously mentioned drug metabolizing enzymes and transporters was observed.

In vivo

Based on the mechanism of action of OCA as an FXR agonist and data generated from in vitro studies, the potential of OCA to influence the expression and/or reversibly inhibit multiple CYP450 enzymes and drug transporters in the liver and other tissues was assessed in clinical studies. Five clinical studies were conducted to assess the effect of OCA on the single dose plasma PK of substrate probes for CYP3A4, CYP1A2, CYP2C9, CYP2C19, CYP2D6 and transporters (P-glycoprotein, BCRP, OATP1B1 and OATP1B3) and the effect of omeprazole on OCA PK as follows:

- 747-109: caffeine (CYP1A2 substrate) and midazolam (CYP3A4 substrate)
- 747-110: S-warfarin (CYP2C9 substrate)
- 747-111: rosuvastatin (OATP1B1, OATP1B3, BCRP substrates)
- 747-112: omeprazole (CYP2C19 substrate) and dextromethorphan (CYP2D6 substrate)
- 747-114: digoxin (P-glycoprotein substrate)

OCA caused either no or weak effects on metabolizing CYP450 (CYP) enzymes and transporters after daily administration. Taken together, these data suggest that concomitant administration of OCA would not likely produce clinically relevant changes in exposure of drugs metabolized via CYP3A4, CYP2C9,

CYP2C19, CYP2D6 and/or transported by P-gp, BCRP, OATP1B1, and OATP1B3. OCA did show the potential for weak suppression of CYP1A2.

Additionally, the effect of omeprazole on OCA and its conjugates was assessed. Omeprazole 20 mg was dosed daily for one week, resulting in modest increases in unconjugated and conjugated OCA exposure of <20% (OCA 10 mg) and <35% (OCA 25 mg) suggesting that co-administration of medications that alter gastric pH (proton pump inhibitors and H2 antagonists) will not meaningfully effect total OCA absorption.

The effect of bile acid sequestrants (BAS) on the PK of OCA was examined in Study 747-301 (747-301 Double-Blind Phase). A comparison of trough concentrations of OCA at Month 6 and Month 12 for patients taking BAS versus patients not taking BAS showed modestly lower trough concentrations of OCA at Month 6 and Month 12 that was associated with a modest attenuation of efficacy for the 5 mg (titration) dose group but no meaningful effect for the 10 mg dose group.

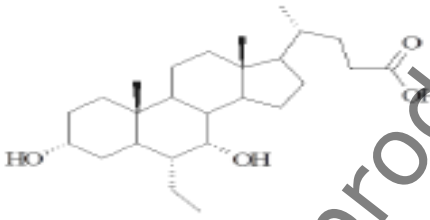
Pharmacokinetics using human biomaterials

Please refer to specific chapters above

2.3.3. Pharmacodynamics

Mechanism of action

Obeticholic Acid (OCA) is a farnesoid X receptor (FXR) agonist and modified bile acid being developed for the treatment of primary biliary cirrhosis (PBC) and other chronic liver diseases. Bile acids are amphipathic, detergent-like molecules synthesized in the liver from cholesterol by multiple enzymatic steps.



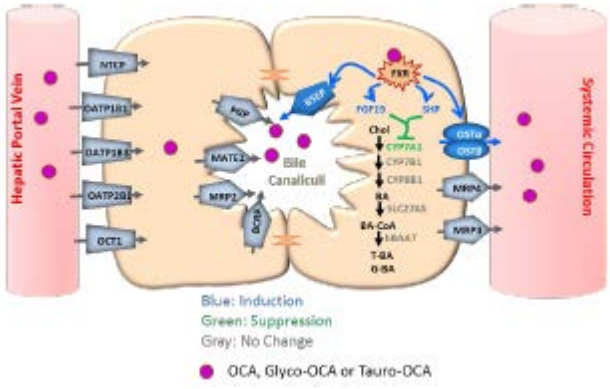
OCA is a selective FXR agonist that targets genes that regulate the synthesis, transport, and hepatic concentrations of bile acids. Similar to other nuclear receptors, once activated, FXR translocates to the cell nucleus where it works in concert with other transcription factors to down regulate the expression of CYP7A1, which is the enzyme that catalyzes the rate-limiting step of bile acid synthesis.

Activation of FXR protects against the toxic accumulation of bile acids by decreasing bile acid synthesis from cholesterol, increased basolateral efflux into the sinusoidal space (and thus into the systemic circulation), and apical secretion into bile canaliculi (and thus into the intestinal lumen). These mechanisms limit the overall size of the circulating bile pool while promoting choleresis, thus reducing hepatic exposure to bile acids. Thus, as a bile acid sensor, FXR controls bile acid homeostasis. In addition to suppression of CYP7A1 and bile acid synthesis, the key mechanisms of action underpinning the hepatoprotective effects of OCA in PBC include choleresis, regulation of transporter expression, anti-inflammatory and antifibrotic effects.

This reduction of bile acid synthesis is complemented by the effects of OCA to increase expression of bile acid transporters thus promoting choleresis (Figure 10, Rizzo 2010). Induction of the bile salt excretory

pump (BSEP) leads to transport of conjugated bile acids from the liver in to bile, while induction of the heterodimer protein organic solute transporter α/β (OST α/β) leads to transport of conjugated bile acids from the liver to the systemic circulation. The combination of decreased bile acid synthesis and increased transport of bile acids out of the hepatocyte serves to combat the toxic burden of hepatic bile acid accumulation in cholestasis.

Figure 10 Effect of FXR Activation of OCA and Metabolism Enzymes and Transporters Responsible for the Regulation of Bile Acids in Human Hepatocytes



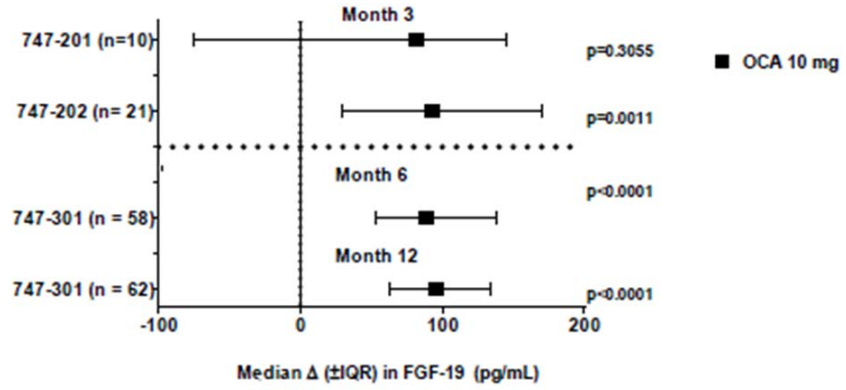
The PD data are supportive of the hypothesis that OCA mediates its action primarily via FXR agonism wherein FGF-19 released from gut enterocytes (in response to compounds with FXR agonist properties) into portal circulation down regulates endogenous bile acid synthesis in the liver. OCA treatment resulted in a significant and a dose-dependent increase in the levels of FGF-19, and consequently a decrease in the levels of endogenous bile acids and C4 (a bile acid precursor).

Primary and Secondary pharmacology

Primary pharmacology

The regulation of bile acid homeostasis primarily underlies the therapeutic rationale for FXR agonists in PBC and has been assessed in clinical studies, through examination of FGF-19, C4, and bile acid levels. Fibroblast growth factor-19 (FGF-19) is an ileal enterokine controlled by FXR and has been studied as a marker of FXR activation in the clinical development program of OCA. FGF-19 along with FXR activation in the liver inhibits the transcription of cholesterol 7α-hydroxylase (CYP7A1) which regulates bile acid synthesis (Hofmann 2009). 7α-hydroxy-4-cholesten-3-one (C4), a marker for bile acid synthesis and thus CYP7A1 activity, was also studied in the development program of OCA. Therefore, the relationship of the three markers of FXR activation (FGF-19, C4, and bile acids,) and systemic OCA exposure was explored. OCA increased FGF-19 levels in all 3 double-blind studies. For Study 747-301, Month 6 was the earliest visit FGF-19 was assessed. Consistent with FXR agonist effects, statistically significant increases in FGF-19 from Baseline to Month 3 were observed in Study 747-202 and at Month 6 and Month 12 in Study 747-301 for OCA compared with placebo. The increase observed in Study 747-201 was not statistically significant. The median difference (95% CI) for OCA 10 mg compared with placebo for each individual study is summarized in Figure 11. In the double-blind Phase 2 Study 747-202 which evaluated a range of doses (10 mg, 25mg and 50 mg), the increase in levels of FGF-19 were dose dependent.

Figure 11: Double-Blind Median Difference (95% IQR) in FGF-19: ITT Population (N = 265, Placebo and OCA 10 mg), Individual Studies

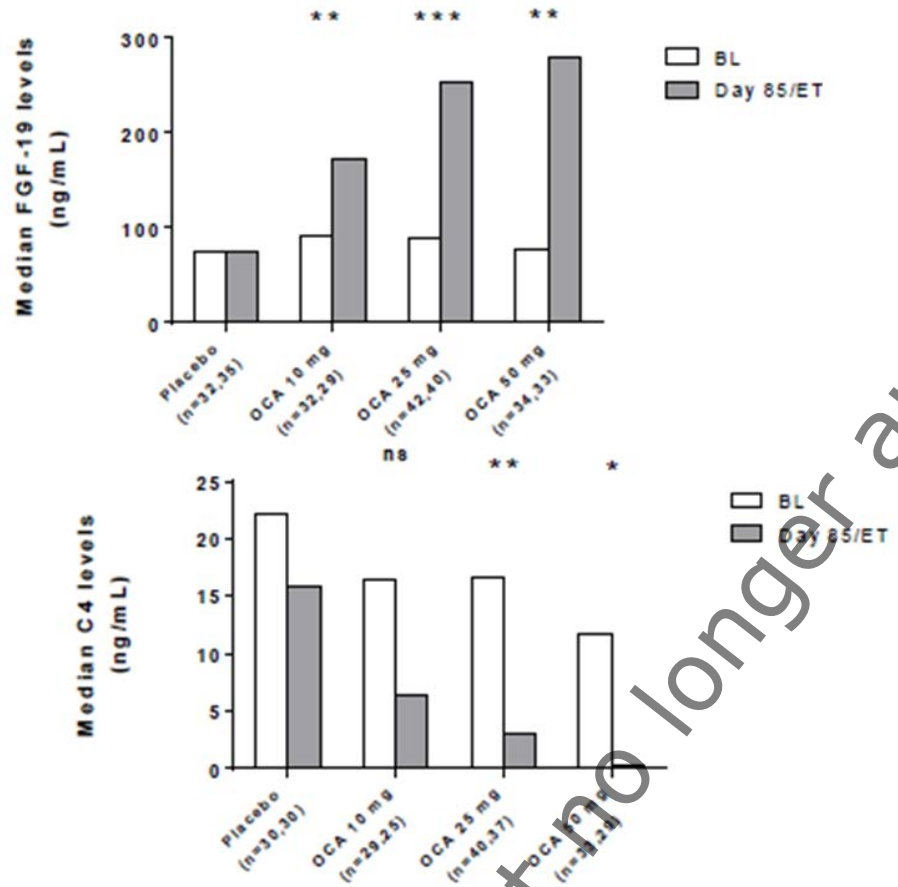


FGF-19 = fibroblast growth factor-19; ITT = intent-to-treat; LLN = lower limit of normal; OCA = obeticholic acid
p-value for comparing active treatments to placebo were obtained using the Wilcoxon rank-sum test.
Hodges-Lehmann estimates for the median difference (OCA - Placebo).
For Studies 747-201 and 747-202 the LLN = 31 pg/mL and the ULN = 554 pg/mL. For Study 747-301, the LLN = 157 pg/mL and the ULN = 229 pg/mL.

FGF-19 activation was associated with a reduction in C4 (7alpha-hydroxy-cholest-4-ene-3-one) and endogenous bile acids. In Study 747-202, C4 levels decreased with increasing exposure of total OCA consistent with regulation of CYP7A1 by FGF-19 (Figure 12). In Study 747-301, reductions in total endogenous bile acid were observed for subjects receiving OCA titration (-1.41 µmol; p-value = 0.0553) and OCA 10 mg (-5.72 µmol; p-value = 0.0035), while an increase from Baseline was observed for subjects receiving placebo (2.24 µmol; p-value = 0.1212). Statistically significant mean absolute reductions in total endogenous bile acids from Baseline to Month 12 were observed for the OCA titration (-2.86 µmol; p = 0.0010) and OCA 10 mg (-4.70 µmol; p = 0.0037). Importantly, LCA, a toxic secondary bile acid, remained stable across all treatment groups at Month 6 and Month 12, compared with Baseline (absolute change ranging from -0.01 µmol to 0.05 µmol).

Mechanistically, the pharmacodynamic data are supportive of the hypothesis that OCA mediates its action primarily via FXR agonism wherein FGF-19 released from gut enterocytes (in response to compounds with FXR agonist properties) into portal circulation down regulates endogenous bile acid synthesis in the liver. OCA treatment resulted in a significant and a dose-dependent increase in the levels of FGF-19, and consequently a decrease in the levels of endogenous bile acids and C4 (a bile acid precursor) in this study.

Figure 12: FGF-19 and C4 Levels at Baseline and Day 85 After Daily Administration of Placebo, 10 mg OCA, 25 mg OCA, and 50 mg OCA/ET: ITT Population (N = 165) (Study 747-202)



Secondary Pharmacology

A thorough QT study (747-108) designed according to the FDA E14 guidance was performed in healthy subjects in which the potential effects of OCA (100 mg for 4 days) and its active conjugates (glyco-OCA and tauro-OCA) on the QT interval at both therapeutic and supratherapeutic concentrations were assessed.

Results confirmed that OCA did not cause QT prolongation at supratherapeutic or therapeutic plasma concentrations. Results according to Bazett's and Fridericia's corrections were supportive of the primary QTc analysis and did not show a relevant impact on QT interval.

2.3.4. Discussion on clinical pharmacology

The PK properties of OCA closely resemble those of endogenous bile acids, with fecal excretion as the main elimination route and extensive enterohepatic circulation. Following oral administration, OCA is rapidly absorbed, followed by extensive conjugation to glycine and taurine to form glyco-OCA and tauro-OCA. PK exposure of OCA and its conjugates generally increased dose proportionally based on AUC0-24 and Cmax up to 100 mg.

Food consumption increased OCA exposure by approximately 15%. This is not expected to be clinically relevant and accordingly OCA can be taken with or without food. Bioequivalence between the OCA formulation used in the clinical trials and the OCA formulation to be marketed was assessed in two BE studies (745-115 and 747-116). The obtained results were within the CI, thus demonstration BE of both formulations.

Although there is limited PK data for OCA in patients with PBC, results from Studies 747-205 and 747-301 suggest that PK of OCA is consistent to that observed in healthy subjects after similar doses (747-105).

Obeticholic acid has minimal renal elimination with less than 3% of the dose recovered in urine. Based on population pharmacokinetic analysis, renal function did not have a meaningful effect on the pharmacokinetics of obeticholic acid.

Available data from patients with moderate or severe liver impairment is very limited and has been added as missing information into the RMP safety specification. Hepatic impairment was identified as a predictor of OCA systemic exposure via PK modelling. This was further assessed in a dedicated study with non-PBC patients/subjects with liver impairment and in cirrhotic patients (non-PBC patients), study 747-103. Data from these studies and additional PK modelling indicate that OCA exposure increases with increasing severity of the liver impairment. In patients with moderate and severe hepatic impairment there was an increase in systemic exposure of OCA of approximately 4- fold (Cmax and AUC; LS mean) and approximately 10 to 17-fold (Cmax and AUC; LS mean); respectively. Similar increased systemic exposure was observed in the study of subjects taking 10 mg or 25 mg of OCA in patients with alcoholic cirrhosis and portal hypertension (moderate to severe hepatic impairment) relative to healthy subjects. The Applicant proposed dose recommendations for patients with hepatic impairment based on data from the phase 1 hepatic impairment study and PK simulations performed. These data demonstrated that liver exposures of OCA 10 mg twice weekly in patients with moderate and severe hepatic impairment would be approximately equivalent to a 5 mg and 6 mg once daily dose in patients with no hepatic impairment. The expected increase in liver exposure resulting from this posology is unlikely to be sufficient to achieve the liver exposures associated with hepatotoxicity observed at higher doses (250 mg).

Therefore a modified dosing regimen of OCA in patients with moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) was included in the SmPC to establish tolerability at lower doses than those proposed in patients with no hepatic impairment, after which, patients may titrate to higher doses based on response. The recommended starting dosage for moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment was adapted to 5 mg once weekly. If an adequate reduction in alkaline phosphatase and/or total bilirubin has not been achieved after 3 months of OCA 5 mg once weekly, and the patient is tolerating the medicinal product, increase the dose of OCA should be increased to 5 mg twice weekly (at least three days apart) and subsequently to 10 mg twice weekly (at least three days apart) depending on response and tolerability.

The impact of several other intrinsic factors, such as weight, age, gender and race, was explored via PK modelling. The impact of these factors is not considered to be relevant on OCA systemic exposure.

There are limited pharmacokinetic data in elderly patients (>65 years). Population pharmacokinetic analysis, developed using data from patients up to 65 years old, suggested that age should not significantly influence obeticholic acid clearance from the circulation. The SmPC reflects this information adequately.

In interaction studies OCA showed weak suppression of CYP1A2 which may produce clinically relevant increases in exposure for drugs that are metabolized by CYP1A2 and have a narrow therapeutic window. This is appropriately mentioned in the SmPC.

Concomitant bile acid sequestrants (BAS) absorb and reduce bile acids and lowered trough concentrations and efficacy of OCA in clinical studies and attenuate its efficacy. Therefore OCA should be taken at least 4-6 hours before or 4-6 hours after (or at as great an interval as possible) taking bile acid resin as outlined in the SmPC.

No further clinically significant DDIs are expected based upon metabolic profiles of the most widely used concomitant medications in PBC patients.

From a clinical point of view, the information regarding OCA´s PD, in particular on the mechanistic of the anti-inflammatory effect that has been provided by the Applicant is rather limited and adds to the conclusion that confirmation on disease progression needs to be given within a conditional marketing authorisation (see also discussion on clinical efficacy).

2.3.5. Conclusions on clinical pharmacology

The Applicant has presented sufficient Clinical Pharmacology data to characterize the PK profile. Adequate information for the dose adjustments in patients with hepatic impairment has been included in the SPC.

2.4. Clinical efficacy

2.4.1. Dose response studies

Study 747-201

This was a 3-month, double-blind, placebo-controlled, study in subjects with a proven/likely diagnosis of PBC. OCA doses of 10 mg and 50 mg were evaluated as monotherapies.

The primary efficacy endpoint was the percent change (%) in serum ALP from Baseline to End of Study (EOS). Key secondary efficacy endpoints were:

- Absolute changes in serum ALP levels from Baseline to Day 15, Day 29, Day 57, Day 85/ET and Follow-Up (Day 99);
- Percentage of subjects who meet the definition of PBC responder criteria per the Paris I, Toronto I, Toronto II, Toronto III, Toronto IV, Mayo II, and Barcelona disease prognostic risk criteria at Day 85/ET;
- Absolute and percent change in serum aspartate aminotransferase (AST), alanine aminotransferase(ALT), gamma-glutamyl-transferase (GGT), and conjugated (direct) bilirubin values from Baseline to Day 15, Day 29, Day 57, Day 85/ET and Follow-Up (Day 99).

A total of 59 subjects were enrolled and received investigational product. Of them, 48 completed the double-blind phase of the study (i.e., provided assessments up to Day 85). Of the subjects who discontinued early, the primary reason was an AE of pruritus.

Mean baseline ALP levels were 3.5x ULN to 3.9x ULN across treatment groups (range 408 U/L to 462 U/L). Results of the primary endpoint after 12 weeks of treatment were:

Table 8: Percent Change in ALP Levels (U/L) from Baseline to EOS: ITT Population (N = 59)

Percent Change	Placebo (n = 23)	OCA 10 mg (n = 20)	OCA 50 mg (n = 16)
Mean (SD)	0.4 (15.3)	-44.5 (24.4)	-37.6 (21.0)
Median	-0.8	-53.9	-37.2
p-value[a,b]	NA	<0.0001	<0.0001

a Per SAP, comparisons of OCA treatment groups versus Placebo are regarded as confirmatory analyses (applying for a hierarchical order): Step 1 - OCA 10 mg versus placebo; Step 2 - OCA 50 mg versus placebo.
b Wilcoxon-Mann-Whitney p-values compared to placebo.

There was no apparent difference in the magnitude of improvement between the 2 OCA doses.

The secondary efficacy endpoints were supportive of primary endpoint analyses. Across the efficacy evaluations, both OCA doses, 10 mg and 50 mg, were equally effective, and no dose-response relationship was observed for the majority of the efficacy endpoints.

Study 747-202

This was a 3-month, double-blind, placebo-controlled study in subjects with a proven/likely diagnosis of PBC who were suboptimally controlled. OCA doses of 10 mg, 25 mg, and 50 mg were evaluated as add-on therapy to UDCA. Subjects had to be on a stable dose of UDCA therapy for at least 6 months prior to Screening.

The primary efficacy endpoint was the percent change in serum ALP level from Baseline to End of Study (Week 12 or last observed ALP value on treatment).Secondary efficacy variables included the following: hepatocellular injury(aminotransferase and other hepatic enzymes and analytes); liver function (prothrombin time, albumin, and other laboratory tests); disease-specific and general health questionnaires (PBC-40, 5D and SF-36);symptoms (pruritus visual analog scale [VAS] questionnaire); and biomarkers of hepatic inflammation and fibrosis (various biochemical assessments of cytokines and other analytes).

A total of 165 subjects were randomized to study medication as follows: placebo (N = 38), OCA 10 mg (N = 38), OCA 25 mg (N = 48), and OCA 50 mg (N = 41). Mean baseline ALP levels were approximately 2.5 x ULN across treatment groups (range 275 U/L to 294 U/L).

Results of the primary endpoint after 12 weeks of treatment were:

Table 9: Percent Change in Serum ALP Levels (U/L) from Baseline to EOS: mITT Population (n = 161)

Percent Change	Placebo (n = 37)	OCA 10 mg (n = 38)	OCA 25 mg (n = 47)	OCA 50 mg (n = 39)
Mean (SD)	-2.6 (12.5)	-23.7 (17.8)	-24.7 (17.9)	-21.0 (27.6)
Median	-3.1	-22.0	-27.5	-25.3
P-value[a]	NA	<0.0001	<0.0001	<0.0001

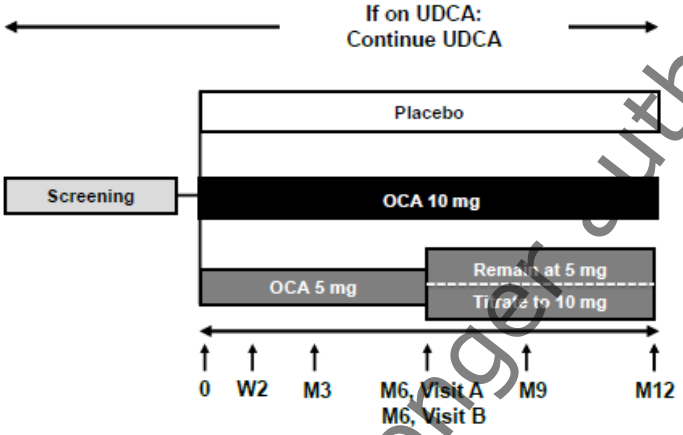
[a] p-value compares OCA treatment groups to placebo on the change from Baseline to Day 85/ET using Wilcoxon-Mann-Whitney test.

2.4.2. Main study

Study 747-301

This was a randomized, double-blind, placebo-controlled, multi-dose, parallel-group study evaluating OCA in subjects with PBC who were either taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Baseline (Day 0) or unable to tolerate UDCA (no UDCA for ≥3 months) prior to Baseline (Day 0).

Figure 13: Study Design for Double-Blind Phase of 747-301



M = month; OCA= obeticholic acid; UDCA = ursodeoxycholic acid; W = week

Methods

Study Participants

Main Inclusion Criteria

- Definite or probable PBC diagnosis (consistent with AASLD and EASL Practice Guidelines);
- At least 1 of the following qualifying biochemistry values: ALP ≥1.67x ULN, total bilirubin >ULN but <2 x ULN;
- Age ≥18 years
- Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 0, or unable to tolerate UDCA (no UDCA for ≥3 months) prior to Day 0.
- Contraception: Female subjects had to be postmenopausal, surgically sterile, or, if premenopausal, had to be willing to ≥ 1 effective method of contraception during the study and for 30 days after the EOT Visit;
- Must have provided written informed consent and agreed to comply with the study protocol.

Key Exclusion Criteria

- History or presence of other concomitant liver diseases including: HCV infection, active HBV infection, primary sclerosing cholangitis, alcoholic liver disease, definite autoimmune liver disease or overlap hepatitis, non-alcoholic steato-hepatitis (NASH), Gilbert's Syndrome (due to interpretability of bilirubin levels).

- Presence of clinical complications of PBC or clinically significant hepatic decompensation, including: history of liver transplantation, current placement on a liver transplant list or current Model for End Stage Liver Disease (MELD) score ≥15, portal hypertension with complications, cirrhosis with complications, hepatorenal syndrome (type I or II) or Screening serum creatinine>2 mg/dL (178 µmol/L)
- Subjects with severe pruritus, or those requiring systemic treatment for pruritus (e.g., with bile acid sequestrants [BAS] or rifampicin) within 2 months of Day 0.
- Administration of the a prohibited medications prior to Day 0
- Subjects who had previously participated in a clinical study of OCA
- History or presence of clinically concerning cardiac arrhythmias
- If female: known pregnancy, or had a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
- Known history of HIV infection
- Presence of any other disease or condition that was interfering with the ADME of drugs including bile salt metabolism in the intestine.
- Medical conditions that could cause non-hepatic increases in ALP (e.g., Paget's disease) or that could diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukaemia)
- Other clinically significant medical conditions that were not well controlled or for which medication needs were anticipated to change during the study
- Anticipated changes to current concomitant medications during the course of the study

Treatments

Three treatment groups were evaluated in the double-blind phase of the study: placebo, OCA titration, or (c) OCA 10. Investigational product was to be administered PO, QD for 12 months. Each dose was made up of 1 tablet.

Patients were instructed to begin dosing on the day after the Day 0 visit (i.e., on Day 1) and to take investigational product with water, approximately 30 minutes prior to breakfast. Subjects were instructed to swallow the tablet whole and to not chew, divide, or crush the tablet.

Method of Assigning Subjects to Treatment

Allocation to 1 of 3 treatment arms occurred on a 1:1:1 ratio across sites based on a predefined randomization code (generated by Sharp Clinical Services [formerly Bilcare]) using an IWRS that served as a computer-based subject registration system at: Screening and Day 0 (randomization). The IWRS served as an investigational product inventory and management system. The Investigator or designee was required to register the subject in the IWRS and could be prompted to provide subject data necessary to properly randomize and allocate the subject to treatment. A randomization number was assigned according to the master randomization schedule and as allocated by IWRS in strict sequential order within the appropriate randomization strata.

Duration

All subjects randomized to the OCA titration group received OCA 5 mg the initial 6 months. At Month 6, subjects from the OCA titration group who were deemed eligible to up-titrate received OCA 10 mg for the remaining 6 months of the double-blind period.

Dose reductions/Interruptions

Per protocol, subjects were to receive investigational product QD the entire 12-month duration of the double-blind phase; however, less frequent dosing regimens (i.e., alternative dosing regimens) or Investigator-prescribed drug holidays were permissible at any point in the study for subjects who were experiencing tolerability issues due to pruritus.

Prohibited and/or Restricted Treatments

Administration of the following medications was prohibited as specified below:

- Prohibited 6 months prior to Day 0 and throughout the study: azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline, fenofibrate or other fibrates– budesonide and other systemic corticosteroids – potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproicacid,isoniazide, or nitrofurantoin);
- Prohibited 12 months prior to Day 0 and throughout the study: Antibodies or immunotherapy directed against interleukins or other cytokines or chemokines.

Administration of the following medications was permitted:

- Topical or inhaled corticosteroids;
- Herbal supplements or botanical preparations that were purported to affect the liver (eg, milk thistle) were permitted to take during the study, provided that the dose and treatment regimen of these agents was kept constant during the double-blind phase;
- UDCA treatment dose and regimen were captured in the eCRF. Subjects who entered the study as OCA monotherapy subjects (i.e., not taking UDCA)
- could not initiate treatment with UDCA at any time during the double-blind phase.
- Subjects taking a BAS or aluminum hydroxide or smectite containing antacids were instructed to stagger their dosing of investigational product (and UDCA) and BAS, ensuring at least 4 hours between doses of the BAS and/or these antacids and investigational product (and UDCA).
- Hormonal contraceptives.

Objectives

The primary objectives of the study were to assess the effects of OCA in subjects with primary biliary cirrhosis (PBC) on the following:

- Serum alkaline phosphatase (ALP) and total bilirubin (composite endpoint);
- Safety

The secondary objectives were to assess the effects of OCA in subjects with PBC on the following:

- Hepatocellular injury and liver function, including histology (inflammatory, structural [portal, parenchymal], and fibrotic assessments);

- Disease-specific symptoms;
- Biomarkers and non-invasive assessments of liver fibrosis;
- Bile acids.

Outcomes/endpoints

Efficacy

The Primary Endpoint was a composite endpoint, defined as the percentage of subjects (OCA 10 mg vs. placebo) reaching an ALP <1.67 x ULN and a ≥15% reduction in ALP and a total bilirubin ≤ULN at Month 12.

A Key Secondary Endpoint was the percentage of subjects (OCA titration vs. placebo) achieving composite endpoint at Month 12.

Other Secondary Endpoints:

- Absolute and percent change from Baseline in ALP, gamma-glutamyl-transferase (GGT), alanine aminotransferase (ALT), AST, total bilirubin, conjugated (direct) bilirubin, albumin, prothrombin time and international normalized ratio (INR) at all timepoints;
- Percentage of subjects with a decrease in ALP of ≥10%, ≥15%, ≥20%, and ≥40% from Baseline or ≤ULN.
- Percentage of subjects achieving the biochemical treatment response criteria associated with improved clinical outcomes in subjects with PBC (ALP ≤3x ULN and AST ≤2x ULN and bilirubin ≤ULN [Paris I modified], ALP ≤1.5x ULN and AST ≤1.5x ULN and bilirubin ≤ULN [Paris II], ALP ≤1.67x ULN and bilirubin ≤ULN [Mayo II], ALP ≤1.76x ULN [Toronto II], normal bilirubin (values ≤ULN) and/or normal albumin (values ≥lower limit of normal [LLN] [Rotterdam]);
- Absolute change from Baseline at Month 12 for enhanced liver fibrosis (ELF) and hepatic stiffness (at select sites) as assessments of end stage liver failure
- Absolute and percent change from Baseline at all timepoints on C-reactive protein (CRP), tumour necrosis factor-alpha (TNF-α), tumour necrosis factor-beta (TGF-β), fibroblast growth factor-19 (FGF-19) levels, interleukin-6 (IL-6), and CK-18;
- Absolute and percent change from Baseline at all timepoints on PBC-40 domains;
- Percentage of subjects with each response on the Patient Research Questionnaire at Month 12.

Exploratory Endpoints:

Exploratory endpoints included absolute and percent change from Baseline on PBC auto-antibodies (IgA, IgG, IgM) and interleukins (IL-12 [p40], IL-23).

Pharmacokinetic and Pharmacodynamic Endpoints:

Plasma OCA concentrations at Month 6 and Month 12 including OCA (unconjugated), conjugates (glyco-OCA and tauro-OCA), and total OCA (the sum of OCA unconjugated, glyco-OCA, and tauro-OCA); absolute change from Baseline to Month 6 and Month 12 for total bile acids, endogenous bile acids, and individual total and unconjugated bile acids (UDCA, deoxycholic acid, cholic acid and lithocholic acid), glyco-conjugate, and tauro-conjugate; proportion of each of the individual bile acids to total bile acids; Bile acid sequestrant (BAS) concomitant exposure

Safety Assessments:

Safety was assessed by treatment-emergent adverse events (TEAEs), vital sign measurements, weight, BMI, 12-lead electrocardiograms (ECGs), physical examinations, clinical laboratory results, dual-emission x-ray absorptiometry (DEXA) scans, Mayo Risk Score (MRS), and Model for End Stage Liver Disease (MELD) scores.

Patient questionnaires (5-dimensional [5-D] pruritus, and pruritus visual analog scale [VAS])

Sample size

The planned sample size was approximately 180 subjects (60 subjects in each of the 3 groups). An analysis of this study's endpoint was conducted on the Phase 2 study (adding OCA to UDCA therapy) dataset: 9% of the placebo subjects and 40% of the subjects receiving OCA 10 mg had a positive response. The sample size was then calculated using slightly more conservative numbers. Assuming responder rates in the placebo and the OCA 10 mg groups of 14% and 40%, respectively, and based on the use of a 2-sided test of equality of binomial proportions at the 5% level of significance, a sample size of 60 subjects per group would provide 90% power to detect a difference between the OCA 10 mg group and placebo. Due to a screening window of up to 8 weeks, some subjects had already successfully completed screening procedures, met all inclusion criteria, and had been scheduled for randomization(Protocol 747-301, Amendment 3 [Version 3, dated 24 Sep 2012]) although the planned sample size of 180 subjects was met. These subjects proceeded to be randomized upon approval by the Sponsor.

Randomisation

Randomization was done using an IWRS that served as a computer-based subject registration system at: Screening and Day 0 (randomization).

Blinding (masking)

To maintain the blind, all tablets of investigational product (ie, placebo, OCA 5 mg, and OCA 10 mg) were identical in appearance, and all subjects from all treatment groups were assessed by the Investigator for titration eligibility at Month 6, based on ALP and/or total bilirubin response and tolerability of investigational product.

Statistical methods

Study Populations:

Intent-to-Treat (ITT) Population: All randomized subjects who received at least 1 dose of investigational product (N = 216). Treatment assignment was based on the randomized treatment.

Completer Population: All randomized subjects who received at least 1 dose of investigational product and participated through the end of the double-blind phase (Month 12; N = 198). Treatment assignment was based on the randomized treatment.

Efficacy Evaluable (EE) Population: All subjects in the Completer Population who did not have any major protocol deviations that could potentially affect the efficacy of the investigational product (N = 192). Treatment assignment was based on randomized treatment.

Efficacy: Analyses for the composite endpoint were completed using a Cochran–Mantel–Haenszel (CMH) test stratified by the randomization stratification factor based on the ITT population. Missing values were considered a non-response. Statistical significance of the difference between placebo and OCA 10 mg was defined as a p-value ≤0.05. Sensitivity analyses were performed on the primary efficacy endpoint using observed data only. The primary efficacy analyses were repeated using the EE and Completer populations.

The CMH test was also used for ALP responder analyses, disease prognostic risk responder analyses, and subgroup analyses. Sensitivity analyses were performed using the ITT population on all responder endpoints using a logistic regression model with response as the endpoint and treatment group and randomization strata as factors.

Efficacy laboratory parameters were analyzed using an analysis of covariance (ANCOVA) model with absolute change and percent change from Baseline as the dependent variable including treatment group and randomization stratification factor as fixed effects and Baseline as a covariate.

PK: The PK population was used to summarize OCA and bile acid concentrations. The change from Baseline concentrations within each treatment group was compared using a paired t-test. Descriptive statistics of OCA plasma concentrations and the extent of BAS concomitant exposure were provided by treatment group. Initial evaluation of the effects of BAS on OCA, total bile acid concentrations, and ALP was performed using a correlation analysis.

Safety: All safety analyses were based on the Safety population. TEAEs were summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and preferred term by severity and by causal relationship to OCA. Pruritus was considered an adverse event (AE) of special interest.

Safety laboratory parameters, MRS, MELD scores, vital signs, body weight, and body mass index (BMI) values (absolute and change from Baseline) were summarized by treatment group using descriptive statistics at Baseline and at each post-Baseline visit.

The 5-D pruritus questionnaire values and change from Baseline were summarized by treatment using descriptive statistics for each domain score and the total score by visit. The pruritus VAS was summarized in the same manner.

Correlation analyses and categorical summaries were presented for ECGs.

Unless otherwise noted, all statistical testing was 2-sided and was performed at the 0.05 significance level. Tests were declared statistically significant if the calculated p-value was ≤0.05. Continuous variables were summarized with means, standard deviations, standard error of the mean, medians, minimums, and maximums. Categorical variables were summarized by counts and by percentage of subjects in corresponding categories. All summary tables were presented by treatment group. Baseline summaries also included a total summary column.

Individual subject data obtained from the eCRFs, central clinical lab, central ECG lab, other external laboratory data, and any derived data were presented by subject in data listings. Data from all assessments during the double-blind phase, whether scheduled or unscheduled, were listed by treatment assignment, subject, and visit.

The analyses described in the SAP were considered a priori in that they were defined prior to database lock and prior to breaking the blind. Any analyses performed subsequent to breaking the blind were considered post-hoc and exploratory. All analyses and tabulations were performed using SAS® Version 9.2 or higher. The Baseline value used for the statistical analyses of quantitative parameters (e.g., for

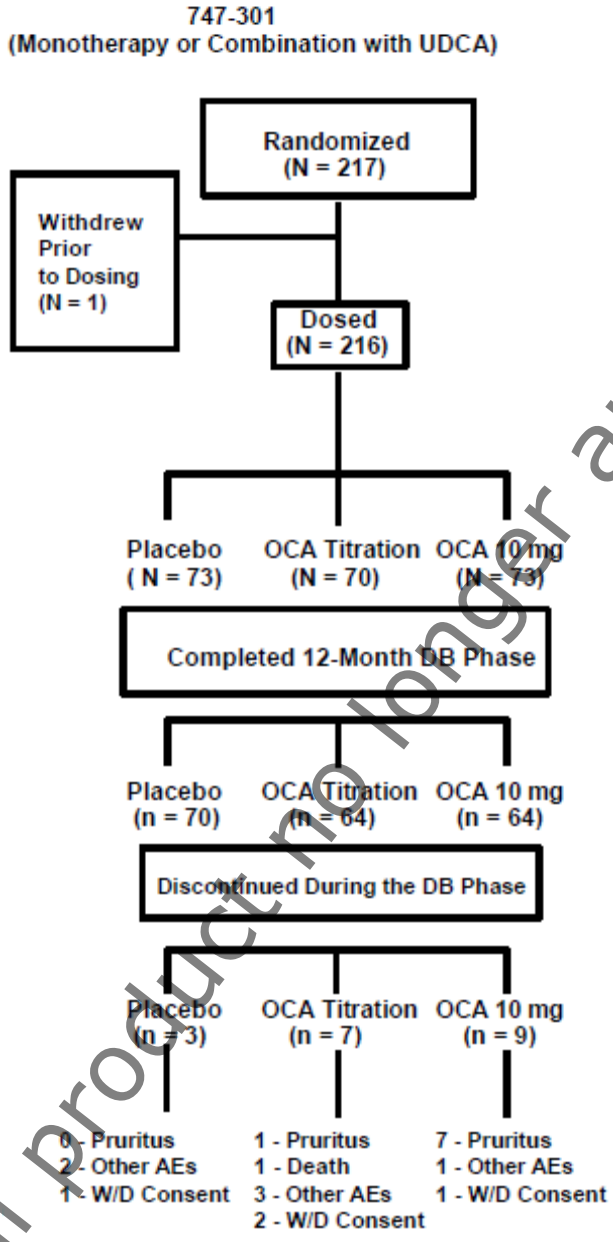
numerical change from Baseline analyses) was defined as the mean of all available evaluations prior to treatment. If only 1 evaluation was expected, the available data were used as the Baseline value.

The Baseline value used for statistical analyses of qualitative parameters (e.g., normal/abnormal) was defined as the last observed value before the first dose of investigational product.

Missing data were handled as follows:

- For responder analyses, any subject who did not provide an assessment at the specified timepoint for the defining of response was considered to be a non-responder.
- For efficacy endpoints that utilized an analysis of covariance (ANCOVA) model, observed cases served as the primary analysis. Sensitivity analyses to assess the effect of missing data were conducted where missing data was imputed using last observation carried forward (LOCF). For efficacy endpoints that utilized the MMRM, no imputations were made for missing values.
- **Results**

Participant flow



Recruitment:

Fifty-nine investigators from 13 countries participated in this study including: 15 sites in the United States (US); 10 sites in Germany; 9 sites in the United Kingdom (UK); 5 sites in Poland; 4 sites each in The Netherlands and Italy; 3 sites in Australia; 2 sites each in Canada, Spain, and Austria; and 1 site each in Belgium, France, and Sweden. The study took place from March 2012 to December 2013.

A total of 217 patients were randomized, and 216 subjects received at least 1 dose of investigational product (i.e., ITT population).

The majority of the population was European (67%), followed by North American (29%), and Australian (4%).

Conduct of the study

The original Protocol 747-301 (Version 1), dated 06 Sep 2011, was amended 3 times during the double-blind phase of the study.

- Protocol 747-301, Amendment 1 (Version 1.1, dated 18 Jan 2012): This protocol amendment addressed comments raised under Voluntary Harmonisation Procedure (VHP) and was submitted in Europe only. It included editorial changes, update to Sponsor contact, correction of spelling errors, and clarification regarding the timing of BAS dosing, definition of study end and dosing instructions regarding other antacids;
- Protocol 747-301, Amendment 2 (Version 2, dated 04 Apr 2012): This protocol amendment addressed comments raised by Investigators and included other editorial changes and clarifications by the Sponsor.
- Protocol 747-301, Amendment 3 (Version 3, dated 24 Sep 2012): This protocol amendment included additional minor editorial changes and clarifications.

Major Protocol deviations per category and treatment group are summarized in Table 11. Four were due to exclusion criterion number 3 (i.e., subjects with severe pruritus or requiring systemic treatment for pruritus with BAS or rifampicin within 2 months of Day 0 will be excluded).

The deviations are as follows:

- Three subjects (two on placebo and one OCA titration) received BAS within 2 months of Randomization (Day 0) and thus were excluded from both the EE and PK populations.
- One subject (OCA 10 mg) also received BAS within 2 months prior to Randomization (Day 0). The subject was excluded from the PK population.
- One subject (OCA titration) had a visit schedule deviation per the Investigator; however, it is the Sponsor's assessment the subject had a deviation from inclusion criterion 5 (any measure of contraception). One subject (placebo) was noncompliant with investigational product for >1 month direction from their physician to intermittently stop taking the investigational product. The subject was excluded from both the EE and PK populations.

Table 10: Major Protocol Deviations: ITT Population (N = 216)

	Number of Subjects, n (%)			
	Placebo (N = 73)	Titration OCA (N = 70)	OCA 10 mg (N = 73)	Total (N = 216)
Major Protocol Deviation				
Inclusion/Exclusion Deviations	2 (3)	1 (1)	1 (1)	4 (2)
Noncompliance	1 (1)	0	0	1 (<1)
Visit Schedule	0	1 (1)	0	1 (<1)

Baseline data

A total of 216 patients were included, 81% of them were <65 years of age, predominantly female (91%) and white (94%). The majority of the population was European (67%), followed by North American (29%), and Australian (4%). The mean body weight and BMI were 69.8 kg and 26.0 kg/m2, respectively,

with 82% of subjects having a BMI <30 kg/m2. The majority (93%) of the population was on UDCA at Baseline.

Table 11: Demographic and Baseline Characteristics: ITT Population (N = 216)

Number of Subjects	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)	Total (N = 216)
Age (years)				
n	73	70	73	216
Mean (SD)	55.5 (10.0)	55.8 (10.5)	56.2 (11.0)	55.8 (10.5)
Median	55.0	54.5	56.0	55.0
Min, Max	35, 78	29, 83	30, 86	29, 86
Age subgroups, n (%)				
<65 years	60 (82)	60 (86)	56 (77)	176 (81)
≥65 years	13 (18)	10 (14)	17 (23)	40 (19)
Sex, n (%)				
Male	5 (7)	5 (7)	10 (14)	20 (9)
Female	68 (93)	65 (93)	63 (86)	196 (91)
Race/Ethnicity, n (%)				
White	66 (90)	67 (96)	70 (96)	203 (94)
Non-White	7 (10)	3 (4)	3 (4)	13 (6)
Body Weight (kg)				
n	73	70	73	216
Mean (SD)	70.2 (13.3)	68.2 (13.1)	71.0 (15.3)	69.8 (13.9)
Median	70.5	65.2	67.6	67.5
Min, Max	41.0, 106.0	46.7, 101.8	50.8, 134.0	41.0, 134.0
Region, n (%)				
Europe	49 (67)	45 (64)	51 (70)	145 (67)
North America	21 (29)	20 (29)	21 (29)	62 (29)
Australia	3 (4)	5 (7)	1 (1)	9 (4)
BMI (kg/m^2)				
n	73	70	73	215
Mean (SD)	26.2 (4.4)	25.8 (4.9)	26.3 (5.1)	26.0 (4.8)
Median	25.9	24.5	25.1	25.0
Min, Max	16.4, 37.6	17.7, 40.7	20.4, 49.2	16.4, 49.2
BMI subgroups, n (%)				
<30 kg/m^2	58 (79)	58 (83)	61 (84)	177 (82)
≥30 kg/m^2	15 (21)	11 (16)	12 (16)	38 (18)
Pretreatment Liver Biopsy Performed, n (%)				
Yes	7 (10)	13 (19)	9 (12)	29 (13)
No	66 (90)	57 (81)	64 (88)	187 (87)
UDCA Use at Baseline, n (%)				
Yes	68 (93)	65 (93)	67 (92)	200 (93)
No	5 (7)	5 (7)	6 (8)	16 (7)

PBC Baseline disease characteristics are summarized in Table 13. In general, each variable was well balanced across treatment groups. Overall, the median age at time of diagnosis was 47.5 years. The mean duration of PBC at time of study entry was 8.6 years, with a comparable percentage of subjects with a duration of PBC of ≤7.5 years versus >7.5 years. There were slightly more subjects at Baseline <50 years of age at PBC diagnosis (58%), compared with ≥50 years of age at PBC diagnosis (42%).

At Baseline, 128 (59%) subjects reported pruritus assessed by the Investigator as follows: 43% mild, 15% moderate, and 1% severe. The overall incidence of pruritus at Baseline was slightly higher for subjects in the placebo treatment group (64%) and OCA 10 mg group (60%), compared with the OCA titration group (53%). A total of 128 (59%) subjects reported a history of fatigue prior to entering the study, with the incidence in the severity of the most recent fatigue events as follows: 34% mild, 19% moderate, and 5% severe. The overall incidence of fatigue was slightly higher for subjects in the placebo treatment group (67%), compared with the OCA titration and OCA 10 mg groups (54% to 56%, respectively).

Table 12: PBC Disease Characteristics: ITT Population (N = 216)

Disease Characteristic	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)	Total (N = 216)
History of Pruritus, n (%)				
Yes	47 (64)	45 (64)	45 (62)	137 (63)
No	26 (36)	25 (36)	28 (38)	79 (37)
Severity of Most Recent Pruritus Event for Subjects who had a History of Pruritus, n (%)				
n	n = 47	n = 45	n =45	n = 137
Mild	31 (66)	29 (64)	34 (76)	94 (69)
Moderate	14 (30)	13 (29)	8 (18)	35 (26)
Severe	1 (2)	2 (4)	3 (7)	6 (4)
Unknown	1 (2)	1 (2)	0 (0)	2 (1)
Pruritus at Baseline[a], n (%)				
Yes	47 (64)	37 (53)	44 (60)	128 (59)
Mild	32 (44)	27 (39)	33 (45)	92 (43)
Moderate	13 (18)	10 (14)	10 (14)	33 (15)
Severe	2 (3)	0 (0)	1 (1)	3 (1)
No	26 (36)	33 (47)	29 (40)	88 (41)
History of Fatigue, n (%)				
Yes	49 (67)	38 (54)	41 (56)	128 (59)
No	24 (33)	32 (46)	32 (44)	88 (41)
Overall Severity of PBC Related Fatigue, n (%)				
n	n = 73	n = 70	n = 73	n = 216
Mild	28 (38)	17 (24)	29 (40)	74 (34)
Moderate	16 (22)	16 (23)	8 (11)	40 (19)
Severe	3 (4)	5 (7)	3 (4)	11 (5)
Age at PBC diagnosis (years)				
Mean (SD)	47.3 (9.3)	47.6 (11.7)	47.1 (10.6)	47.3 (10.5)
Median	48.0	48.0	47.0	47.5
Min, Max	31, 74	25, 82	24, 78	24, 82
Age at PBC Diagnosis Subgroups, n (%)				
<50 years	45 (62)	38 (54)	42 (58)	125 (58)
≥50 years	28 (38)	32 (46)	31 (42)	91 (42)

Duration of PBC (Years)				
Mean (SD)	8.3 (5.4)	8.3 (5.8)	9.2 (6.9)	8.6 (6.0)
Median	7.4	7.2	8.5	7.8
Min, Max	0.9, 21.8	0.3, 27.0	0.0, 32.3	0.0, 32.3
Duration of PBC Subgroups, n (%)				
≤7.5 years	39 (53)	36 (51)	30 (41)	105 (49)
>7.5 years	34 (47)	34 (49)	43 (59)	111 (51)

[a] Based on "Is the subject currently experiencing pruritus?" and the severity of pruritus collected Day 0 VAS eCRF.

Mean Baseline laboratory values indicative of intrahepatic cholestasis, hepatocellular injury, and synthetic hepatic function were well balanced across treatment groups. In addition, the majority (94% to 99%) of subjects had a Baseline INR ≤1.3, further indicative of a PBC subject population in an earlier stage of disease progression. However, the mean conjugated bilirubin levels at Baseline were above the ULN (approximately 1.5x to 2.0x ULN) indicating evidence of some hepatic dysfunction in the study population.

Mean Baseline ALP values were well balanced across treatment groups (327.5 U/L, 325.9 U/L, and 316.3 U/L for placebo, OCA titration, OCA 10 mg groups, respectively), with 29% of subjects with a Baseline ALP >3x ULN. Mean Baseline total bilirubin values ranged from 10.3µmol/L to 11.8µmol/L across treatment groups, with 92% of subjects within normal range.

GGT was substantially elevated across all 3 treatment groups (approximately 9x ULN to 12x ULN). Mean Baseline GGT levels were slightly higher in the placebo group (309.6 U/L), compared with OCA titration (252.8 U/L) and OCA 10 mg (261.1 U/L) groups; however, it should be noted the placebo group had a larger degree of variability compared to the OCA groups. Hepatocellular transaminases (ALT and AST) were also elevated across all treatment groups, albeit to a much smaller magnitude (approximately 2x ULN) compared with GGT.

Medical history abnormalities were generally similar across treatments and were most commonly reported in the following system categories, which were consistent with the underlying disease and/or the predominance of females in the study: musculoskeletal (67%), genitourinary/reproductive (61%), gastrointestinal (54%), hepatic (49%), endocrine and metabolic (47%), and dermatological (43%), and cardiovascular (39%). For the hepatic system category, the recording of PBC medical history was inconsistent across sites and thus does not total to 100%.

Concomitant Medications

New concomitant medications were defines as those medications that were started on or after the initial dose of investigational product. New concomitant medications that were most commonly taken overall (>10% of subjects) included: anilides (eg, acetaminophen, paracetamol; 29%), BAS (19%), propionic acid derivatives (eg, ibuprofen, naproxen; 19%), proton pump inhibitors (18%), and penicillins with extended spectrum (11%). A higher incidence of propionic acid derivatives and BAS was observed in both OCA treatment groups, compared with the placebo group. Consistent with the higher incidence of pruritus observed in OCA-treated subjects as compared to placebo-treated subjects, the incidence of new BAS was 11%, 20%, and 27%, for the placebo, OCA titration, and OCA 10 mg groups, respectively.

Numbers analysed

The percentage of subjects in each analysis population is summarized in Table 14.

Table 13: Analysis Populations

	Number of Subjects, n (%)			
	Placebo	OCA Titration	OCA 10 mg	Total
Enrolled / Randomized	73	71	73	217
ITT Population,[a] n (%)[b]	73 (100)	70 (99)	73 (100)	216 (<100)
Completer Population,[c] n (%)[b]	70 (96)	64 (90)	64 (88)	198 (91)
EE Population[d] n (%)[b]	67 (92)	63 (89)	62 (85)	192 (88)
PK Population[e] n (%)[b]	0 (0)	66 (93)	60 (82)	126 (58)
Safety Population[f] n (%)[b]	73 (100)	70 (99)	73 (100)	216 (<100)

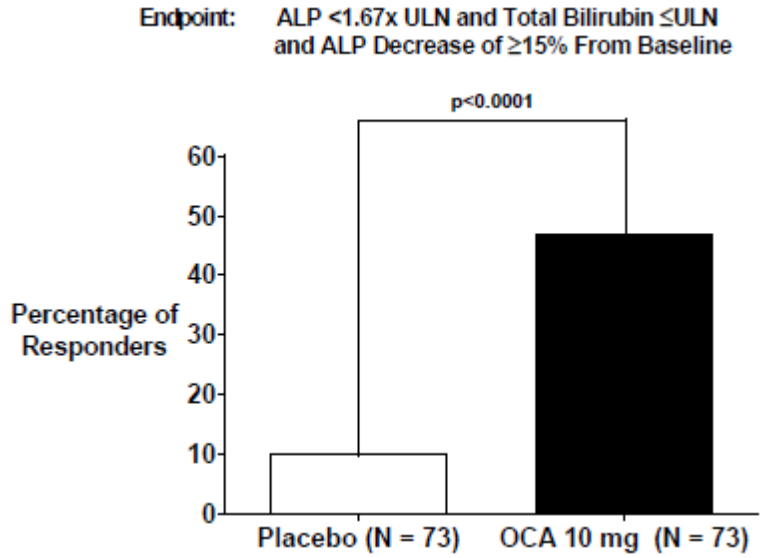
a All randomized subjects who received at least 1 dose of investigational product. Treatment assignment is based on the randomized treatment. b Denominator is based off the number of subjects from the ITT population. c All randomized subjects who received at least 1 dose of investigational product and participated through the end of the double-blind phase (Month 12). Treatment assignment is based on the randomized treatment. d All subjects in the Completer Population who did not have any major protocol deviations that could have potentially affected the efficacy of the investigational product. Treatment assignment is based on the randomized treatment. e All randomized subjects who received at least 1 dose of OCA who have at least 1 confirmed fasted sample at Month 6 or Month 12 visits (subject must have been fasting for approximately 8 hours prior to the visit) and who did not have any major protocol deviations that could have potentially affected exposure levels. f All subjects who received at least one dose of study drug. Treatment assignment was based on the treatment actually received.

Outcomes and estimation

Primary Efficacy Endpoint

In the primary analysis, the OCA 10 mg treatment group was superior to placebo in achieving the primary efficacy composite endpoint (Figure 14). At Month 12, a total of 34 (47%) subjects from the OCA 10 mg group achieved the composite endpoint, compared with 7 (10%) subjects from the placebo group. The difference between placebo and the OCA 10 mg group was statistically significant (p <0.0001).

Figure 14: Percentage of Subjects Achieving Primary Efficacy Composite Endpoint at Month 12 Using Imputed Data: ITT Population (Placebo and OCA 10 mg,N = 146)



Missing values were considered a non-response. p-value obtained using CMH test stratified by randomization strata factor.

Key Secondary Endpoint

The key secondary endpoint was the percentage of subjects from the OCA titration group achieving the composite endpoint at Month 12.

A total of 32 (46%) subjects in the OCA titration group achieved the composite endpoint at Month 12 compared with 7 (10%) subjects in the placebo group. The difference between placebo and the OCA titration group was statistically significant (p <0.0001).

Both OCA treatment groups were superior to placebo in achieving the composite endpoint at all timepoints across the 12-month treatment period (p<0.0001 versus placebo). At Month 6, a higher percentage of subjects in the OCA 10 mg group (51%) achieved the composite endpoint compared with the OCA titration group (34%), which was statistically significant (p-value = 0.0358; Month 6 was the only visit statistical testing between the 2 treatment groups was performed).

Other Secondary Endpoints

ALP

The LS mean (SE) absolute and percent change from Baseline in ALP at Month 6 and Month 12 for the ITT population is shown in Table 15.

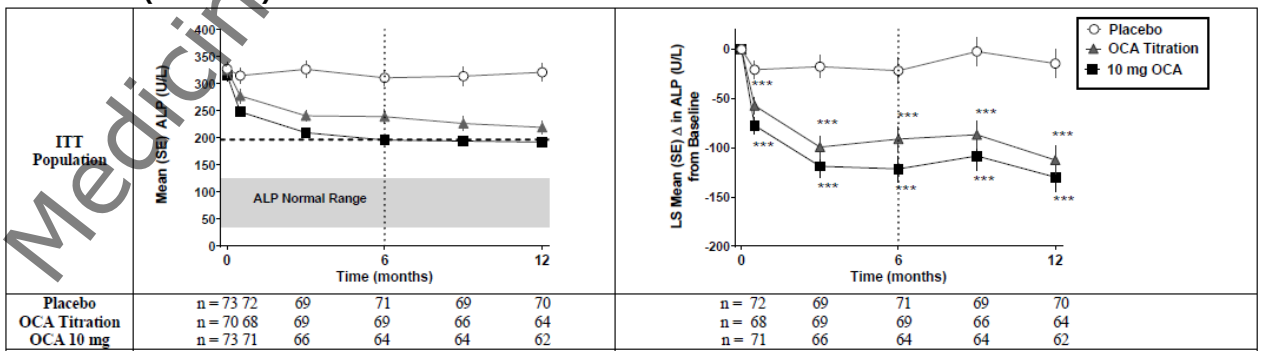
Table 14: ALP Absolute and Percent Change From Baseline at Month 6 and Month 12: ITT Population (N = 216)

	Placebo		OCA Titration		OCA 10 mg	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
ALP (U/L)						
Baseline	73	327.5 (13.5)	70	325.9 (13.9)	73	316.3 (12.2)
Month 6	71	311.1 (14.4)	69	239.3 (13.2)	64	196.1 (8.4)
LS Mean Absolute Change	71	-21.7 (13.2)	69	-91.2 (12.9)	64	-121.5 (13.2)
OCA – Placebo Difference	NA		-69.6 (11.7)		-99.9 (12.0)	
p-value	NA		<0.0001		<0.0001	
LS Mean Percent Change	71	-6.8 (3.5)	69	-27.4 (3.4)	64	-36.5 (3.5)
OCA – Placebo Difference	NA		-20.7 (3.1)		-29.8 (3.2)	
p-value	NA		<0.0001		<0.0001	
Month 12	70	321.3 (17.1)	64	219.5 (12.5)	62	192.3 (7.8)
LS Mean Absolute Change	70	-14.4 (14.7)	64	-112.5 (14.4)	62	-129.9 (14.6)
OCA – Placebo Difference	NA		-98.1 (13.1)		-115.5 (13.2)	
p-value	NA		<0.0001		<0.0001	
LS Mean Percent Change	70	-4.8 (3.8)	64	-33.0 (3.7)	62	-39.1 (3.8)
OCA – Placebo Difference	NA		-28.2 (3.4)		-34.4 (3.4)	
p-value	NA		<0.0001		<0.0001	
ALP ULN = 118.3 U/L (females) and 124.2 U/L (males)						

Baseline is defined as the mean of all available evaluations prior to treatment. p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor. For both OCA treatment groups improvements from Baseline were observed at both Month 6 and Month 12, compared with placebo (p <0.0001 versus placebo). At Month 12, the LS mean percent change from Baseline was -33% and -39% for the OCA titration and 10 mg groups, respectively, compared with only -5% for the placebo group.

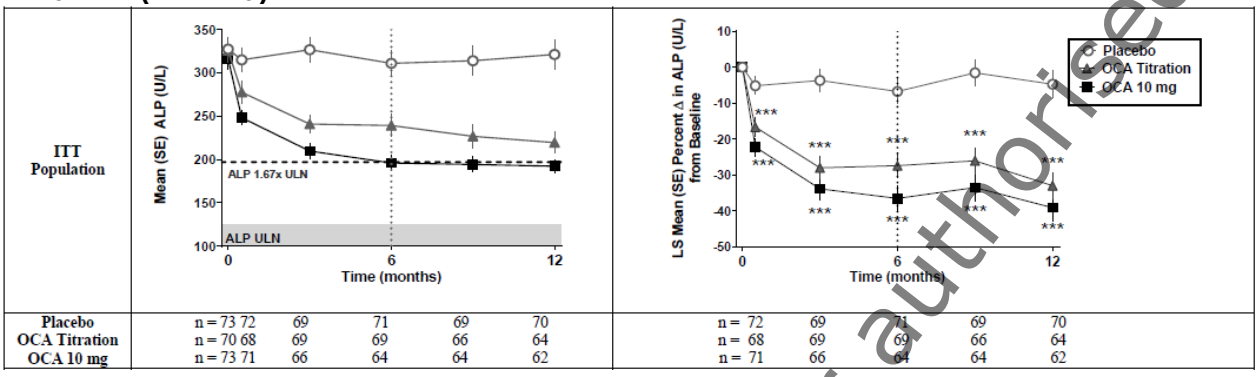
ALP changes over time are summarized in Figure 15 (absolute change) and Figure 16(percent change) for the ITT population. The y-axis of the figure also denotes 1.67x ULN for ALP, which has been shown to be predictive of improved transplant-free survival independent of total bilirubin.

Figure 15: (modified by the assessor): ALP Values and Absolute Change from Baseline Over Time: ITT (n = 216)



***p <0.0001 vs placebo; p-value for comparing active treatments to placebo is obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor. Given the majority of the population was female, ALP ULN values shown were based on criteria for females (118.3 U/L).

Figure 16: (modified by the assessor): ALP Values and Percent Change from Baseline Over Time: ITT (n = 216)



Placebo	n = 73	72	69	71	69	70	n = 72	69	71	69	70
OCA Titration	n = 70	68	69	69	66	64	n = 68	69	69	66	64
OCA 10 mg	n = 73	71	66	64	64	62	n = 71	66	64	64	62

*p <0.0001 vs. placebo; p-values were obtained using P-value for comparing active treatments to placebo is obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor. Given the majority of the population was female, ALP ULN values shown are based on criteria for females (ULN: 118.3 U/L). Across the 3 treatment groups, mean ALP values at Baseline were well balanced, and approximately one-third of subjects had an ALP >3x ULN. Treatment with OCA (titration or10 mg) resulted in statistically significant improvements in ALP levels as early as 2 weeks of treatment. For the OCA 10 mg group, the mean reduction in ALP peaked at Month 6 (at approximately 1.67x ULN) and was sustained through Month 12. For the OCA titration group, the mean reduction had not plateaued at Month 12 (approaching 1.67x ULN).

For placebo-treated subjects, ALP values remained similar to Baseline values throughout the 12-month treatment period. It should also be noted that during the initial 6 months of treatment, the OCA 10 mg group had larger reductions from Baseline, compared with the OCA titration group (i.e., 5 mg), further supportive of a dose response between OCA 5 mg and 10 mg.

For both OCA groups (ITT population), the difference in LS mean (SE) absolute and percent reductions from Baseline in ALP were statistically significant ($p \leq 0.0001$) at all timepoints relative to placebo. Similar statistically significant results were observed for the EE and Completer populations (not shown).

Total Bilirubin and Conjugated Bilirubin

The LS mean (SE) absolute and percent change from Baseline to Month 6 and Month 12 are summarized in Table 16(total bilirubin) and Table 17 (conjugated bilirubin). Bilirubin and conjugated bilirubin data are summarized over the 12-month period in Figure 17 and Figure 18, respectively, for the ITT population.

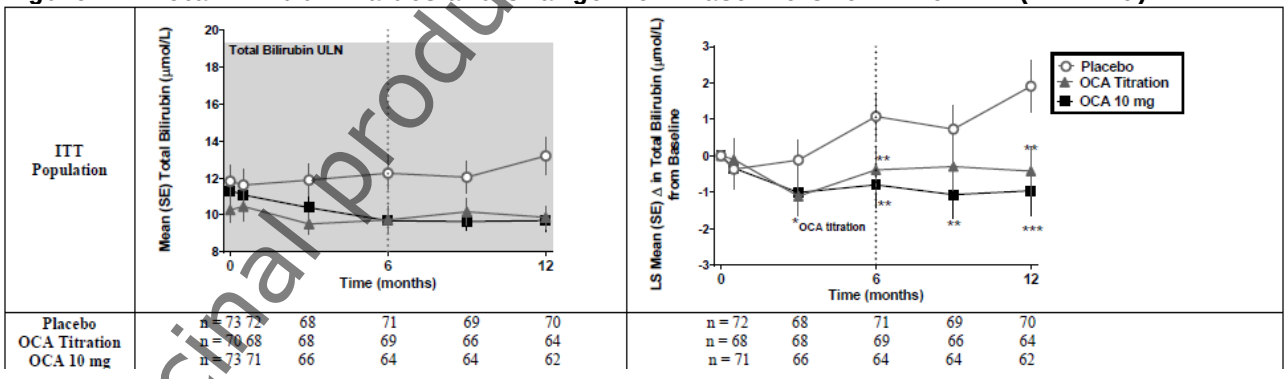
For the ITT population, the Baseline mean total bilirubin was below the ULN (19µmol/L for females, 25µmol/L for males) for all treatment groups. Decreases in the absolute change from Baseline in total bilirubin were observed for both OCA treatment groups, compared with increases for the placebo treatment group. The difference in the absolute change from Baseline in total bilirubin between placebo and each respective OCA treatment group was statistically significant (p <0.01) at Month 6 and all subsequent timepoints (Figure 17) with the exception of the OCA titration group at Month 9.

Table 15: Total Bilirubin Absolute and Percent Change From Baseline at Month 6 and Month 12: ITT Population (N = 216)

	Placebo		OCA Titration		OCA 10 mg	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Total Bilirubin (µmol/L)						
Baseline	73	11.8 (0.9)	70	10.3 (0.7)	73	11.3 (0.8)
Month 6	71	12.3 (0.9)	69	9.7 (0.7)	64	9.7 (0.5)
LS Mean Absolute Change	71	1.1 (0.6)	69	-0.4 (0.6)	64	-0.8 (0.6)
OCA – Placebo Difference		NA		-1.5 (0.6)		-1.9 (0.6)
p-value				**0.0089**		**0.0011**
LS Mean Percent Change	71	13.8 (8.8)	69	-3.0 (8.6)	64	7.4 (8.9)
OCA – Placebo Difference				-16.8 (8.1)		-6.5 (8.2)
p-value		NA		**0.0381**		**0.4307**
Month 12	70	13.2 (1.0)	64	9.9 (0.6)	62	9.7 (0.6)
LS Mean Absolute Change	70	1.9 (0.7)	64	-0.4 (0.7)	62	-1.0 (0.7)
OCA – Placebo Difference		NA		-2.3 (0.6)		-2.9 (0.7)
p-value				**0.0004**		**<0.0001**
LS Mean Percent Change	70	19.5 (6.8)	64	1.2 (6.7)	62	-0.2 (6.9)
OCA – Placebo Difference		NA		-18.3 (6.3)		-19.8 (6.3)
p-value				**0.0039**		**0.0020**
Total Bilirubin ULN: 19.32 µmol/L (Female) and 25.48 µmol/L (Male)						

Baseline is defined as the mean of all available evaluations prior to treatment. p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Figure 17: Total Bilirubin Values and Change from Baseline Over Time: ITT (n = 216)



*p <0.05, **p <0.01, ***p <0.0001; p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Given the majority of the population was female, ULN values shown are based on criteria for females (19.32 µmol/L).

For the ITT population, the Baseline conjugated bilirubin was elevated (approximately 1.5x ULN to 2x ULN) across treatment groups consistent with intrahepatic obstruction observed in PBC.

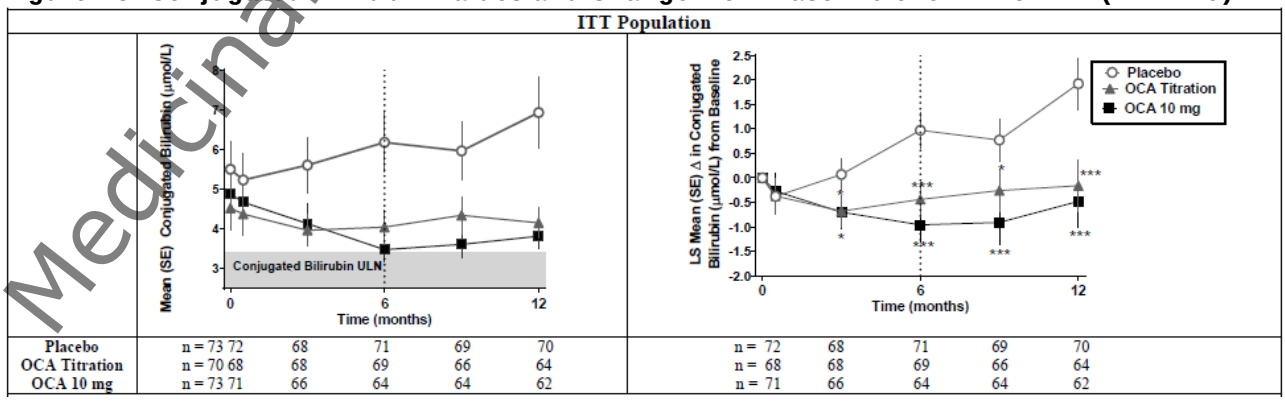
Mean Baseline conjugated bilirubin was 5.5 µmol/L, 4.5 µmol/L, and 4.9 µmol/L, for placebo, OCA titration, and OCA 10 mg, respectively. Both OCA-treatment groups approached the ULN for conjugated bilirubin (3.42 µmol/L), while placebo increased from Baseline at all timepoints. For both OCA treatment groups, statistically significant differences ($p<0.05$) in both the absolute and percent change from Baseline relative to placebo were observed at Month 3 and all subsequent timepoints. At Month 12, statistically significant differences at $p<0.0001$ for each OCA treatment group versus placebo were observed.

Table 16: Conjugated Bilirubin Absolute and Percent Change From Baseline at Month 6 and Month 12: ITT Population (N = 216)

	Placebo		OCA Titration		OCA 10 mg	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Conjugated Bilirubin (µmol/L)						
Baseline	73	5.5 (0.7)	70	4.5 (0.5)	73	4.9 (0.5)
Month 6	71	6.2 (0.8)	69	4.0 (0.4)	64	3.5 (0.3)
LS Mean Absolute Change	71	1.0 (0.4)	69	-0.4 (0.4)	64	-1.0 (0.4)
OCA – Placebo Difference	NA		-1.4 (0.3)		-1.9 (0.3)	
p-value	NA		**<0.0001**		**<0.0001**	
LS Mean Percent Change	71	23.0 (6.0)	69	-1.0 (6.0)	64	-6.0 (7.0)
OCA – Placebo Difference	NA		-24.0 (6.0)		-28.0 (6.0)	
p-value	NA		**0.0001**		**<0.0001**	
Month 12	70	6.9 (0.9)	64	4.2 (0.4)	62	3.8 (0.3)
LS Mean Absolute Change	70	1.9 (0.5)	64	-0.2 (0.5)	62	-0.5 (0.5)
OCA – Placebo Difference	NA		-2.1 (0.5)		-2.4 (0.5)	
p-value	NA		**<0.0001**		**<0.0001**	
LS Mean Percent Change	70	39.0 (7.0)	64	12.0 (7.0)	62	5.0 (7.0)
OCA – Placebo Difference	NA		-27.0 (7.0)		-34 (7.0)	
p-value	NA		**<0.0001**		**<0.0001**	
Conjugated Bilirubin ULN: 3.42 µmol/L (Female and Male)						

Baseline is defined as the mean of all available evaluations prior to treatment.p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Figure 18: Conjugated Bilirubin Values and Change from Baseline over Time: ITT (N = 216)



*p <0.05, **p <0.01, ***p <0.0001; p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor. Conjugated Bilirubin ULN = 3.42 µmol/L for both females and males.

Similar trends were observed for both total bilirubin and conjugated bilirubin for the EE and the Completer populations (not shown).

GGT, ALT, and AST

Values over time are summarized in Figure 19 and individually in Table 18, Table 19, and Table 20, respectively.

Baseline GGT was substantially elevated across all 3 treatment groups (approximately 9x ULN to 12x ULN). Mean hepatocellular transaminases (ALT and AST) were also elevated at Baseline, albeit to a smaller magnitude (approximately 2x ULN) compared with GGT. This is not unexpected given that PBC is often associated with mild and less consistent elevations of ALT and AST, which are typically more indicative of liver damage rather than intrahepatic cholestasis.

Table 17: GGT Absolute and Percent Change From Baseline at Month 6 and Month 12: ITT Population (n = 216)

	Placebo		OCA Titration		OCA 10 mg	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
GGT (U/L)						
Baseline	73	309.6 (52.6)	70	252.8 (20.0)	73	261.1 (24.3)
Month 6	71	270.7 (41.0)	69	136.4 (12.3)	64	95.2 (11.4)
LS Mean (SE) Absolute Change	71	-32.4 (19.3)	69	-132.1 (18.8)	64	-181.5 (19.6)
OCA – Placebo Difference	NA		-99.8 (17.5)		-149.2 (17.8)	
p-value	NA		<0.0001		<0.0001	
LS Mean (SE) Percent Change	71	-9.0 (5.0)	69	-44.0 (4.8)	64	-64.1 (5.1)
OCA – Placebo Difference	NA		-35.0 (4.5)		-55.1 (4.6)	
p-value	NA		<0.0001		<0.0001	
Month 12	70	301.8 (51.1)	64	114.2 (12.5)	62	91.9 (10.2)
LS Mean (SE) Absolute Change	70	6.7 (25.6)	64	-140.8 (24.7)	62	-176.7 (25.6)
OCA – Placebo Difference	NA		-147.5 (23.1)		-183.4 (23.3)	
p-value	NA		<0.0001		<0.0001	
LS Mean (SE) Percent Change	70	0.8 (5.7)	64	-50.3 (5.5)	62	-63.7 (5.7)
OCA – Placebo Difference	NA		-51.1 (5.1)		-64.5 (5.2)	
p-value	NA		<0.0001		<0.0001	
GGT ULN: 23.6 U/L (Female) and 35.2 U/L (Male)						

Baseline is defined as the mean of all available evaluations prior to treatment. p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Table 18: ALT Absolute and Percent Change From Baseline at Month 6 and Month 12: ITT Population (n = 216)

	Placebo		OCA Titration		OCA 10 mg	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
ALT (U/L)						
Baseline	73	56.0 (3.5)	70	61.6 (4.7)	73	56.3 (4.7)
Month 6	71	49.7 (3.0)	69	40.7 (3.8)	64	32.7 (2.2)
LS Mean (SE) Absolute Change	71	-6.8 (3.0)	69	-18.8 (3.0)	64	-23.4 (3.1)
OCA – Placebo Difference	NA		-12.0 (2.8)		-16.5 (2.8)	
p-value	NA		**<0.0001**		**<0.0001**	
LS Mean (SE) Percent Change	71	-9.3 (3.8)	69	-31.1 (3.8)	64	-36.2 (3.9)
OCA – Placebo Difference	NA		-21.9 (3.5)		-26.9 (3.5)	
p-value	NA		**<0.0001**		**<0.0001**	
Month 12	70	52.8 (3.4)	64	39.0 (4.2)	62	32.1 (2.6)
LS Mean (SE) Absolute Change	70	-5.0 (3.3)	64	-21.3 (3.3)	62	-25.3 (3.4)
OCA – Placebo Difference	NA		-16.3 (3.0)		-20.4 (3.1)	
p-value	NA		**<0.0001**		**<0.0001**	
LS Mean (SE) Percent Change	70	-4.7 (5.0)	64	-35.5 (4.9)	62	-41.7 (5.0)
OCA – Placebo Difference	NA		-30.9 (4.5)		-37.0 (4.6)	
p-value	NA		**<0.0001**		**<0.0001**	
ALT ULN: 22.9 U/L (Female) and 33.4 U/L (Male)						

Baseline is defined as the mean of all available evaluations prior to treatment. p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Table 19: AST Absolute and Percent Change From Baseline at Month 6 and Month 12: ITT Population (n = 216)

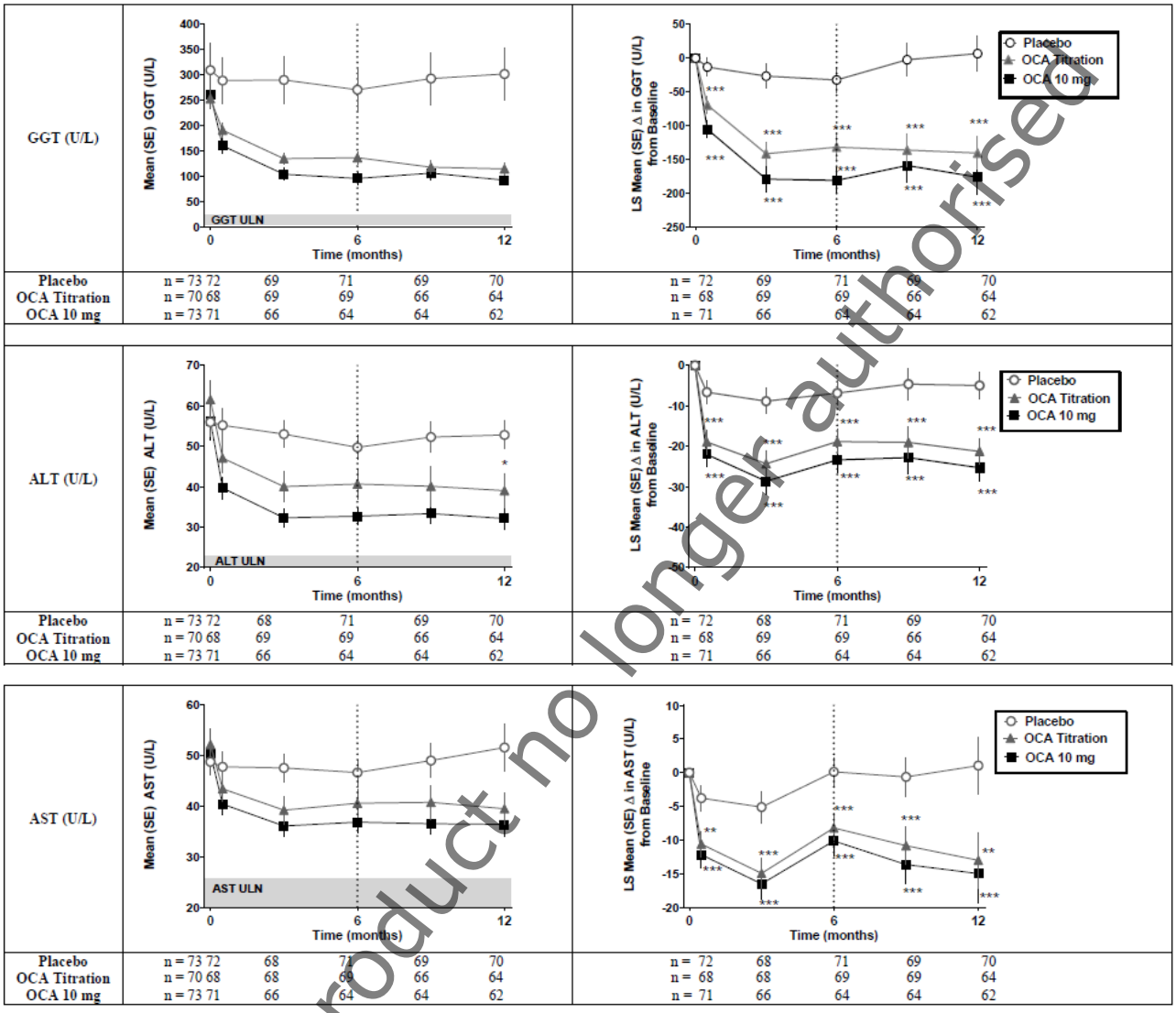
	Placebo		OCA Titration		OCA 10 mg	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
AST (U/L)						
Baseline	73	48.8 (2.6)	70	52.3 (3.0)	73	50.5 (3.6)
Month 6	71	46.7 (2.5)	69	40.6 (2.7)	64	36.8 (2.1)
LS Mean (SE) Absolute Change	71	0.1 (2.2)	69	-8.2 (2.1)	64	-10.2 (2.2)
OCA – Placebo Difference	NA		-8.3 (2.0)		-10.3 (2.0)	
p-value	NA		**<0.0001**		**<0.0001**	
LS Mean (SE) Percent Change	71	2.1 (3.5)	69	-15.4 (3.5)	64	-15.4 (3.6)
OCA – Placebo Difference	NA		-17.5 (3.2)		-17.5 (3.2)	
p-value	NA		**<0.0001**		**<0.0001**	
Month 12	70	51.6 (4.7)	64	39.5 (3.1)	62	36.4 (2.4)
LS Mean (SE) Absolute Change	70	1.0 (4.2)	64	-13.0 (4.2)	62	-15.0 (4.3)
OCA – Placebo Difference	NA		-14.1 (3.8)		-16.0 (3.9)	
p-value	NA		**0.0003**		**<0.0001**	
LS Mean (SE) Percent Change	70	7.7 (8.8)	64	-21.9 (8.7)	62	-23.7 (8.9)
OCA – Placebo Difference	NA		-29.6 (8.0)		-31.4 (8.1)	
p-value	NA		**0.0003**		**0.0001**	
AST ULN: 25.7 U/L (Female) and 33.0 U/L (Male)						

Baseline is defined as the mean of all available evaluations prior to treatment. p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor.

As shown in Figure 19, subjects treated with OCA (10 mg or titration) had statistically significant improvements from Baseline in all 3 laboratory parameters (GGT, ALT, and AST). Improvements were observed as early as 2 weeks, with the largest magnitude of response generally observed by Month 3. Following Month 3, the magnitude of response was sustained through Month 12 for GGT values, while the response was more variable for ALT and AST values. Notably, the mean ALT values for the OCA 10 mg group approached within normal limits by Month 3, which was sustained for the remainder of the treatment period. For both OCA treatment groups and across all 3 liver parameters, the differences in LS mean (SE) reductions from Baseline were statistically significant at all timepoints relative to placebo (p-value $\leq$ 0.0001 for placebo versus each OCA treatment group for all 3 parameters with the exception of the OCA titration group for AST at Week 2 [p = 0.0004] and Month 12 [p = 0.0003]).

At Month 12, LS mean percent changes from Baseline in the OCA titration and 10 mg groups were respectively: GGT -50.3% and -63.7%, ALT: -35.5% and -41.7%, and AST -21.9% and -23.7% (Table 18, Table 19, and Table 20).

Figure 19: GGT, ALT, and AST Values and Change from Baseline Over Time: ITT Population (n = 216)



**p <0.01; ***p ≤ 0.0001; P-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor. Given the majority of the population was female, ULN values are based on criteria for females (i.e., GGT 23.6 U/L, ALT 22.9 U/L, and AST 25.7 U/L). In contrast, for placebo-treated subjects, GGT, ALT, and AST values remained similar to Baseline values throughout the 12-month treatment period. The difference from placebo was statistically significant for all 3 parameters at Month 12(p-value<0.0001 for placebo versus each treatment group for all 3 parameters with the exception of the OCA titration group for AST p = 0.0003).

Albumin, Prothrombin Time, and INR

Baseline albumin, prothrombin time, and INR values were within normal ranges across all 3 treatment groups. No clinically meaningful changes were observed in albumin and INR in OCA-treated or placebo-treated subjects. No statistical differences between placebo and OCA treatment groups were observed; however, there was no worsening of these parameters over the 12-month period.

No clinically meaningful or statistically significant differences from Baseline were observed for this parameter (p-value of OCA versus placebo not significant for either OCA treatment group).

Indirect Inflammatory markers

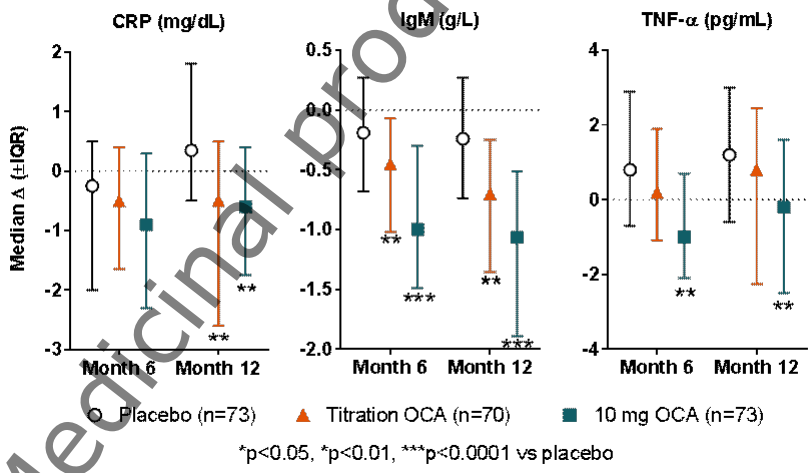
CRP: In Study 747-301, statistically significant decreases in CRP values were observed at Month 6 and Month 12 for both OCA treatment groups. The median (IQR) change at Month 12 was statistically superior to placebo (p = 0.0022).

Decreases from baseline in the median (IQR) plasma CK-18 levels values were observed for both OCA treatment groups at Month 6 and Month 12, while increases from baseline were observed for placebo-treated subjects. The median median (IQR) changes between placebo and OCA titration and OCA 10 mg were statistically significant.

TNF-α:

Baseline median (IQR) levels were above the ULN (8.1 pg/mL) for TNF-α across all 3 treatment groups and slightly higher in placebo (11.8 [10.1, 15.2]) compared to the OCA titration (10.1 [8.2, 12.5]) and OCA 10 mg (10.8 [8.9, 13.8]) groups. Despite having a lower Baseline, the OCA titration group had smaller increases in TNF-α at Month 6 and Month 12, compared with placebo, while decreases from Baseline were observed for the OCA 10 mg group. The differences in the change from Baseline compared to placebo was significant for the OCA 10 mg treatment group at Month 6 (p = 0.0002) and Month 12 (p = 0.0077).

IgM: Median (IQR) Baseline IgM levels were 4.44 (3.16, 5.42) g/L, 3.73 (2.33, 5.77) g/L, and 3.51 (2.49, 5.56) g/L for the placebo, OCA titration, and OCA 10 mg groups, respectively (IgM ULN = 2.3 g/L). Median (IQR) values were markedly reduced at both Month 6 and Month 12 for the OCA titration and OCA 10 mg groups, compared with minimal decrease in the placebo group. At Month 12, median IgM values approached the ULN for both the OCA titration and OCA 10 mg groups, with the 25th percentile within the normal range. A statistically significant difference was observed at both Month 6 (p = 0.0039 for OCA titration, p <0.0001 for OCA 10 mg) and Month 12 (p = 0.0004 for OCA titration, p <0.0001 for OCA 10 mg) for both OCA treatment groups compared with placebo.

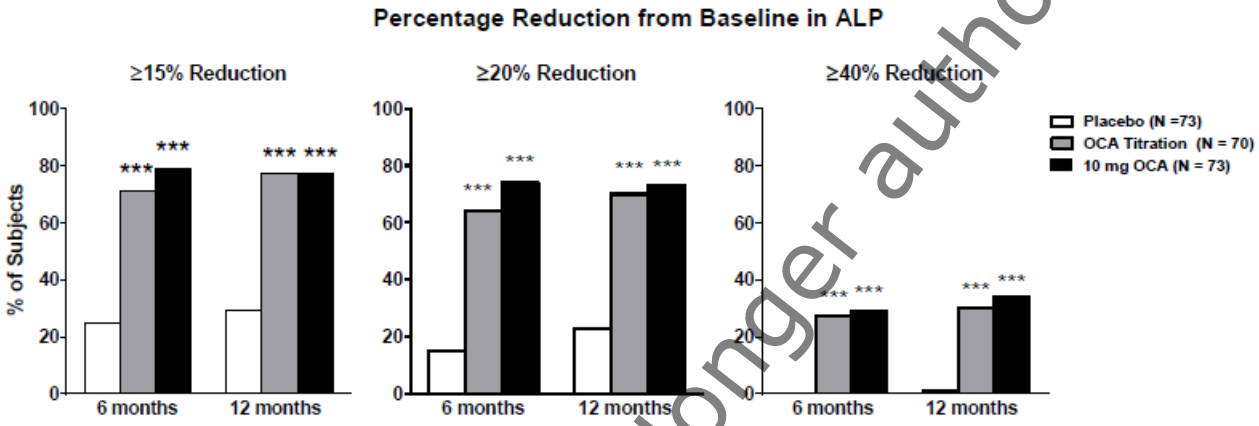


Responder Analyses

ALP

At Month 6 and Month 12 and for each ALP category, a statistically significantly higher percentage of OCA-treated subjects achieved the reduction in ALP compared with placebo (p ≤0.0001 versus placebo) (Figure 20). At Month 12, 21 (30%)and 25 (34%) subjects from the OCA titration and OCA 10 mg groups, respectively, achieved an ALP reduction from Baseline ≥40% compared with 1 (1%) placebo subject. Notably a decrease of ALP of >40% in patients with PBC has been associated with survival rates comparable to healthy matched control populations.

Figure 20: Percentage of Subjects Achieving ALP Response Criteria: ITT Population (n = 216)



Missing values were considered a non-response, thus, n at each timepoint was 73 for placebo, 70 for OCA titration, and 73 for OCA 10 mg. *p >0.0001; p-value obtained using the CMH test stratified by randomization strata factor.

The odds ratios of achieving a reduction (Table 21) at Month 12 were 8.4 (≥15%), 7.8 (≥20%), and34.7 (≥40%) for the OCA titration group and 8.2 (≥15%), 8.8 (≥20%), and 43.0 (≥40%) for the OCA 10 mg group. At Month 6, the odds ratios were greater for the OCA 10 mg group compared to OCA titration group (i.e., 5 mg) for reductions from Baseline of ≥15% and ≥20%, indicative of a dose response; however, the odd ratios were generally comparable at Month 12.

Table 20: Odds Ratio of Percentage Reduction in ALP From Baseline: ITT Population (n= 216)

Visit	≥15% Reduction		≥20% Reduction		≥40% Reduction	
	OCA Titration	OCA 10 mg	OCA Titration	OCA 10 mg	OCA Titration	OCA 10 mg
Month 6	7.8 (3.7, 16.5)	12.1 (5.5, 26.5)	10.2 (4.5, 22.8)	16.1 (7.0, 36.8)	NA	NA
p-value	<0.0001	<0.0001	<0.0001	<0.0001	NA	NA
Month 12	8.4 (4.0, 17.9)	8.2 (3.9, 17.3)	7.8 (3.7, 16.4)	8.8 (4.2, 18.7)	34.7 (4.4, 271.3)	43.0 (5.5, 334.9)
p-value	<0.0001	<0.0001	<0.0001	<0.0001	0.0007	0.0003

NA = not applicable given zero subjects from the placebo group achieved a ≥40% reduction from Baseline at Month 6.p-values for comparing treatments are obtained using a logistic regression model with terms for treatment and the randomization strata factor.

One (1%) subject from OCA titration group and 5 (7%) subjects from the OCA 10 mg group achieved ALP values within normal limits (i.e., 118 U/L [females] and 124 U/L [males]) at Month 12, while no placebo-treated subjects had an ALP value within the normal limits. The difference between the OCA 10 mg and placebo groups for achieving ALP <ULN was statistically significant (p = 0.0221).

Responders Based on of Biochemical Treatment Response Criteria

Several studies have evaluated other biochemical endpoints based on various combinations of markers of cholestasis, hepatocellular injury, and synthetic liver function (ALP, AST, total bilirubin, and albumin) in terms of predicting clinical outcomes and long-term prognosis of subjects with PBC. These endpoints are summarized in Table 22.

Table 21: Biochemical Treatment Response Criteria

Criteria Label	Endpoint	Reference
Paris I[a]	ALP ≤3x ULN, and AST ≤2x ULN, and Total Bilirubin ≤ULN[b]	(Corpechot 2008)
Paris II	ALP ≤1.5x ULN, and AST ≤1.5x ULN and Total Bilirubin ≤ULN	(Corpechot 2011)
Mayo II	ALP ≤1.67x ULN and Total Bilirubin ≤ULN	(Momah 2012)
Toronto II	ALP ≤1.76x ULN	(Kumagi 2010b)
Rotterdam	Normal: Normal Bilirubin and Normal Albumin (Normal bilirubin (values ≤ULN) and/or normal albumin (values ≥lower limit of normal [LLN]) Moderately Advanced: Abnormal Bilirubin or Abnormal Albumin Severe: Abnormal Bilirubin and Abnormal Albumin	(Kuiper 2009)

[a] This criteria was a stratification factor for randomization into this study.
[b] Deviation from Paris I: incorporation of total bilirubin ≤ULN instead of ≤1 mg/dL of normal total bilirubin levels.

A higher percentage of OCA-treated subjects responded to each respective endpoint at Month 6 and Month 12, compared with placebo-treated subjects. The difference between placebo and each OCA treatment group was statistically significant at both timepoints (Table 23). One exception was the Rotterdam criteria, wherein the number of subjects who were non-responders at Baseline was low (ie, most subjects were responders at Baseline defined as total bilirubin ≤ULN and an albumin ≥LLN). No statistical differences were noted for this endpoint, although the percentage of responders was numerically higher in the OCA-treated subjects.

Table 22: Percentage of Responders and Odds Ratios of Biochemical Treatment Response Criteria in Subjects Who Were Non-Responders at Baseline: ITT Population (n = 216)

ENDPOINT	Percentage of Responders at Month 6 and Month 12 in Subjects Who Were Non-responders at Baseline					
	Placebo		OCA Titration		OCA 10 mg	
	M6	M12	M6	M12	M6	M12
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Paris I: ALP ≤3x ULN and AST ≤2x ULN and Total Bilirubin ≤ULN[a]						
Non-responders at Baseline, N	34		36		35	
Responders, n (%)	6 (18)	6 (18)	20 (56)	23 (64)	18 (51)	20 (57)
p-value	NA	NA	**0.0013**	**0.0002**	**0.0025**	**0.0007**
Odds Ratio (CI)	NA	NA	6.0 (1.9, 18.6)	9.4 (2.8, 31.0)	5.2 (1.7, 16.0)	7.2 (2.2, 23.7)
p-value	NA	NA	**0.0019**	**0.0002**	**0.0045**	**0.0011**
Paris II: ALP ≤1.5x ULN and AST ≤1.5x ULN and Total Bilirubin ≤ULN						
Non-responders at Baseline, N	73		70		73	
Responders, n (%)	3 (4)	3 (4)	13 (19)	19 (27)	19 (26)	19 (26)
p-value	NA	NA	**0.0055**	**0.0001**	**0.0001**	**0.0002**
Odds Ratio (CI)	NA	NA	5.8 (1.5, 21.9)	9.1 (2.5, 32.6)	9.4 (2.6, 34.5)	8.5 (2.4, 30.6)
p-value	NA	NA	**0.0095**	**0.0007**	**0.0007**	**0.0010**
Mayo II: ALP ≤1.67x ULN and Total Bilirubin ≤ULN						
Non-responders at Baseline, N	73		69		73	
Responders, n (%)	8 (11)	11 (15)	23 (33)	32 (46)	38 (52)	36 (49)
p-value	NA	NA	**0.0010**	**<0.0001**	**<0.0001**	**<0.0001**
Odds Ratio (CI)	NA	NA	4.5 (1.8, 11.2)	5.7 (2.5, 13.1)	10.7 (4.3, 26.5)	6.4 (2.8, 14.7)
p-value	NA	NA	**0.0013**	**<0.0001**	**<0.0001**	**<0.0001**

Toronto II: ALP ≤1.76x ULN						
Non-responders at Baseline, N	70		67		70	
Responders, n (%)	10 (14)	11 (16)	31 (46)	34 (51)	41 (59)	42 (60)
p-value	NA	NA	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Odds Ratio (CI)	NA	NA	6.5 (2.7, 15.5)	7.2 (3.0, 17.2)	11.9 (4.9, 29.0)	11.5 (4.7, 27.7)
p-value	NA	NA	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Rotterdam (Normal Range): Total Bilirubin ≤ULN and Albumin ≥LLN						
Non-responders at Baseline, N	17		12		13	
Responders, n (%)	2 (12)	1 (6)	3 (25)	2 (17)	3 (23)	3 (23)
p-value	NA	NA	**0.4170**	**0.3537**	**0.3412**	**0.0992**
Odds Ratio (CI)	NA	NA	3.0 (0.4, 23.2)	4.3 (0.3, 58.8)	2.7 (0.4, 20.3)	6.2 (0.5, 72.0)
p-value	NA	NA	**0.2980**	**0.2704**	**0.3239**	**0.1429**

M6 = Month 6, and M12 = Month 12

a Deviation from Paris I: incorporation of total bilirubin ≤ULN instead of ≤1 mg/dL of normal total bilirubin levels. Paris I (Corpechot 2008), Paris II (Corpechot 2011), Mayo II (Momah 2012), Toronto II (Kumagi 2010b), and Rotterdam (Kuiper 2009); p-value for comparing treatments were obtained using CMH General Association test were stratified by randomization strata factor.

Ancillary analyses

The primary efficacy analysis was repeated using the EE population and Completer populations. As shown in Table 24, Month 12 results in both analysis populations were numerically comparable with the ITT population and statistically significant compared with placebo (p <0.0001).

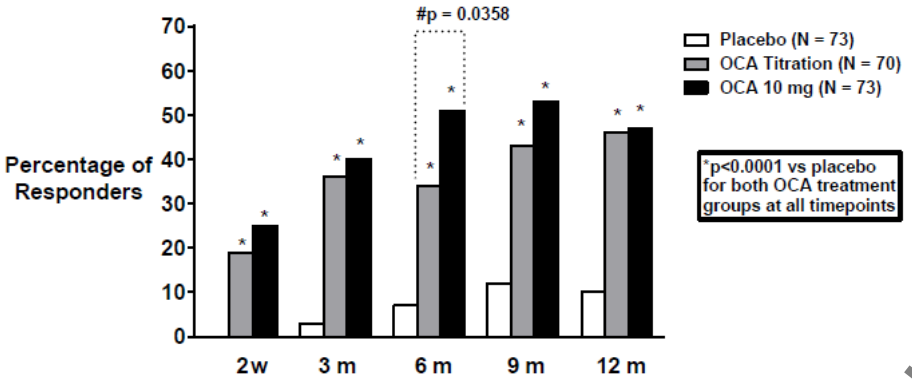
Table 23: Primary Efficacy Composite Endpoint at Month 12 Using Imputed Data: Completer (Placebo and OCA 10 mg, N = 134) and EE (Placebo and OCA 10 mg, N = 129) Populations

Month 12	ALP <1.67x ULN and Total Bilirubin ≤ULN and ALP Decrease ≥15% From Baseline	
	Placebo	OCA 10 mg
Completer Population		
n	70	64
Number of Responders, n (%)	7 (10)	34 (53)
CMH p-value[a]	NA	**<0.0001**
EE Population		
n	67	62
Number of Responders, n (%)	7 (10)	34 (55)
CMH p-value[a]	NA	**<0.0001**

Missing values were considered a non-response.
[a] p-values obtained using CMH test stratified by randomization strata factor.

Other secondary analyses of the primary endpoint included the percentage of subjects achieving the endpoint at Week 2, Month 3, Month 6, and Month 9. In addition, the 10 mg OCA group was compared to OCA titration group at Month 6 (Figure 21).

Figure 21: Percentage of Subjects Achieving Primary Composite Endpoint Over Time Using Imputed Data: ITT Population (N = 216)



Missing values were considered a non-response.

*p-value for treatment group versus placebo; #P-value for the between treatment group comparison at Month 6 of OCA titration (5 mg) and OCA 10 mg. P-value obtained using CMH test stratified by randomization strata factor.

For the key secondary analysis, a total of 32 (46%) subjects in the OCA titration group achieved the composite endpoint at Month 12 compared with 7 (10%) subjects in the placebo group. The difference between placebo and the OCA titration group was statistically significant (p <0.0001).

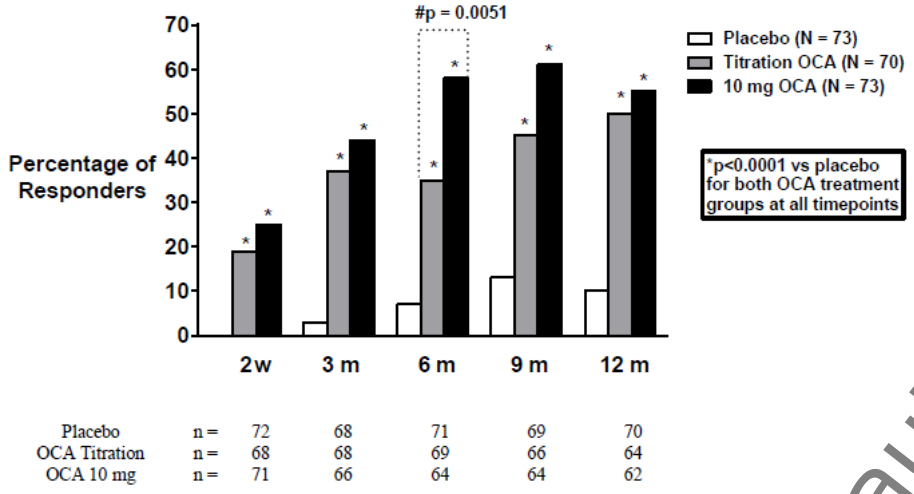
Both OCA treatment groups were superior to placebo in achieving the composite endpoint at all timepoints across the 12-month treatment period (p<0.0001 versus placebo). At Month 6, a higher percentage of subjects in the OCA 10 mg group (51%) achieved the composite endpoint compared with the OCA titration group (34%), which was statistically significant (p-value = 0.0358; Month 6 was the only visit statistical testing between the 2 treatment groups was performed).

Sensitivity Analyses of Primary Endpoint

Observer Data

Sensitivity analyses were performed on the primary efficacy endpoint for the ITT population using observed data only (Figure 22). Notably, both OCA treatment groups were superior to placebo at all timepoints, with the difference between placebo and each OCA treatment group statistically significant (p <0.0001) as early as Week 2 (the first measured timepoint) and then at all subsequent timepoints through Month 12.

Figure 22: Percentage of Subjects Achieving Primary Composite Endpoint Over Time Using Observed Data: ITT Population (N = 216)



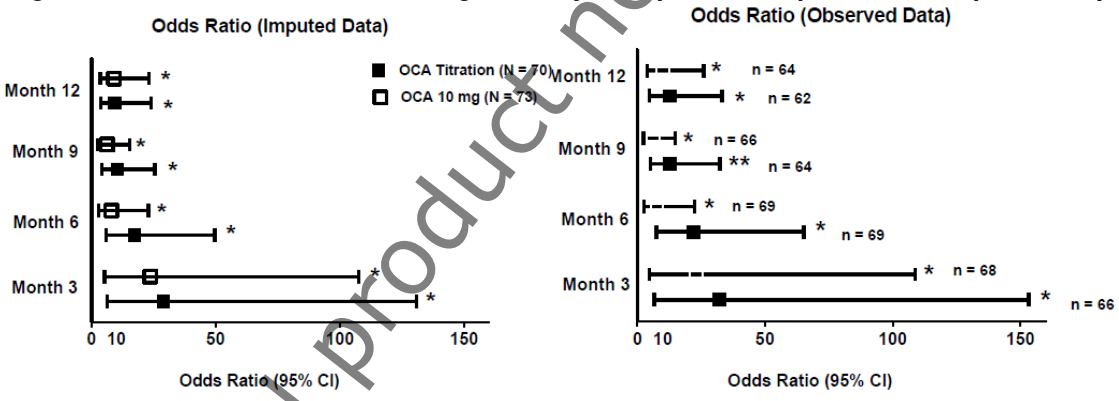
		2w	3 m	6 m	9 m	12 m
Placebo	n =	72	68	71	69	70
OCA Titration	n =	68	68	69	66	64
OCA 10 mg	n =	71	66	64	64	62

*p<0.0001; #p = 0.0051 for the between treatment group comparison at Month 6 of OCA titration (5 mg) and OCA 10 mg. p-value obtained using CMH test stratified by randomization strata factor.

ORR

Sensitivity analyses were also performed using a logistic regression model with response as the endpoint and treatment group and randomization strata as factors to estimate the odds of being a responder with each OCA treatment group relative to placebo (an odds ratio greater than 1 favored the OCA treatment group).

Figure 23: Odds Ratio of Achieving Primary Composite Endpoint: ITT Population (N = 216)



For imputed data, missing values were considered a non-response. Per X axis, a ≤1 represents no difference in association between OCA and placebo. *p≤0.0001, **p = 0.0002; P-values for comparing treatments are obtained using a logistic regression model with terms for treatment and the randomization strata factor.

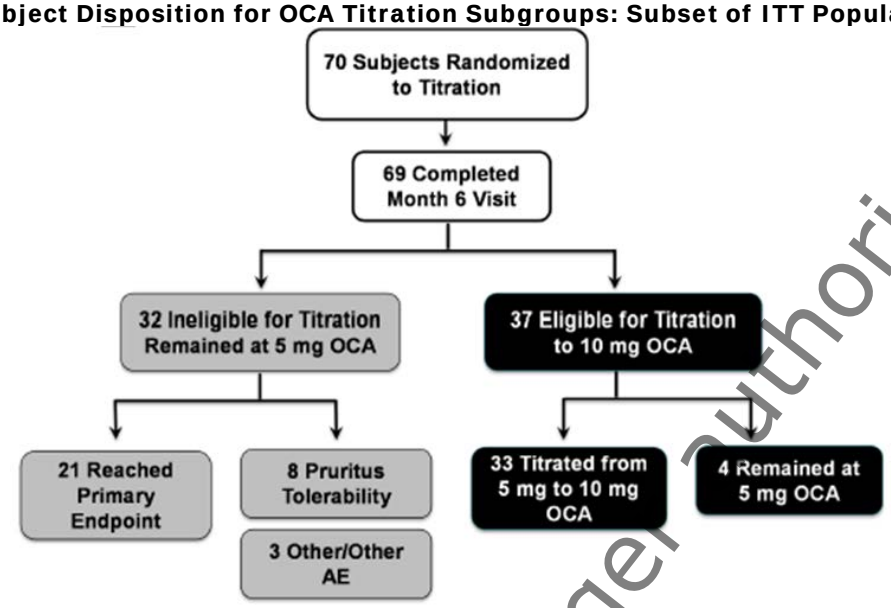
OCA titration group

Primary endpoint

A total of 69 subjects from the OCA titration group completed Month 6. Of these, 36 (52%) remained at 5 mg for the duration of the 12-month treatment period and 33 (48%) who did not meet the primary composite endpoint but tolerated investigational product titrated to 10 mg for the last 6 months of the 12-month period. Of the 36 subjects who did not titrate, 21 (58%) of subjects achieved the primary

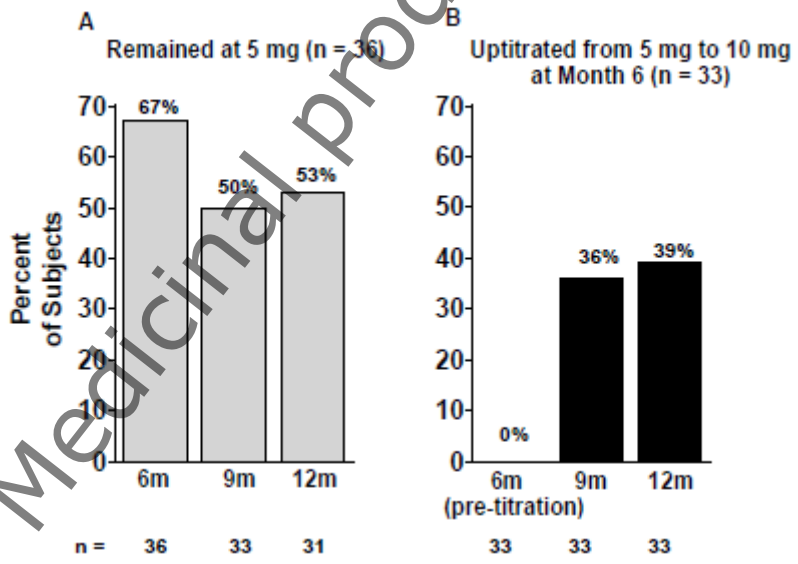
endpoint at Month 6 and 8 (22%) subjects had pruritus during the initial 6-month treatment period (1 event was mild, 5 events were moderate, and 2 events were severe).

Figure 24: Subject Disposition for OCA Titration Subgroups: Subset of ITT Population (N = 70)



A total of 36 subjects remained at OCA 5 mg for the latter 6-month period. Of these, 24 (67%) achieved the composite endpoint at Month 6 and thus had a clinically meaningful response to OCA. The other 11 had tolerability issues, other AEs, or other reasons. Similar responses were observed at Month 9 (50%) and Month 12 (53%) for this subgroup. The 33 subjects who uptitrated to OCA 10 mg following Month 6 were by definition non-responders at Month 6 (ie, did not achieve the composite endpoint). These subjects, who by protocol definition showed no evidence of tolerability issues at Month 6, received incremental benefit by uptitrating to OCA 10 mg (Figure 25).

Figure 25: (modified): Composite Endpoint by OCA Titration Subgroup Imputed Data: ITT Population (OCA Titration Subgroups, N = 70)

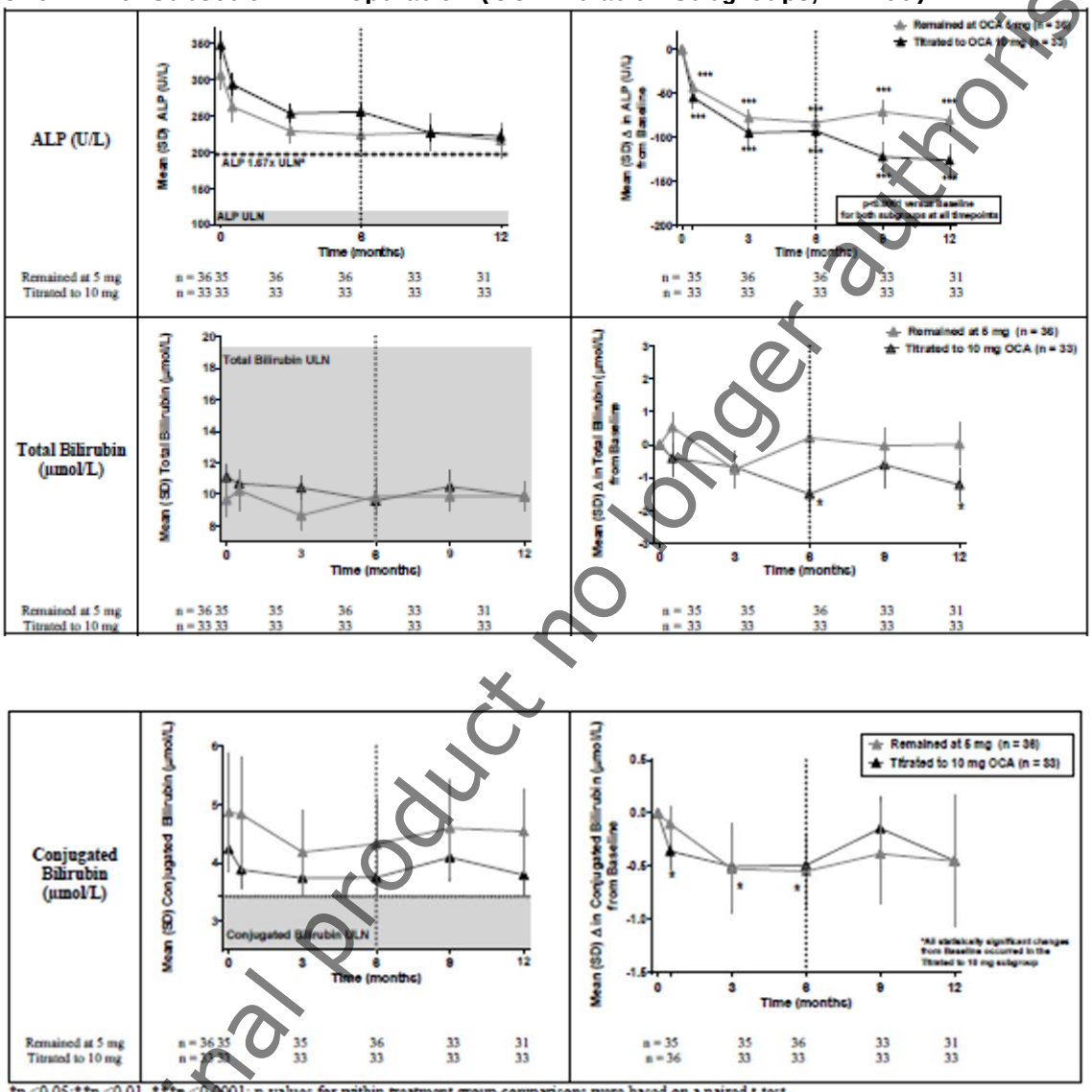


m = month; w = week Missing data were considered non-responders (ie, imputed data).

ALP, total bilirubin, conjugated bilirubin

ALP, total bilirubin, and conjugated bilirubin values over the 12-month treatment period by OCA titration subgroup and placebo are shown in Fig 44. Both Baseline ALP and total bilirubin values were higher in the subgroup that titrated OCA from 5 mg to 10 mg, compared with the subgroup that remained at OCA 5 mg, while Baseline conjugated bilirubin was generally comparable.

Figure 26: ALP, Total Bilirubin, and Conjugated Bilirubin Values and Change from Baseline Over Time: Subset of ITT Population (OCA Titration Subgroups, N = 69)



*p <0.05;**p <0.01, ***p <0.0001; p-values for within treatment group comparisons were based on a paired t-test.
Given the majority of the population was female, ULN values are based on criteria for females: ALP ULN = 118.3 U/L; Total Bilirubin ULN: 19.32 µmol/L. Conjugated Bilirubin ULN = 3.42 µmol/L for both females and males.

Statistically significant absolute and percent reductions from Baseline in ALP were observed for both OCA titration subgroups (within treatment group comparisons based on a paired t-test.). For subjects who uptitrated to 10 mg, mean percent change from Baseline in ALP was -22.2% at Month 6 prior to uptitration, and -32.5% at Month 12, 6 months after uptitrating to 10 mg. Month 12 mean absolute values (216.5 U/L for those who remained at 5 mg versus 222.4 for those who titrated) were comparable between the 2 subgroups.

The mean change from Baseline in total bilirubin was statistically significant at both Month 6 and Month 12 for subjects who uptitrated to 10 mg; however, the absolute value was similar for Month 6 (9.6 µmol/L)

and Month 12 (9.9 µmol/L). This was not unexpected given Baseline total bilirubin was within normal ranges. Baseline conjugated bilirubin was higher in subjects who remained at OCA 5 mg (4.9 µmol/L) compared with subjects who uptitrated to OCA 10 mg (4.2 µmol/L). The within group change from Baseline in conjugated bilirubin was statistically significant at Month 6 (p = 0.0378) for the subgroup who uptitrated to OCA 10 mg. No other notable changes were observed for either subgroup in terms of conjugated bilirubin.

Summary of main study

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 24: Summary of efficacy for trial 747-301

Title: A Phase 3, Double Blind, Placebo Controlled Trial and Long Term Safety Extension of Obeticholic Acid in Patients with Primary Biliary Cirrhosis Acronym: PBC OCA International Study of Efficacy (POISE).			
Study identifier	747-301		
Design	A randomized, double-blind, placebo-controlled, parallel-group, 12-month study evaluating OCA in subjects with PBC who were either taking: 1) ursodeoxycholic acid (UDCA), the current standard of care for PBC, for at least 12 months (stable dose for ≥3 months) or 2) subjects who were unable to tolerate UDCA and did not receive UDCA for ≥3 months prior to Day 0.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months (Double-Blind) ≤8 weeks (Screening Period) 2+ years, Ongoing up to 5 years (optional LTSE; not summarized here)
Hypothesis	Superiority of OCA + Standard of Care therapy for PBC (UDCA, where tolerated) vs Standard of Care alone		
Treatments groups	Placebo		Placebo ± UDCA. 12 months, 73 randomized
	OCA Titration		OCA 5 mg for 6 months, titrated to OCA 10 mg based on tolerability ± UDCA. 12 months total exposure to OCA, 71 randomized
	OCA 10 mg		OCA 10 mg ± UDCA. 12 months, 73 randomized
Endpoints and definitions	Primary endpoint	Composite Endpoint	Percentage of subjects (OCA 10 mg vs. placebo) achieving composite endpoint at Month 12. (Defined as the percentage of subjects reaching an ALP <1.67x ULN and a ≥15% reduction in ALP and a total bilirubin ≤ULN)
	Key Secondary Endpoint	Composite Endpoint	Percentage of subjects (OCA titration vs placebo) achieving composite endpoint at Month 12
	Other Secondary Endpoints	Absolute & percent change from Baseline at all timepoints	ALP, GGT, ALT, AST, Total Bilirubin, Conjugated Bilirubin
Database lock	10 March 2014		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to Treat. Double Blind: Month 12			
Descriptive statistics and estimate variability	Treatment group	Placebo	Titration OCA	10 mg OCA
	Number of subject	73	70	73
	Responders Composite Primary Efficacy Criteria, n(%)	7 (10)	32 (46)	34 (47)
	CMH p-value	NA	<0.0001	<0.0001
	ALP (U/L) Mean (SE) Absolute change from Baseline			
	6 months	-18.45 (8.156)	-87.14 (9.860)	-111.42 (10.097)
	12 months	-7.71 (10.513)	-103.53 (10.879)	-117.67 (9.306)
	ALP (U/L) Mean (SE) percentage change from Baseline			
	6 months	-5.21 (2.13)	-25.87 (2.39)	-34.36 (2.22)
	12 months	-2.49 (2.85)	-30.45 (2.37)	-36.35 (1.91)
	Total Bilirubin Mean (SE) Absolute change from Baseline			
	6 months	0.517 (0.399)	-0.610 (0.382)	-1.122 (0.532)
	12 months	1.388 (0.493)	-0.621 (0.417)	-1.231 (0.559)
	Total Bilirubin Mean (SE) percentage change from Baseline			
	6 months	11.64 (4.88)	-1.64 (4.59)	7.39 (8.33)
	12 months	17.02 (4.96)	1.31 (4.34)	-0.90 (4.63)
	Conjugated Bilirubin Mean (SE) Absolute change from Baseline			
	6 months	0.706 (0.248)	-0.520 (0.205)	-1.014 (0.340)
	12 months	1.421 (0.400)	-0.449 (0.315)	-0.764 (0.383)
	Conjugated Bilirubin Mean (SE) percentage change from Baseline			
	6 months	19 (5)	-3 (4)	-7 (4)
	12 months	28 (5)	3 (6)	-4 (4)
Notes	Composite Efficacy Endpoint: ALP <1.67x ULN and a ≥15% reduction in ALP and a total bilirubin ≤ULN			

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

Due to different study durations and some differences in study design, side-by-side and pooled analyses provided limited additional evidence.

OCA Monotherapy

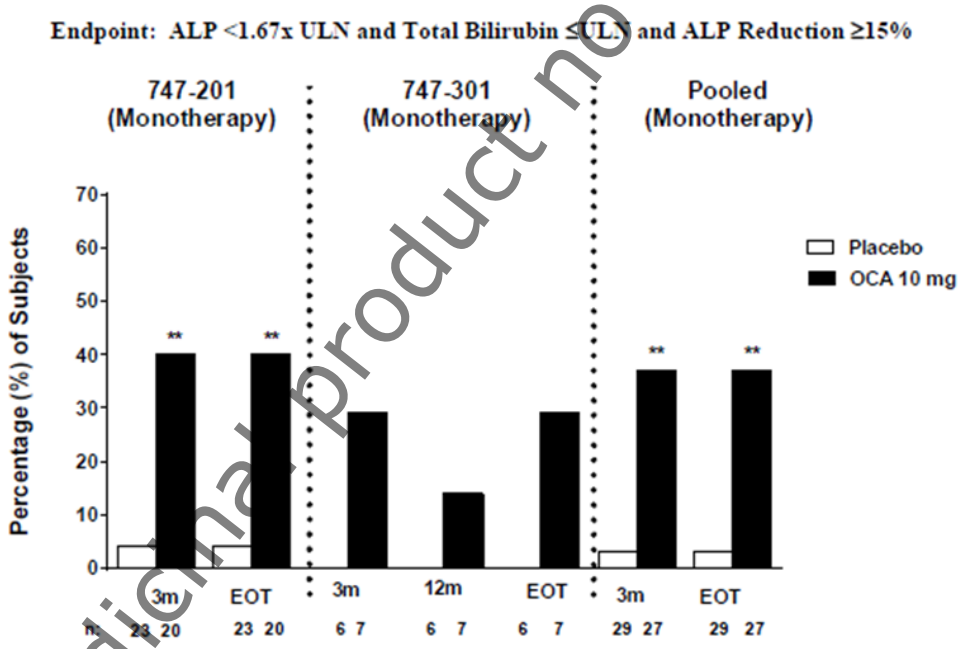
The Applicant claims OCA therapeutic indication as monotherapy in adults unable to tolerate UCDA. The proposed dose is the same as for the add-on indication (OCA 5 mg which could be up-titrated to 10 mg after 3 months).

Data in support of the monotherapy use are those coming from 61 subjects, **54** of whom were the ITT population:

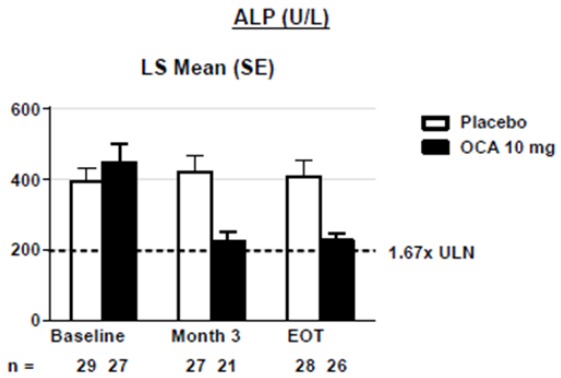
-the phase II 747-201 study (43 subjects, 20 OCA 10mg and 23 PLB);

-the subset of 18 (8%) subjects from the 747-301 study who were randomized to receive investigational product monotherapy as they were unable to tolerate UDCA therapy for at least 3 months prior to study entry.

Double-Blind Percentage of Subjects Achieving Primary Composite Endpoint: ITT Population (N=54), Monotherapy



Double-Blind Phase LS Mean (SE) ALP Values at Baseline, Month 3, and EOT: ITT Population (N = 54), Monotherapy



Monotherapy versus combination therapy with UCDA

A summary of results is reported below:

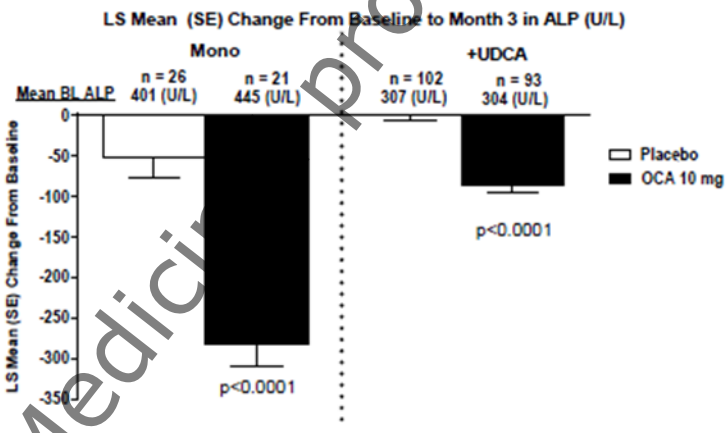
-Baseline ALP was higher in those subjects receiving OCA as monotherapy compared with those who added OCA to UDCA (approximately 400 U/L versus 300 U/L; Figure below);

-the LS mean change from Baseline in ALP was larger for the OCA 10 mg monotherapy group compared to the OCA+UDCA group (Figure below), however the Month 3 values were comparable (Figure below). For both regimens, the difference from placebo was statistically significant (p <0.0001).

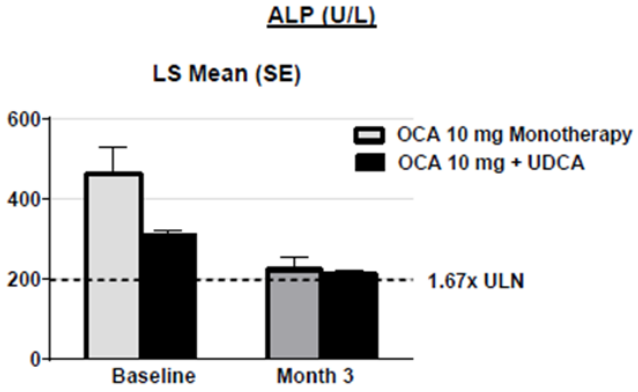
- the percentage of subjects achieving the primary composite endpoint at Month 3 is similar (approximately 40%) irrespective if OCA 10 mg was used as monotherapy or in combination with UDCA. For both regimens, the difference from placebo was statistically significant (p <0.0001; Table below);

-the ALP levels for OCA 10 mg monotherapy and OCA 10 mg + UDCA approached 1.67x ULN by Month 3.

Double-Blind Phase LS Mean (SE) Change in ALP From Baseline to Month 3: ITT Population (N = 440), Monotherapy versus Combination with UDCA



Double-Blind Phase LS Mean (SE) ALP Values at Baseline and Month 3: ITT Population (N = 440), Monotherapy Versus Combination with UDCA



Comparison of Percentage of Subjects Achieving Primary Endpoint – Monotherapy Versus in Combination with UDCA: Pooled Doses at Month 3, ITT Population

Month 3	Composite Endpoint: ALP <1.67x ULN and Total Bilirubin ≤ULN, and ALP Decrease of ≥15% from Baseline	
	Responder	CMH p-value[a]
Monotherapy		
Placebo (N = 28)	1 (4)	NA
OCA 10 mg (N = 26)	10 (38)	0.0010
Combination (+ UDCA)		
Placebo (N = 106)	5 (5)	NA
OCA 10 mg (N = 105)	43 (41)	<0.0001

Baseline is defined as the mean of all available evaluations prior to double-blind treatment. Subjects with missing values are considered non-responders.

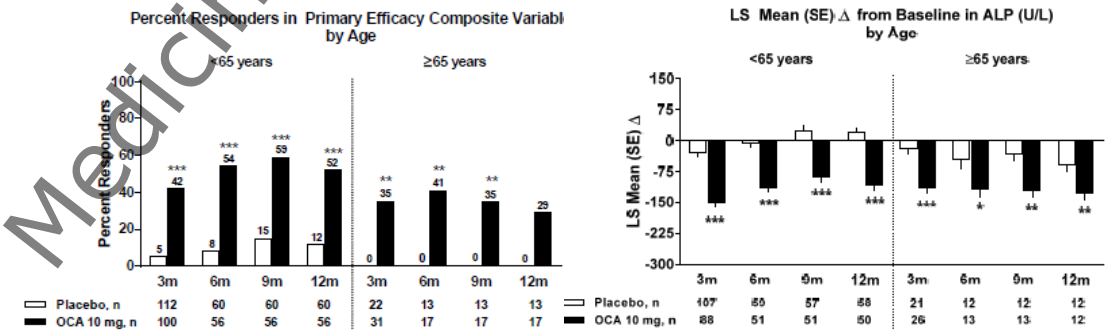
[a] p-values for comparing treatments are obtained using CMH General Association test stratified by UDCA usage (yes/no) and total bilirubin ≥ULN at Baseline (yes/no).

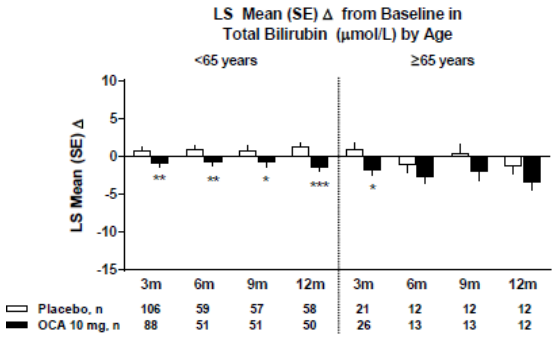
Clinical studies in special populations

Elderly patients

No dedicated study in elderly patients has been conducted.

The number of patients >65 years of age included in the phase II and pivotal studies is limited, particularly very elderly patients (≥ 75). The Applicant initially provided pooled data from the main studies (see figure below), by also pooling both doses.





Separate efficacy results were provided as a response to the CHMP D120 LoQ.

Table 25: Double-Blind Phase Percentage of Patients Achieving the Primary Composite Endpoint at Baseline and Month 12 by Age Subgroup: Study 747-301, ITT Population (n = 143)

Achieved an ALP <1.67x ULN and Total Bilirubin ≤ULN and an ALP Decrease ≥15% from Baseline	OCA Titration (N=70)			OCA 10 mg (N=73)		
	N	Month 12 n (%)	p-value versus placebo	N	Month 12 n (%)	p-value versus placebo
Age at Baseline (years)						
<65 years	60	28 (47)	**<0.0001**	56	29 (52)	**<0.0001**
≥65 years	10	4 (40)	**0.0377**	17	5 (29)	**0.0417**

p-values based on difference between OCA treatment and placebo and were obtained using CMH General Association test stratified by randomization strata factor. Missing data considered non-responders.

Table 26: Double-Blind Phase ALP and Total Bilirubin Baseline and Change from Baseline to Month 12 by Age Subgroup: Study 747-301, ITT Population (N = 216)

	OCA Titration (N=70)					OCA 10 mg (N=73)				
	n	Mean (SE) Baseline	n	LS Mean (SE) Δ From Baseline at Month 12	p-value	n	Mean (SE) Baseline	n	LS Mean (SE) Δ From Baseline at Month 12	p-value
ALP (U/L)										
<65 years	60	320.0 (13.2)	56	-109.3 (23.0)	**<0.0001**	56	322.5 (14.7)	50	-131.8 (23.9)	**<0.0001**
≥65 years	10	361.0 (58.2)	8	-124.3 (21.0)	**0.0405**	17	296.1 (19.3)	12	-133.8 (25.0)	**0.0053**
Total Bilirubin (µmol/L)										
<65 years	60	10.4 (0.7)	56	-1.2 (1.0)	**0.0015**	56	10.8 (0.8)	50	-1.6 (1.1)	**0.0003**
≥65 years	10	9.4 (1.2)	8	-1.6 (1.5)	**0.0459**	17	13.1 (2.1)	12	-0.3 (1.6)	**0.0653**

P-value for comparing active treatments to placebo is obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Paediatric population

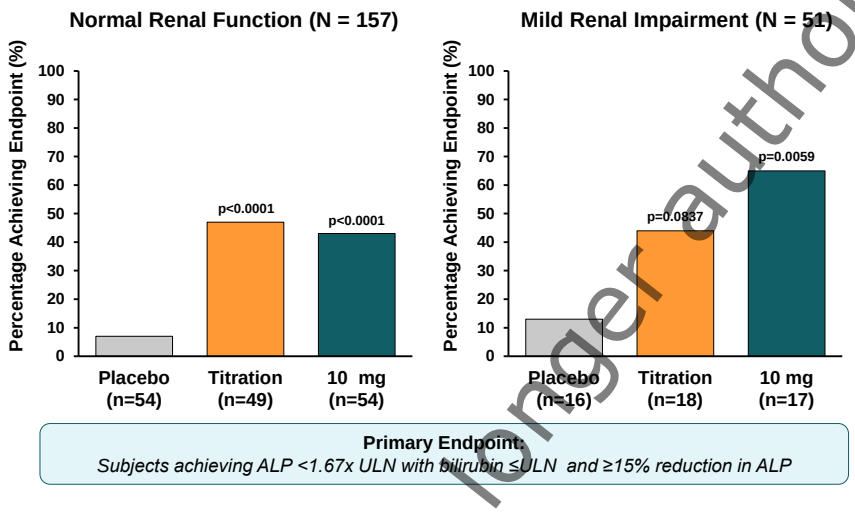
A waiver was granted for all subsets of the paediatric PBC population from birth to less than18 years of age, since PBC does not occur in the specified paediatric subsets.

Patients with renal impairment

Patients with renal (mild-moderate) or hepatic impairment were not explicitly excluded from OCA phase II and III studies. Separate efficacy (and safety data) for these patients was provided as response to the D120.

Due to the small number with patients with moderate renal impairment, only results for patients with mild impairment have been presented.

Figure 27: **Proportion of Patients Achieving Primary Composite Endpoint by Renal Status at Month 12: Study 747-301 (ITT Population)**



Observed data. p-values for comparing treatments are obtained using the Cochran-Mantel-Haenszel (CMH) General Association test stratified by randomization stratification factor.

Renal Function Status Based on Creatinine Clearance Values: Normal: >80 mL/min; Mild: >50 to 80 mL/min.

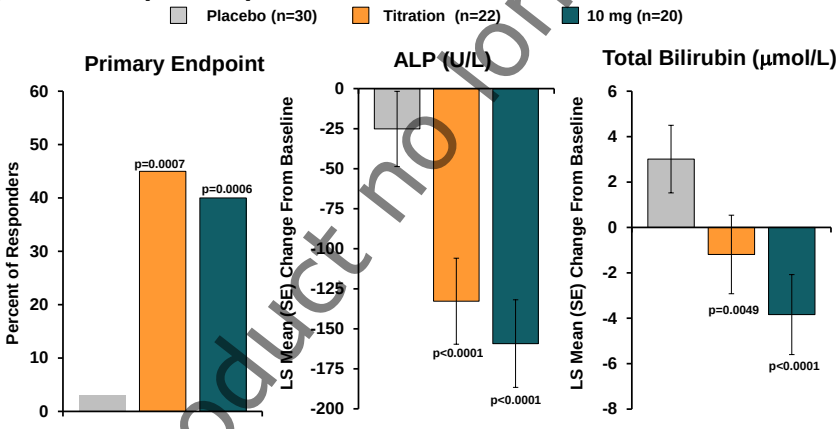
Patients with a more advanced disease stage

In addition, the Applicant tried to characterise the efficacy (and safety) of OCA in a more advanced PBC population by developing a clinical algorithm that would identify these patients.

Table 27: **Definitions Used to Evaluate Patients With Advanced Disease in Study 747-301**

Advanced Disease Stage Definition Based on Clinical Criteria (Biochemical Criteria, Non-Invasive Measures, Biopsies, and/or Medical History of Decompensation)	
Clinical Composite	Meets at least 1 of the following criteria: Baseline total bilirubin >ULN Baseline ALP >5 x ULN Baseline transient elastography ≥10.7 kPa (advanced fibrosis or cirrhosis) Cirrhosis based on initial or "in study" biopsy Medical history of hepatic decompensation
Advanced Disease Stage Definition Based on Biochemical Criteria Only	
Rotterdam (Kuiper 2009)	Moderately Advanced: Baseline total bilirubin >ULN or albumin <LLN Severe: Baseline total bilirubin >ULN and albumin <LLN
Advanced Disease Stage Definition Based on Biopsy Staging Only	
Cirrhosis	Cirrhosis was defined as an Ishak score 6 or Ludwig/Scheuer PBC Stage 4. (The most recent biopsy report based on either an "in study" or "historical" biopsy were used for this assessment.)

Figure 28: Key Efficacy in Patients With Advanced Disease Based on Clinical Composite Criteria: Study 747-301 (N = 72)



The primary endpoint was defined as the percentage of patients achieving ALP <1.67x ULN with bilirubin ≤ULN and ≥15% reduction in ALP based on observed data. p-values for comparing treatments are obtained using the Cochran-Mantel-Haenszel (CMH) General Association test stratified by randomization stratification factor. Patients with missing values were considered non-responders.

For ALP and total bilirubin, N at Month 12 was 28, 19, and 15, for placebo, titration, and 10 mg, respectively. The p-value for comparing active treatments to placebo is obtained using an ANCOVA model with baseline value as covariate and fixed effects of treatment, double-blind baseline UDCA usage (yes/no) and double-blind baseline total bilirubin (≤ULN/>ULN).

Supportive studies

Study 747-205

This open-label study assessed the effects of OCA on lipoprotein metabolism in patients with PBC. It evaluated only the 10mg OCA dose (as add-on to UDCA, for 8 weeks), and the efficacy variables were

related with different lipid metabolism parameters (HDLc concentration, total cholesterol, etc.). Key entry criteria were similar to those in the pivotal study.

A total of 33 subjects were screened, 26 subjects were enrolled and 25 subjects completed the study. In subjects with PBC, 10-mg OCA reduced HDL cholesterol but did not change the concentration of total serum HDL particles. Consistent with the clearance of cholesterol from HDL, particle size was significantly reduced with a mean decrease in large HDL particle concentration and an increase in small HDL particle concentration. Withdrawal of OCA treatment returned HDL parameters to near baseline values.

A modest increase in LDL cholesterol was observed for the OCA 10 mg group, which was statistically significant from Baseline. In longer term studies, this effect has been shown to be transient with levels returning to baseline with extended treatment. Total LDL particle concentration increased significantly with OCA treatment with a mean decrease in LDL particle size; this was due to formation of small LDL particles. Minimal changes were observed in VLDL cholesterol, size or particle concentration.

Total cholesterol concentration tended to decrease commensurate the decrease in HDL and the modest increase in LDL cholesterol.

Components of reverse cholesterol transport were affected by 10-mg OCA treatment. Macrophage cholesterol efflux was significantly reduced at Week 4 but returned to values comparable to baseline at Week 8. This may have initially due to a decrease in LCAT activity with subsequent significant increases in pre-B1 HDL and small HDL which are efficient substrates for cholesterol efflux.

Consistent with PBC, ALP and GGT were elevated at baseline and exhibited marked declines at Week 4 and Week 8 with OCA treatment. ALT and AST were mildly elevated but within the normal range for the majority of subjects at baseline and exhibited mean decreases at Week 4and Week 8 with OCA treatment. Mean total bilirubin remained generally comparable to baseline; however, mean decreases in conjugated (direct) bilirubin were noted at Week 4 and Week 8. Following withdrawal of OCA treatment at Week 8, ALP, GGT, ALT, AST, total bilirubin, and conjugated bilirubin concentrations increased and either returned to baseline levels or had more modest declines from baseline compared to Week 8. Notably, total and conjugated bilirubin increased above baseline at Week 12; this was due to high levels of both parameters in the subject who experienced the SAE of jaundice during the follow-up period.

LTSE studies

After the double-blind studies, patients were allowed to enroll in their open label extension studies. The LTSE phases of Studies 747-201 and 747-301 remained on-going at the time of the initial submission (data cut-off of 31 Aug 2014).

At entry (in studies 747-201-LTSE and 747-202-LTSE), patients from the phase II studies remained at the DB dose (placebo started OC at 10 mg) and in subsequent visits, if clinically indicated, they could titrate every 8 weeks up to 50 mg. All patients from the phase III study started the LTSE (study 747-301-LTSE) at OCA 5 mg (regardless of their previous dose) and at month 3 they could either remain at 5mg or titrate in 5 mg increments to a maximum of 25 mg in 3 months intervals.

Efficacy variables were those from their respective double-blind periods. As in their respective double-blind periods, no clinical outcome variables were included in the LTSE studies.

- **747-201 LTSE**

At the time of the initial submission, 18 out of 28 patients (64%) were continuing to receive OCA treatment. Twenty-three (82%) subjects participated in the LTSE phase for at least 1 year, and 17 (61%) participated for at least 4 years. Long-term treatment with OCA in the LTSE phase of the study was associated with sustained reductions in ALP that were consistent with the observed effect of OCA in the

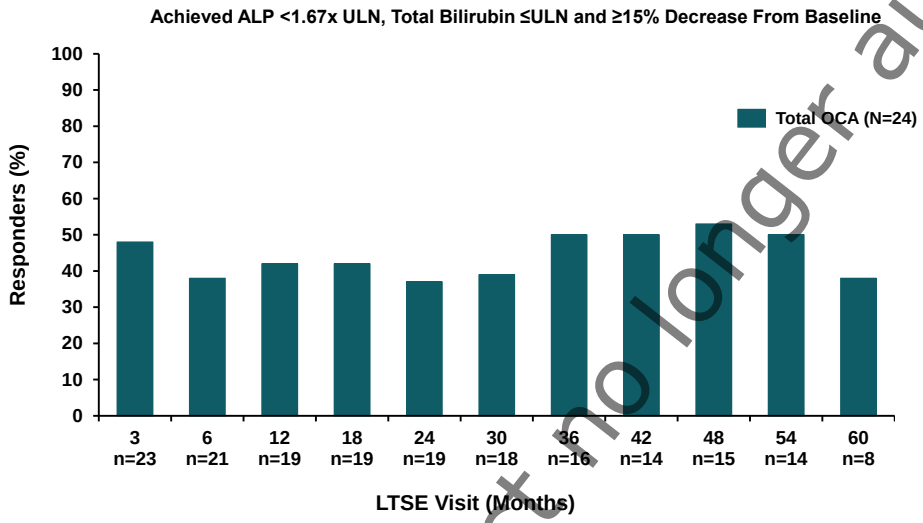
double-blind phase of the study, showing the consistency and durability of OCA treatment. The apparent further decrease in ALP in the LTSE Safety Population was due to the transitioning of placebo subjects to OCA treatment, which further decreased mean ALP of the entire cohort.

Sustained mean reductions in AST, ALT, GGT, and total bilirubin were observed at most LTSE timepoints. Changes in conjugated tended to be more variable; however, generally remained comparable to baseline.

As part of the responses to the CHMP´s D120 LoQ, the Applicant provided an update of the results for study 747-201 LTSE.

As of the data cut-off of 29 Jun 2015, 18 (64%) patients were ongoing and a total of 11 (39%) had up to 5 years of exposure to OCA. A post hoc analysis of Study 747 201 LTSE using the primary endpoint from Study 747-301 has been performed. (Figure 29)

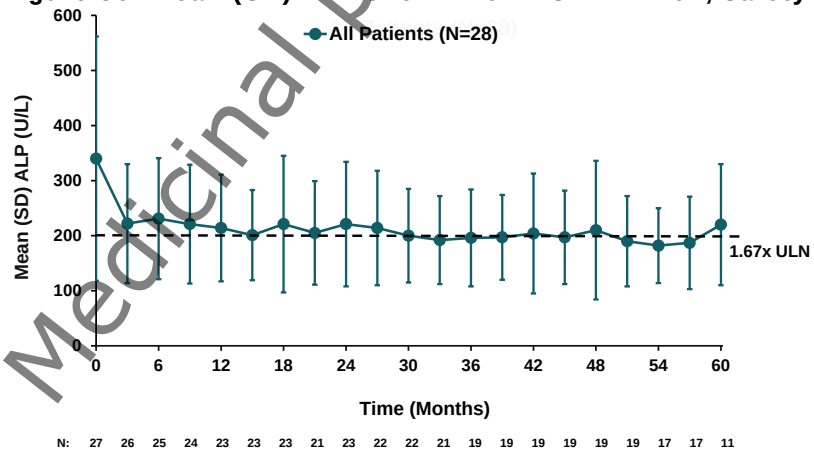
Figure 29: **Percentage of Patients Achieving the Primary Endpoint: LTSE 747-201, Patients Who Were Non-Responders at Baseline (N = 24)**



Observed data based on the 29 Jun 2015 data cut (percentage at each visit based on the responders/total based on the N for that visit). The number of patients at each visit may be lower than Safety Population due to missing or unsuitable samples or due to patient discontinuations or visits.

Mean (SD) of ALP over the 5 year duration of Study 747-201 LTSE is shown in Figure 30.

Figure 30: **Mean (SD) ALP Over Time: LTSE 747-201, Safety Population (N = 28)**



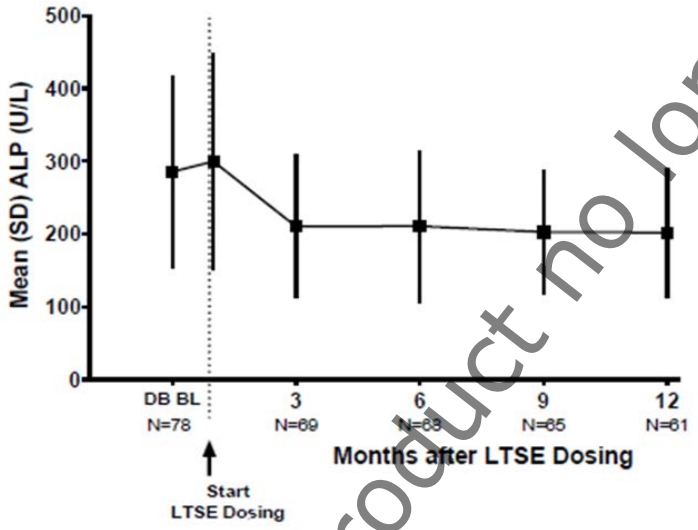
LTSE = long-term safety extension. Data are based on a 29 Jun 2015 data cut. ULN = 117 U/L for females.

- **747-202 LTSE**

Of the 165 subjects enrolled in the double-blind phase of the study, 78 subjects (21 of whom had received placebo) entered the open-label LTSE phase of the study. The most frequent reason for discontinuation was administrative reasons for 59 (76%) of subjects. Two subjects (3%) withdrew consent, 1 subject (1%) discontinued due to a major protocol violation, and 2 subjects (3%) withdrew for other reasons. A total of 14 subjects (18%) withdrew due to AEs, of these, 10 (13%) withdrawals were due to pruritus.

Due to administrative reasons, subjects were off investigational product for up to 9 months before starting LTSE dosing. Further, the duration of time between the last dose in the double-blind phase and initiation of dosing in the LTSE was variable across subjects. Given these varied gaps in exposure, the changes in efficacy were assessed relative to both the double blind and LTSE Baselines to post Baseline, 3, and 6 month visits, and study completion/ET LTSE visit.

Figure 31: Mean (SD) ALP From Double-Blind Baseline to 12-Month LTSE Visit:Safety Population (N = 78)



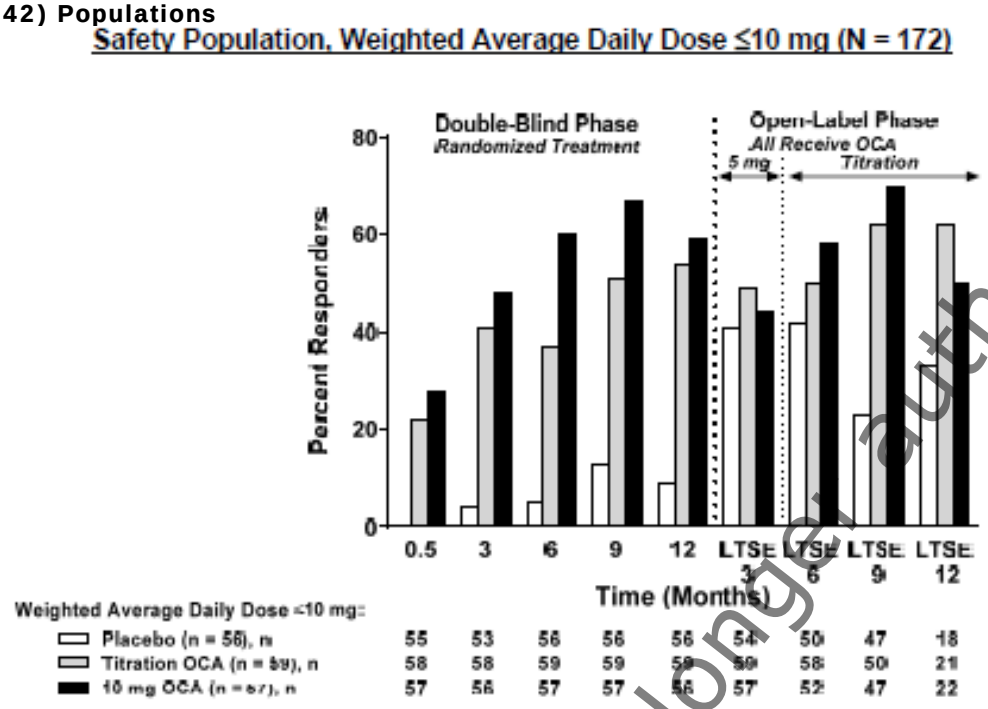
ALP = alkaline aminotransferase; DB BL = double-blind Baseline; LTSE = long-term safety extension; SD = standard deviation
Note: For administrative reasons, dosing was not continuous between the end of the double-blind phase and start of LTSE dosing.

- **747-301 LTSE**

For subjects previously randomized to OCA and who continued treatment with OCA in the LTSE, the percentage of subjects achieving the primary composite endpoint at the end of the double-blind phase, i.e., Month 12 (51% for OCA titration and 56% for OCA 10 mg), was sustained over the subsequent 12-month open-label period (52% for OCA titration and 44% for OCA 10 mg at LTSE Month 12).

Following completion of the double blind phase, 193 subjects (89% of the double blind Intent-to-Treat Population) opted to continue into the LTSE and are summarized as the Safety Population. For subjects previously randomized to OCA and who continued treatment with OCA in the LTSE, the percentage of subjects achieving the primary composite endpoint at the end of the double-blind phase, i.e., Month 12 (51% for OCA titration and 56% for OCA 10 mg),was sustained over the subsequent 12-month open-label period (52% for OCA titration and 44% for OCA 10 mg at LTSE Month 12).

Figure 32: (modified): Percentage of Subjects Achieving Primary Composite Endpoint Based on Double-Blind Baseline: LTSE of Study 747-301 Safety (N = 172) and 2-Year Completer (N = 42) Populations



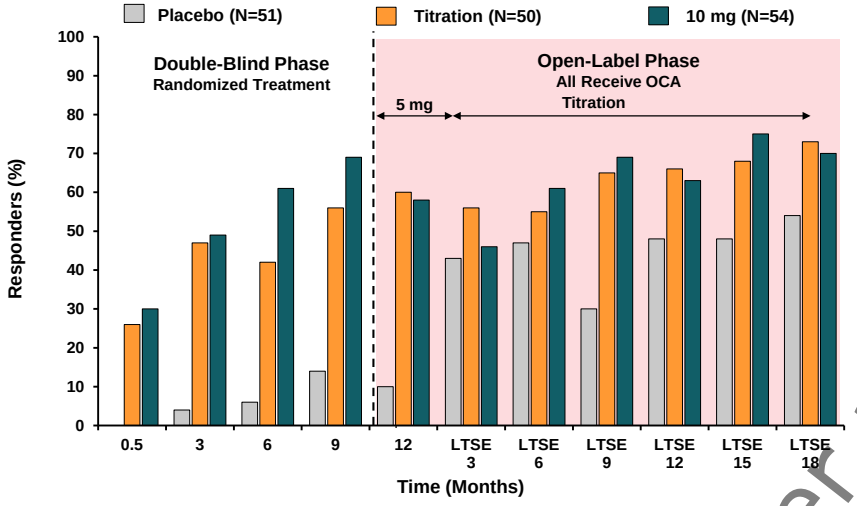
As part of the responses to the CHMP´s D120 LoQ, the Applicant provided an update of the results for study 747-301 LTSE.

As of the data cut-off of 29 Jun 2015, 173/193 (90%) patients were ongoing and 20 patients had cumulatively discontinued from the LTSE phase of the study, including 10 patients who discontinued between 31 Aug 2014 and 29 Jun 2015.

The percentage of OCA-treated patients from LTSE 747-301 who achieved the primary composite endpoint is summarized in Figure 33.

Patients treated with placebo in the double-blind phase had a response in the LTSE phase after starting OCA that was a similar trend (slightly lower) to those observed for patients continuously treated with OCA. It should be noted that placebo patients received a lower weighted average daily dose in the LTSE (35% of placebo patients received a weighted average daily dose ≤5 mg compared to 16% of OCA titration patients and 3% of OCA 10 mg patients).

Figure 33: Percentage of Patients Achieving Primary Composite Endpoint: LTSE 747-301 LTSE Weighted Average Daily Dose of ≤10 mg (N = 155). Data are Summarized Based on Double-Blind, Randomized Treatment



The mean (SD) absolute values at Baseline, LTSE Day 0, and LTSE Month 18 and the means (SD) change from baseline in ALP data over a 30-month treatment period (12 months double-blind and 18 months open-label) show reductions in ALP from Month 3 that were maintained throughout 2.5 years.

2.4.3. Discussion on clinical efficacy

The efficacy of obeticholic acid (OCA) in the treatment of PBC is mainly based on one single pivotal phase III study (747-301), two phase II studies (747-201 and 747-202) and their long-term safety extension (LTSE) studies (747-301-LTSE, 747-201-LTSE and 747-202-LTSE). Additional support is provided by study 747-205 (primary treatment phase).

Design and conduct of clinical studies

Dose finding

Dose selection for the phase III study was based on 2 phase II studies, 747-201 and 747-202. Both studies included patients with a proven or likely diagnosis of PBC, who were suboptimally controlled with UDCA or were intolerant to it. Both studies evaluated several doses of OCA, up to 50 mg, as monotherapy (study 747-201) or as add-on to UDCA (study 747-202) and the primary efficacy endpoint for both was the percent change (%) in serum ALP from Baseline to End of Study.

There are some differences between the design of the pivotal study and the supportive phase II studies (747-201 and 747-202). These differences mainly consist of: liver entry criteria (ALP between 1.5 and 10 ULN in the phase II ≥1.67 ULN in the pivotal), duration (phase II only 3 months), doses (higher doses were assessed in the phase II, as they were dose-ranging studies), presence of mandatory discontinuation criteria (no mandatory discontinuation criteria were implemented in the pivotal study, while in the phase II patients with a 2-fold increase in bilirubin or 3-fold in AST/ALT were required to discontinue) and primary endpoint (composite endpoint vs. %change in ALP from baseline until 3 months of treatment in the phase II studies). Overall, the doses tested demonstrated superiority over placebo. However, OCA doses >10 mg, did not show any additional benefits in terms of improvements in ALP or other liver biochemistry markers; on the contrary, higher doses were associated with higher incidence of

AEs, in particular pruritus. This effect was observed for both, monotherapy as well as add-on to UDCA, in comparison to placebo.

The titration approach was not tested during the phase II studies. Based on the results of the phase II studies, the 5 mg and 10 mg doses were selected for the phase III program. Following the recommendations received from the CHMP PA (EMEA/H/SA/2016/1/2010/PA/III), the Applicant implemented a 3 arm design, which compared the titration regimen and the fixed 10 mg regimen with placebo (as add-on to UDCA).

Pivotal study 747-301

Study 747-301 was a randomized, multi-dose, parallel group, double-blind, placebo-controlled, Phase 3 that was designed to assess efficacy, safety, and tolerability of OCA in subjects with PBC over a 12-month treatment period. Subjects with a probable or confirmed diagnosis of PBC who, prior to baseline, were either taking UDCA for at least 12 months (stable dose for ≥3 months) or were unable to tolerate UDCA (no UDCA for ≥3 months) were eligible for enrolment. To note, patients with total bilirubin ≥ 2x ULN, severe portal hypertension or hepatic failure were excluded from 747-301 study as from the two supportive studies. Thus, the enrolled population consisted of PBC patients with compensated disease.

In the clinical setting no agreed definition of response to treatment currently exists and different criteria have been developed and are used at the clinic. Due to this fact, at the CHMP PA (EMEA/H/SA/2016/1/2010/PA/III) received by the Applicant, the inclusion criteria (as definition of insufficient response to UDCA) was considered acceptable. Regarding to the inclusion of patients unable to tolerate UDCA, the Applicant clarified that patients were considered “intolerant” based on the review of the patient´s medical history and the investigator´s clinical judgment for each patient

This study evaluated a fixed dose of OCA (10 mg) and the titration approach over the 12-month treatment period (patients received 5 mg during the initial 6 months and could be titrated to 10 mg for the remainder of the 12-month treatment period in case of insufficient response, if no intolerance was present). From a clinical point of view, it would appear reasonable to assess the need to titrate the dose earlier than at 6 months, in order to reach an effective dose as soon as possible. Based on the few data available for the 3-month titration schedule (from the 51 placebo-treated patients who entered the LTSE of the pivotal study), the 3-month titration schedule did not seem to negatively impact tolerability. However, due to the limited data available at this time, the recommendation to increase to the 10mg dose after 6 months of treatment based on assessment of tolerability was considered appropriate by the CHMP for inclusion in the posology information of the SmPC.

The primary endpoint was a composite endpoint, surrogate endpoint, defined as the percentage of subjects (OCA 10 mg vs. placebo) reaching an ALP <1.67x ULN and a ≥15% reduction in ALP and a total bilirubin ≤ULN at Month 12. Biochemical inclusion criteria evolved compared to those used in the Phase II studies. In particular, ALP and bilirubin cut-off values in the pivotal studies were based on data obtained from two PBC cohorts (Global and UK PBC Groups Studies). This was considered acceptable by the CHMP.

Other markers of cholestasis, liver function, and hepatocellular injury were evaluated as secondary efficacy endpoints. No clinical outcome endpoints were included in the pivotal study.

The choice of ALP as a surrogate variable is based on the 10 years-plus experience from UDCA. The adequacy of the primary composite endpoint, solely based on changes in biochemical parameters, was discussed at length during the CHMP PA (EMEA/H/SA/2016/1/2010/PA/III). It was considered acceptable subject to the obligation of the Applicant to collect as much data as possible regarding harder clinical endpoints such as histology, cirrhotic related events, fibrosis markers and elastography.

Only limited non-invasive data (e.g. transient elastography, APRI score and ELF score) have been provided in this application and OCA treatment benefit remains mainly based on the improvement of several biochemical parameters, such as ALP and bilirubin levels. In order to support the clinical relevance of the observed results in the studied population available data derived from two large PBC cohorts (Global PBC Study and UK-PBC Cohorts) were presented. These cohorts included a large number of PBC patients and long-term follow-up. In general, results from these cohorts suggested an association between ALP (and bilirubin) levels and clinical outcomes, such as liver transplant or death. Further the applicant presented post-hoc analyses (performed by applying study 747-301 inclusion criteria and evaluating the primary endpoint in the cohort populations) suggesting that the association between ALP levels (at various thresholds defined by the clinical criteria) and clinical outcomes does not seem to be specific of UDCA treatment.

Furthermore the Applicant developed in order to simulate safety and efficacy in a more advanced disease stages a clinical algorithm that included a clinical composite definition (based on biochemical criteria, non-invasive measures of fibrosis, biopsies, and/or medical history of decompensation), the Rotterdam criteria (biochemical criteria only), and presence of cirrhosis. From an efficacy point of view, results in a more “advanced population” (as defined by the clinical algorithm), were similar to those of the general study population. Although criteria seem reasonable interpretation of this un-validated algorithm remains limited and it is not known how accurately it identifies the target population.

For the pivotal trial GCP inspections were conducted at three clinical investigator sites, one in Belgium and two in the USA (routine inspections) and also at the sponsor site and CRO site in the USA (triggered inspection) on dates between October 2015 and January 2016. The outcome of the inspections carried out was issued on 8 March 2016.

The data obtained at the sites inspected were considered reliable to be accepted as support of the Marketing Authorisation Application submitted to the EMA for approval.

Supportive phase II studies

Study 747-205

This open-label study assessed the effects of OCA on lipoprotein metabolism in patients with PBC. It evaluated only the 10 mg OCA dose (as add-on to UDCA, for 8 weeks), and the efficacy variables were related with different lipid metabolism parameters (HDLc concentration, total cholesterol, etc.). Key entry criteria were similar to those in the pivotal study.

LTSE studies

After the double-blind studies, patients were allowed to enroll in their open label extension studies.

At entry (in studies 747-201-LTSE and 747-202-LTSE), patients from the phase II studies remained at the DB dose (placebo started OC at 10mg) and in subsequent visits, if clinically indicated, they could titrate every 8 weeks up to 50 mg. All patients from the phase III study started the LTSE (study 747-301-LTSE) at OCA 5mg (regardless of their previous dose) and at month 3 they could either remain at 5mg or titrate in 5mg increments to a maximum of 25mg in 3 months intervals.

Efficacy variables were those from their respective double-blind periods. As in their respective double-blind periods, no clinical outcome variables were included in the LTSE studies.

Efficacy data and additional analyses

Pivotal study 747-301

A total of 217 patients were randomised (1:1:1), all but one of them received at least one dose of the study product (ITT population=216; 73 placebo, 70 titration OCA, 73 10 mg OCA). A total of 3, 7 and 9 patients discontinued prematurely in the placebo, OCA titration and fixed 10 mg OCA groups, respectively. The main reasons for not completing the 12-month DB phase were AEs, most commonly pruritus.

Most of the patients included were females (91%), White (94%) and European (67%). Median age was 55 years (range 29-86), with the majority of patients under the age of 65 (81%). Most of the patients (n=200, 93%) were being treated with UDCA at baseline, with only a total of 16 patients (7%) receiving OCA in monotherapy during the study.

Regarding to disease characteristics, most of the patients referred pruritus and a history of fatigue at baseline (59% each), with a slightly higher incidence in the placebo group. Laboratory values and other indicators of liver function and injury were similar across the treatment groups. In general, baseline and disease characteristics were balanced across the 3 treatment groups.

Regarding to the composite primary endpoint results, at month 12, a higher percentage of patients in the fixed OCA 10 mg (n=34, 47%) achieved the primary endpoint compared to placebo (n=7, 10%), thus demonstrating superiority (p<0.0001). A higher percentage of patients (n=32, 46%) in the OCA titration group (key secondary endpoint) also achieved the composite endpoint, compared to placebo (p<0.0001). It is noted that responses are mainly driven by normalisation of ALP. As the vast majority of patients entered with normal/near normal Bilirubin values and remained normal throughout the study duration most information was generated in patients with compensated disease and in patients in early stages of clinical disease with little hepatic dysfunction. Bearing in mind the limited PK and clinical data available in patients with hepatic dysfunction and/or more advanced disease stage, confirmation will need to be given on the extent the results observed in this mild population can be extrapolated to the whole target population, including patients with moderate to severe liver disease, decompensated disease and transplanted patients. This will be addressed by both, study 747-302 and study 742-401 which are conditions to the marketing authorisation.

Additional efficacy analyses of the primary endpoint (based on completer and EE populations) were supportive of the main results.

Regarding to other secondary endpoints (mean absolute and percentage change from baseline to 6 and 12 months in ALP, conjugated bilirubin, GGT, ALT, and AST), statistically significant differences were observed over placebo for both OCA treatment groups for most of the endpoints (with the exception of LS mean percentage change of bilirubin for OCA 10 mg vs. placebo, at 6 months).

No statistically significant changes were observed for either OCA treatment group vs. placebo in terms of albumin, prothrombin time and INR, probably due to the fact the most patients had normal levels at baseline.

Responder analyses were predefined in the protocol as the percentage of subjects with a decrease in ALP of ≥10%, ≥15%, ≥20%, and ≥40% from Baseline or ≤ULN.

At both timepoints, 6 and 12 months, a higher percentage of patients in both OCA treatment groups achieved the ALP reduction, compared to placebo (p≤0.0001). At 12 months, approximately one third of

patients in each OCA treatment group achieved an ALP reduction of >40%, compared with 1% in the placebo group. Only one patient in the OCA titration group and 5 patients in the OCA 10 mg group achieved ALP normal levels, vs. none in the placebo group (statically significant OCA 10 mg vs. placebo). In clinical practice, the normalization of ALP levels is considered a sign of good prognosis and it would add support to the correlation between ALP levels and long-term clinical outcomes. However, few patients achieved this after 12 months of treatment and it is difficult to make any conclusions.

The percentage of subjects achieving the biochemical treatment response criteria (Paris I modified, Paris II, Mayo II, and Toronto II), were also higher in OCA treated patients than in the placebo group. The Rotterdam criteria, with defines responders as the % of patients reaching total bilirubin ≤ULN and albumin ≥LLN, did not reach statistical significance.

Regarding the OCA effect on indirect inflammation markers, several biochemistry markers (IgM, CRP, and TNF-α) were evaluated to assess a potential effect on FXR agonism. After 12 months of OCA treatment, some differences in IgM, CRP and TNF-α are noted between the OCA groups in comparison with placebo (some of them statistically significant); however, their clinical relevance remains unknown.

A total of 36 patients (52%) remained at 5mg dose and did not up titrate to 10mg. The main reason to remain at 5 mg dose was obtaining an efficacy response (n=32). In the subgroup of patients remaining at 5mg, 67%, 50% and 53% achieved the primary endpoint at 6, 9 and 12 months, respectively. Of those who up-titrated (0% had achieved endpoint at 6 months), 36% and 39% reached the primary endpoint at 9 and 12 months, respectively. These results support the up-titration after 6 months of treatment.

Monotherapy use in intolerant patients

Fifty-one PBC patients with baseline ALP 1.67-times ULN or greater and/or total bilirubin greater than ULN were evaluated for a biochemical response to OCA as monotherapy (24 patients received OCA 10 mg once daily and 27 patients received placebo) in a pooled analysis of data from a randomized, double-blind, placebo-controlled 12 month study and from a randomized, double-blind, placebo-controlled, 3-month trial. At Month 3, 9 (38%) OCA-treated patients achieved a response to the composite endpoint, compared to 1 (4%) placebo-treated patient. The mean (95% CI) reduction in ALP in OCA-treated patients was 246 (165, 327) U/L compared to an increase of 17 (-7, 42) U/L in the placebo-treated patients.

These data, although derived from a small sample size, does not suggest a lesser effect in this patient subset. Considering that patients intolerant to UDCA have an unmet medical need and are increased risk of developing adverse outcomes, OCA might represent a viable treatment option for them.

Long term benefit

Two of the LTSE were still on-going at the time of the initial submission. The Applicant provided an efficacy (and safety) for update of these studies (747-301-LTSE, 747-201-LTSE), with a data cut-off date of 29 Jun 2015. These updated results are consistent with the previously observed results and suggest that the effect seems to be maintained over time (up to a maximum of 30 months of treatment).

Special populations

The number of patients >65 years of age included in the phase II and pivotal studies is limited, particularly very elderly patients (≥75 years old). Although the results were statistically significant, the number of patients over the age of 65, and in particular ≥75, is very small, which is considered an important limitation since elderly patients represent a big proportion of the target population. The lack of data is appropriately outlined in the SmPC for the attention of the prescriber and the confirmatory study 747-302 will consider elderly patients as a relevant sub-population. The study is currently ongoing and as

of 03/08/2016, of the 90 patients currently enrolled, 23% patients were ≥65 years, which is comparable to those in the Global PBC Study Group Database.

Few patients with renal impairment were included in the OCA phase II and III studies (most of them with mild renal impairment). Based on the post-hoc analyses performed by the Applicant, mild renal impairment does not seem to have a negative impact on efficacy. Due to the small number of patients with moderate renal impairment, separate efficacy data in this patient subset have not been provided. However, considering that obeticholic acid has minimal renal elimination with less than 3% of the dose recovered in urine and that based on population pharmacokinetic analysis, renal function did not have a meaningful effect on the pharmacokinetics of obeticholic acid the CHMP considered it sufficient to add this information to the SmPC.

In addition, the Applicant tried to characterise the efficacy (and safety) of OCA in a more advanced PBC population by developing a clinical algorithm that would identify these patients. Results on the population identified by this algorithm seem to be similar to those of the study 747-301 population. However, it needs to be highlighted that this algorithm has not been validated. In addition, even assuming that the algorithm correctly selects patients with a more “advanced” disease stage, the overall number of patients continues to be too small to reach a sound conclusion. Results from both, study 747-302 and 747-401 on clinical outcomes are to be provided in order to be able to confirm with certainty on the effects of OCA in this more advanced population. The Applicant will provide annual updates to CHMP on study status/progress, interim results and immediate notification of unforeseen delays or issues with study conduct. In addition, any changes on the conduct of the study derived from the IA and/or DMC´s recommendations, which might result on the premature discontinuation, should be discussed with the CHMP.

Additional efficacy data needed in the context of a conditional MA

The Open-label study (747-201 Phase 2) and a randomised Clinical Trial, (747-301, Phase 3) did not show difference in clinical disease symptoms such as pruritus and fatigue between OCA treatment vs. placebo (=standard of care (UDCA) + placebo). Efficacy has currently been substantiated using surrogate endpoints ALP and bilirubin (which for UDCA are indicators for disease progression). The effectiveness of OCA treatment to reduce clinically relevant disease symptoms (i.e. reducing disease burden for patient) is currently unknown.

Furthermore the clinical follow-up is currently limited, i.e. max 5 years, in a limited number of patients. In the Phase 3 RCT only efficacy data up to 12 months is available, which is considered short in the context of a slowly progressive disease.

Study 747-302 is imposed to address current uncertainties regarding the relationship between biochemical changes and liver clinical outcomes and long-term effects of the treatment

The pivotal RCT (747-301) included mostly patients at an earlier disease stage. It is uncertain whether the effects on biochemical parameters and tolerability observed in this population can be extrapolated to patients with a more advanced disease.

Study 747-401 is imposed to address current uncertainties regarding efficacy, safety and PK in patients with a more advanced disease state.

2.4.4. Conclusions on the clinical efficacy

Efficacy shown in the pivotal trial is mainly based on biochemical changes as surrogate for clinical efficacy.

Available clinical data, although limited, together with the previous experience with UDCA, indicate that OCA treatment may translate into a clinically relevant benefit in the treatment of PBC after failure to UDCA. This is requested to be confirmed by means of the clinical outcome study (747-302) in the scope of this conditional marketing authorisation. In conjunction with study *747-401* the conditions are intended to provide long-term clinical outcome data including data in the more advanced liver disease population.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

Description	Due date
Interventional study 747-302: Description: In order to confirm the efficacy and safety of Ocaliva, the MAH should conduct and submit the results of study 747-302, a confirmatory double-blind, randomised, placebo-controlled multicentre study investigating the clinical benefit associated with Ocaliva treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints. Rationale: to investigate the effect of OCA on clinical outcomes in subjects with PBC	Final report: 2023
Interventional study 747-401: Description: In order to confirm the efficacy and safety of Ocaliva, the MAH should conduct and submit the results of study 747-401, a double-blind, randomised, placebo-controlled study evaluating the efficacy, safety and pharmacokinetics of Ocaliva in patients with PBC and moderate to severe hepatic impairment. Rationale: to investigate the uncertainties related to the lack of data in a population with more advances liver disease	Final report: 2020

2.5. Clinical safety

Patient exposure

A total of 1507 subjects have been exposed to at least a single dose of OCA. This includes 169 subjects from 2 non-Intercept sponsored studies in other indications.

The majority of subjects in the overall population had OCA exposure <3 months, consistent with the extensive Phase 1 program. Excluding 13 subjects received radiolabeled OCA in Study 747-113, of the remaining 1325 subjects, 290 had ≥6 months of exposure and 232 had ≥12 months of exposure, respectively. The mean (SD) number of days on OCA was 141.1 (279.60), the mean exposure was 0.42 (0.797) years, and the mean daily OCA dose received was 22.7 mg (range of mean daily dose 10.8 mg to 28.0 mg). The mean daily OCA dose was predominantly driven by the higher doses evaluated in the Phase 2 programs (up to 50 mg).

Table 28: Cumulative Number (%) of Subjects Exposed to OCA for Various Durations by Dose During the Double-Blind, Placebo-Controlled Studies in Subjects with PBC (All Double-Blind OCA-Treated Subjects, N = 306)

Dose, n (%)	At Least 1 Week Exposure	At Least 1 Month Exposure	At Least 3 Months Exposure	At Least 6 Months Exposure	At Least 9 Months Exposure	At Least 12 Months Exposure
Placebo (N = 134)	133 (99)	132 (99)	76 (57)	70 (52)	70 (52)	26 (19)
OCA Titration (N = 70)*	70 (100)	69 (99)	69 (99)	69 (99)	66 (94)	21 (30)*
OCA 10 mg (N = 131)	131 (100)	122 (93)	69 (53)	64 (49)	64 (49)	16 (12)*
OCA 25 mg (N = 48)	48 (100)	43 (90)	1 (2)	0	0	0
OCA 50 mg (N = 57)	51 (89)	38 (67)	3 (5)	0	0	0
Total OCA (N = 306)	300 (98)	272 (89)	142 (46)	133 (43)	130 (42)	37 (12)*

* Total patient exposure for each subject was defined as the time interval between the first dose and the last dose. Although most subjects completed Study 747-301, their last study visit occurred prior to Day 365 (due to protocol visit windows) and therefore are not included in the calculation of exposure for at least 12 months.

Adverse events

- ***Pivotal study 747-301***

Across treatment groups, a similar number of subjects reported TEAEs (66 subjects [90%] from the placebo group reported 452 TEAEs, 65 subjects [93%] from the OCA titration group reported 471 TEAEs, and 69 subjects [95%] from the OCA 10 mg group reported a total of 467 TEAEs).

The most frequently reported TEAE across all treatment groups was pruritus. Compared with placebo, the overall incidence of treatment-emergent pruritus was greater in the OCA titration and OCA 10 mg groups (28 subjects [38%], 39 subjects [56%], and 51 subjects [70%], respectively. The incidence of related TEAEs appeared to increase with increasing dose (52%, 60%, and 74% in placebo, OCA titration, and OCA 10 mg treatment groups, respectively).

TEAEs that occurred with an incidence of ≥5% and were reported more frequently (at any percentage above placebo) in either OCA treatment group included rash, eczema, fatigue, peripheral oedema, pyrexia, nasopharyngitis, influenza, bronchitis, sinusitis, diarrhoea, constipation, abdominal discomfort, arthralgia, cough, oropharyngeal pain, procedural pain, fractures, palpitations, and hypothyroidism.

There appeared to be a dose-related increase in the incidence of fatigue, arthralgia, and pruritus. Pyrexia was observed in 1 subject (1%) in the placebo group, no subjects in the OCA titration group, and 5 subjects (7%) in the OCA 10 mg group.

Table 29: Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects in Either OCA Treatment Group by System Organ Class and Preferred Term: Safety Population (N = 216)

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
System Organ Class/ Preferred Term, n (%)	Subjects[a] (%)	Subjects[a] (%)	Subjects[a] (%)
All TEAEs	66 (90)	65 (93)	69 (95)
Skin and Subcutaneous Tissue Disorders			
Pruritus	28 (38)	39 (56)	50 (68)
Rash	3 (4)	3 (4)	4 (5)
Eczema	0	4 (6)	2 (3)
General Disorders and Administration Site Conditions			
Fatigue	10 (14)	11 (16)	17 (23)
Oedema peripheral	2 (3)	2 (3)	5 (7)
Pyrexia	1 (1)	0	5 (7)
Infections and Infestations			
Nasopharyngitis	13 (18)	17 (24)	13 (18)
Upper respiratory tract infection	8 (11)	4 (6)	4 (5)
Urinary tract infection	8 (11)	4 (6)	4 (5)
Influenza	4 (5)	5 (7)	4 (5)
Bronchitis	0	4 (6)	1 (1)
Sinusitis	0	1 (1)	4 (5)
Gastrointestinal Disorders			
Nausea	9 (12)	4 (6)	8 (11)
Diarrhoea	8 (11)	2 (3)	8 (11)
Constipation	4 (5)	5 (7)	5 (7)
Abdominal pain upper	5 (7)	5 (7)	4 (5)
Gastrooesophageal reflux disease	4 (5)	2 (3)	4 (5)
Dyspepsia	8 (11)	4 (6)	0
Abdominal discomfort	1 (1)	5 (7)	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	3 (4)	4 (6)	7 (10)
Back pain	8 (11)	4 (6)	4 (5)
Nervous System Disorders			
Headache	13 (18)	12 (17)	6 (8)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	5 (7)	4 (6)	6 (8)
Oropharyngeal pain	1 (1)	5 (7)	6 (8)
Injury, Poisoning and Procedural Complications			
Procedural pain	1 (1)	4 (6)	1 (1)
Fractures[b]	3 (4)	2 (3)	4 (5)
Cardiac Disorders			
Palpitations	1 (1)	2 (3)	5 (7)
Eye Disorders			
Dry eye	4 (5)	2 (3)	4 (5)
Endocrine Disorders			
Hypothyroidism	1 (1)	4 (6)	1 (1)

N = total number of subjects; n = number of subjects experiencing event

Note: A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. a At each level of summation (overall, preferred term), subjects reporting more than one AE are counted only once. b As a post-hoc analysis, fractures are presented as an aggregate of all fractures/skeletal injuries within each treatment group. For the placebo group, 5 fractures (2 tibia fractures, 2 pubis fractures, and 1 upper limb fracture) were experienced by 3 subjects; in the OCA titration group, 2 fractures (1 wrist fracture and 1 ulna fracture) were experienced by 2 subjects; in the OCA 10 mg group, 7 fractures (2 clavicle fractures, 2 radius fractures, 2 wrist fractures, and 1 skeletal injury) were experienced by 4 subjects

The majority of TEAEs were mild to moderate across all treatment groups. The overall incidence of severe events was 12% in the placebo group and 31% and 29% in the OCA titration and OCA 10 mg treatment groups, respectively. The imbalance in the incidence of severe TEAEs between the OCA and placebo groups was primarily attributable to the higher incidence of severe pruritus.

The incidence of subjects reporting at least 1 related TEAE was highest in the OCA 10 mg group (52%, 60%, and 74% in the placebo, OCA titration, and OCA 10 mg groups, respectively). Across treatment groups, of the subjects with related TEAEs, the majority had a related pruritus TEAE and a dose-dependent relationship in the incidence of related pruritus TEAEs was observed. The number of subjects with related TEAEs of pruritus was 27 (37%) in the placebo group, 35 (50%) in the OCA titration group, and 48 (66%) in the OCA 10 mg group.

Fatigue and nausea were the only other TEAEs considered to be related that occurred at an incidence ≥5% in any treatment group.

- **DB, placebo-controlled studies**

In the DB, placebo-controlled studies, 306 patients were exposed to OCA with 201 of them expose to doses ≤10 mg. In the OCA 10 mg group, almost all patients (n= 123, 93%) were exposed for at least 1 month, with 49% of patients (64) exposed for at least 9 months. For OCA doses above 10mg, exposure past 1 month was limited due to the nature of the study designs (DB duration of 3 months) and the poor tolerance observed at higher doses.

The majority (>80%) of patients within each study completed the double-blind phase, with generally similar completion rates across the 3 studies. The most common reason for discontinuation was pruritus.

Pooled data largely supports the safety profile observed in the pivotal studies. Some dose-relationship trends can be observed, especially in terms of pruritus, which showed the highest incidence in the treatment groups that initiated treatment at 50 mg OCA (80%- 94%).

- **AESIs**

The Applicant selected AESIs as those TEAEs frequently reported and assessed as OCA-related (e.g. pruritus), those related to dose-limiting toxicities (e.g. hepatic disorders), lab changes (e.g. lipids, liver enzymes) or other TEAs generally associated with adverse outcomes (e.g. CV AEs). A comparison was made between OCA and placebo groups.

Pruritus

Pruritus is a common symptom associated with PBC and also is an OCA-induced, dose-related TEAE. This is an AE that could impact patient's quality of life and, in some hard to control cases, lead to an early LT due to being treatment-resistant.

In the pivotal study, over half of the patients on any of the treatment groups reported on-going pruritus at baseline (64%, 53% and 60% in the placebo, OCA titration and OCA 10mg groups, respectively). TEAEs of pruritus, defined as new on-set or increasing intensity pruritus, were more frequently reported

in OCA-treated patients than in placebo-treated patients (38%, 56% and 70%, in the placebo, OCA titration and OCA 10 mg groups, respectively). Most of them required an intervention for pruritus (50%, 62% and 59% in the placebo, OCA titration and OCA 10 mg groups, respectively). Discontinuations due to pruritus occurred in approximately 10% of patients (n=8, 1 in the OCA titration group, 7 in the fixed OCA 10 mg group). In terms of severity, more OCA-treated patients reported a maximum severity of moderate/severe events, when compared with placebo treated patients (17%, 40%, and 49%, in the placebo, OCA titration and OCA 10 mg groups, respectively).

Based on the titration subgroups, the percentage of patients that experienced pruritus during the 2nd 6-month period was similar between those who remained at 5mg and those that up-titrated to 10mg (58% vs. 55%). The incidence of pruritus for both titration subgroups was lower during this later period (both 33%), compared with the initial 6 months. Severity (in terms of severe pruritus event days) was lower in those patients that up-titrated than during the initial 6-month period of those from the OCA 10mg group (2.31 days vs. 41.05 days).

Separate data on new on-set or increasing intensity pruritus was presented as response to the D120 LoQ.

Table 30: **Summary of Treatment Emergent Pruritus by Baseline Pruritus Status**

	Placebo (N = 73)	**Titration OCA (N = 70)**	**10 mg OCA (N = 73)**
Any TEAE of Pruritus, (n, %)	28 (38)	39 (56)	51 (70)
Median Time to Onset of Pruritus (Days)	50.5	24.0	9.0
Discontinuations due to Pruritus (n, %)	0	1 (1)	7 (10)
With Baseline Pruritus (n, %)	**47 (64)**	**37 (53)**	**44 (60)**
Any TEAE of Pruritus, (n, %)	7 (15)	17 (46)	26 (59)
Median Time to Onset of Pruritus (Days)	68.0	16.0	7.0
Discontinuations due to Pruritus (n, %)	0	1 (3)	7 (16)
Without Baseline Pruritus (n, %)	**26 (36)**	**33 (47)**	**29 (40)**
Any TEAE of Pruritus, (n, %)	9 (35)	12 (36)	17 (59)
Median Time to Onset of Pruritus (Days)	12.0	46.0	14.0
Discontinuations due to Pruritus (n, %)	0	0	0

n = number of patients. Note: A TEAE of pruritus is defined as any pruritus event that newly appeared, increased in frequency, or worsened in severity following initiation of study drug. Patients reporting more than one TEAE of pruritus are counted only once using the highest severity.

Patient reported outcomes, such as pruritus VAS or the 5-D pruritus questionnaire, seemed to indicate that patient's perception of pruritus severity improved with continued treatment (VAS), and the analysis of the 5-D pruritus questionnaire (by ANCOVA) did not show any significant differences across the different treatment arms at the end of the 12-month double-blind treatment period.

In the DB, placebo-controlled studies, a clear dose-relationship trend can be observed for pruritus, which showed the highest incidence in the treatment groups that initiated treatment at 50 mg OCA (80%-94%).

Hepatic-related effects

The incidence of TEAEs in this SOC group was low in general. However, they seem to be dose-related, with more OCA-treated patients reporting them, compared to the placebo group.

Table 31: Treatment-Emergent Adverse Effects of Special Interest-Hepatic Disorders, Double-Blind, Placebo-Controlled Studies in Subjects with PBC (All Treated Subjects, N = 440)

Incidence						
		OCA				
	PBO (N = 134)	Titration (N = 70)[a]	10 mg (N = 131)	25 mg (N = 48)	50 mg (N = 57)	Total OCA (N = 306)
Special Interest Category	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]
Hepatic Disorders	2 (1)	3 (4)	4 (3)	2 (4)	5 (9)	14 (5)
Exposure Adjusted Incidence						
		OCA				
	Placebo (N=134, PEY=84)	Titration (N=70, PEY=67)	10 mg (N=131, PEY=76)	25 mg (N=48, PEY=10)[b]	50 mg (N=57, PEY=9)[b]	Total OCA (N=306, PEY=163)[b]
Special Interest Category	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]
Hepatic Disorders	2.4	4.5	5.2	19.8	54.5	8.6

[a] In Study 747-301, subjects randomized to OCA 5 mg were assessed at Month 6 for clinical response and tolerability. Subjects who did not achieve the primary composite endpoint and did not have tolerability issues were able to uptitrate to OCA 10 mg.
[b] At each level of summation (overall, system organ class, preferred term), subjects reporting more than one AE are counted only once.
Adverse events reported in the placebo group were: non-serious liver function test abnormal and varices oesophageal (serious).
Adverse events reported for subjects in the Titration and OCA 10 mg groups were: Ascites, varices oesophageal, hepatic pain, International normalised ratio increased, blood bilirubin increased, hepatic enephalopathy, and spider naevus.
Adverse events reported for subjects in the OCA 25 mg and 50 mg groups were: Ascites, biliary cirrhosis primary, hepatomegaly, jaundice, portal hypertension, alanine aminotransferase increased, aspartate aminotransferase increased, and bilirubin conjugated increased.

Lipid-related effects and Cardiovascular TEAE

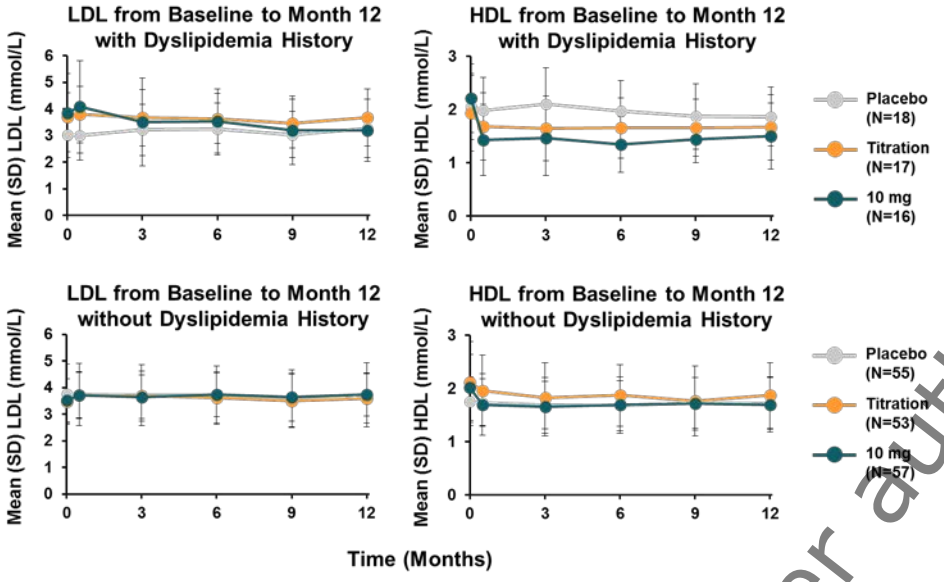
Lipid disorders are commonly seen in patients with PBC. Any relevant changes can be considered as relevant due to the potential long-term implications in CV safety. OCA treatment has been associated with reductions in HLD-c levels and increases in LDL-c.

In 60 OCA-treated subjects, HDLc levels decreased below the LLN at least on 1 day after the first dose of investigational product. In 89 OCA-treated subjects, LDLc levels were >LLN for at least 1 post- day and were increased from Baseline by >10 mg/dL for 2 consecutive visits. Ofthese, altogether 8 OCA-treated subjects experienced a qualifying change in HDLc and/or LDLc levels and also developed a cardiovascular event with 1 OCA-treated subject in Study 747-301 (OCA titration) and 1 OCA-treated subject in Study 747-202 (OCA 50 mg) experiencing an SAE. Thus, changes in post-day 1 HDLc or LDLc did not reveal a clear pattern with regards to the incidence of cardiovascular disorders by dose or between OCA-treated subjects and placebo-treated subjects. There was no difference in the incidence of lipid disorders between OCA and placebo groups.

Dyslipidemia Disorders occurred with an incidence of approximately 2% in all OCA dose groups relative to 1% with placebo treatment. The minimum time to the first onset was sooner in the OCA-treated subjects compared with placebo-treated subjects (80 days vs. 188 days). All events of lipid disorders were mild or moderate in severity. One event of hypercholesterolemia (study 747-202, OCA 25 mg) and 2 events of hyperlipidemia (study 747-301, OCA 10 mg) were considered to be possible related to investigational product. Neither subject experienced a cardiovascular event.

Further details were provided as part of the D120 responses (see below).

Figure 34: **Mean (SD) LDL-C and HDL-C Levels Over Time for Patients With or Without Medical History of Dyslipidemia**



Lower limit of normal for HDL-C 1.04 mmol/L; Upper limit of normal for LDL-C 2.59 mmol/L.

The distribution of patients with a history of cardiovascular conditions at the start of treatment was comparable across treatment groups (40%, 34%, and 42% for placebo, OCA titration, and OCA 10 mg, respectively) and most of the CV events occurred in patients with pre-existing medical conditions (Table 33) and were not associated with vital sign or ECG abnormalities.

Table 32: **Cardiovascular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: Safety Population (N = 216)**

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
System Organ Class Preferred Term	n[a] (%)	n[a] (%)	n[a] (%)
Patients with abnormal CV medical history at Baseline	29 (40)	24 (34)	31 (42)
Cardiac Disorders	2 (7)	3 (13)	4 (13)
Palpitations	1 (3)	1 (4)	3 (10)
Cardiac failure	0	1 (4)	0
Cardiomegaly	1 (3)	0	0
Hypertrophic cardiomyopathy	0	1 (4)	0
Sick sinus syndrome	1 (3)	0	0
Thrombophlebitis	0	0	1 (3)
Patients without CV Medical history	44 (60)	46 (66)	42 (58)
Cardiac disorder	0	1 (2)	2 (5)
Palpitation	0	1 (2)	2 (5)
Overall Incidence of CV events	**2 (3)**	**4 (6)**	**6 (8)**

n = number of patients.

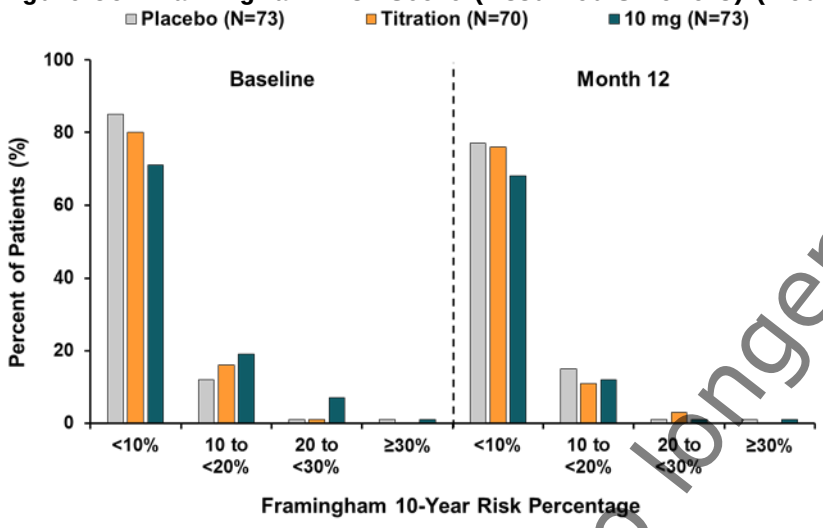
Note: A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. Patients reporting more than one AE within a special interest category, system organ class, or preferred term are counted only once per dose group. Cardiac Disorders are any event in the MedDRA

Cardiac Disorders SOC or the MedDRA SMQs of Embolic and thrombotic events or Ischaemic heart disease.[a]

At each level of summation (overall, system organ class, preferred term), patients reporting more than one AE are counted only once using the closest relationship to investigational product.

The Framingham Risk was used to assess Study 747-301 patients' 10 year risk for developing CV disease (Figure 35). Since smoking status was not collected in the study, a worst case scenario was assumed with all patients assumed to be smokers. The results of this analysis indicated that the vast majority of patients had a <10% risk for developing a CV event when assessed at baseline and after 12 months of treatment demonstrating a stable CV risk profile with OCA treatment.

Figure 35: **Framingham Risk Score (Assumed Smokers) (Double-Blind, Phase 3)**



The long-term cardiovascular implications of changes in serum lipoproteins continue to be investigated in the ongoing LTSE studies and the long-term PBC outcomes study (747-302).

Serious adverse event / deaths / other significant events

Deaths

Across all studies conducted with OCA, a total of 4 treatment-emergent deaths were reported. In addition to two deaths occurred in patients with PBC which were considered not related to OCA, 2 female subjects with non-alcoholic steatohepatitis (NASH) experienced an SAE that was fatal. One of these deaths was considered by the investigator as possibly related to OCA (FLINT).

Serious Adverse Events

In total, 31 subjects experienced SAEs in the clinical pharmacology and double-blind, placebo-controlled studies.

One OCA-treated subject in the clinical pharmacology studies experienced an SAE after the subject had been discontinued from the study. This was a male subject (OCA 25 mg, 747-110) without a prior history of liver disease that was discontinued from the study due to a TEAE of abdominal pain. Eight days after discontinuation, the subject experienced 2 SAEs (Cholecystitis acute and Cholelithiasis). The SAEs were assessed as definitely related to treatment by the Investigator.

In the double-blind, placebo-controlled studies in subjects with PBC, 25 subjects [8%] treated with OCA experienced 33 SAEs, compared with 5 subjects (4%) treated with placebo who experienced 10 SAEs. The incidence of SAEs did not appear to be dose-related. The majority of subjects (n = 21) experienced SAEs

that were assessed as unlikely or not related to treatment and the majority of subjects who experienced an SAE during the double-blind phase did not discontinue treatment or discontinue from the study.

Of SAEs that occurred in OCA-treated subjects, 4 events were considered related to OCA therapy, all of which occurred at the OCA 50 mg dose (Study 747-202) and within 1 month of initiating treatment. Two of these SAEs were in the SOC of "Hepatobiliary Disorders" (jaundice, biliary cirrhosis primary [PBC flare]), 1 in the SOC of Gastrointestinal Disorders (gastrointestinal hemorrhage), and 1 in the SOC of "General Disorders and Administration Site Conditions" (chest pain).

With the exception of varicose vein and osteoarthritis, which were each experienced by 2 OCA-treated subjects (<1%), and dyspnea, which was experienced by 2 placebo-treated subjects (<1%), no SAEs were experienced by more than 1 subject. Overall, each SAE was reported by <1% of subjects indicating no particular pattern or trend for SAEs were seen with OCA treatment. Most SAEs were considered to be recovered, resolved.

More subjects treated with OCA compared with placebo had SAEs in the SOCs of "Gastrointestinal Disorders", "Injury, Poisoning and Procedural Complications", "Musculoskeletal and Connective Tissue Disorders", and "Infections and Infestations".

Within the SOC of Injury, Poisoning, and Procedural Complications, 3 subjects in (4%) the OCA 10 mg group had fracture-related SAEs compared with 1 subject in the placebo group. Each fracture-related SAE was experienced by a single subject and none were considered related to treatment. In a population of mostly women with PBC, these events were not unexpected and a review of the subjects' medical histories indicated that most subjects had a relevant medical history.

The incidence of SAEs in the OCA titration group was higher compared with other doses and compared with placebo. Within this treatment group, there was a clustering of SAEs in the SOC of 'Gastrointestinal Disorders" (4 subjects [6%]). Overall, SAEs that were experienced by OCA-titration-treated subjects were predominantly associated with their history of PBC and none were considered related to investigational product.

Laboratory findings

Hematology

Transient changes in individual subject hematology analytes were experienced across the placebo and OCA-treatment groups. No relevant changes for any hematology parameter were observed in any treatment group.

Serum Chemistry

No clinically meaningful differences in absolute mean changes in serum chemistry parameters from Baseline to each assessed timepoint were observed across treatment groups, with the exception of analytes expected to be affected by OCA (i.e., markers of improvement in intrahepatic cholestasis and hepatocellular injury, synthetic liver function, and changes in lipoprotein metabolism).

Safety in special populations

The majority of subjects treated with OCA from the double-blind studies (747-201, 747-202, and 747-301 [n=306] were <60 years old (190 [62%])**:** 97 (32%) age 60-69, 16 (5%) age 70-79, and three ≥80 (<1%).Subjects in the double-blind phases of PBC studies were pooled and analysed by their "age at time of enrolment" (<65 years and ≥65 years). Of 306 subjects treated with OCA, 252 were <65 years of age

and 54 were ≥65 years of age. The age distribution in the placebo group was similar to that of OCA-treated subjects (112 subjects <65 years of age and 22 were ≥65 years of age).

Although, the disparity in the overall number of subjects between the age groups precludes major conclusions, the incidence of TEAEs in both subgroups was similar (95% of OCA-treated subjects experienced a TEAE in the <65 years age group versus 89% in the ≥ 65 years group), which was also similar to the TEAE incidence in placebo-treated subjects in both age groups (88% and 91%, respectively). Thus, there did not appear to be an age-related increase in the incidence of TEAEs in general and there was no age-related increase in the incidence of common TEAEs (pruritus, nasopharyngitis, fatigue, and headache). In addition, there were no age-related differences by dose.

There appeared to be slightly more OCA-treated subjects ≥65 years of age with a cardiovascular disorder TEAE compared with subjects <65 years of age (7% and 3%, respectively); this pattern was also observed in placebo-treated subjects (9% and 3%, respectively) suggesting this is an age-related observation as opposed to treatment-related. All other AESIs (pruritus, hepatic disorders, and dyslipidemia) were more frequently observed in subjects <65 years of age compared with subjects ≥65 years of age although, the small number ≥65 years subjects precludes definitive conclusions

The incidence of treatment emergent SAEs was similar overall in OCA-treated subjects in both age groups. There was no difference in the types of SAEs occurring in either age group.

Paediatric Population

PBC has only been reported extremely rarely in paediatric patients. Therefore, no clinical studies were conducted in paediatric subjects with PBC.

Hepatic Impairment

The Sponsor did not conduct a study in patients with decompensated PBC. However, data evaluating safety of a single dose of OCA 10 mg in subjects with a spectrum of hepatic impairment (747-103) due to other underlying liver diseases and multiple day dosing (6 to 12 days) at doses of OCA 10 mg and OCA 25 mg in subjects with alcoholic cirrhotic portal hypertension (747-204) are available.

The entirety of data from these studies in combination with information obtained from further modelling the data suggest that although systemic concentrations of OCA increase with increasing severity of hepatic impairment, hepatic concentrations are unlikely substantially different and the safety profile of OCA in subjects with Mild/Moderate/Severe cirrhosis was similar to that observed in the compensated PBC subjects studied.

Based on both Studies 747-103 and 747-204, increased systemic exposure to OCA and its conjugates, in conjunction with increased exposure to endogenous bile acids with increasing severity of cirrhosis, was not associated with an apparent change in the safety profile of OCA as assessed by the incidence and severity of TEAEs or by changes in clinical laboratory tests. No SAEs or study discontinuations were observed in Study 747-103.

The AE profile of hepatically-impaired subjects in Study 747-204 was similar to that observed in double-blind, placebo-controlled subjects with PBC. Pruritus, headache, and nausea were the most commonly observed TEAEs in Study 747-204 and were also common TEAEs (occurring with an incidence of ≥5%) in double-blind, placebo-controlled studies in subjects with PBC. Most events were considered to be of mild severity and aside for pruritus, only nausea was considered to be related in more than 1 subject. No subjects treated with OCA 10 mg reported an SAE or a study discontinuation due to a TEAE; 1 subject treated with OCA 25 mg reported an SAE (lacunar infarction) 3 days after initiating treatment

and was discontinued from the study. The SAE was assessed as unlikely related to OCA. Overall, the severity of TEAEs and incidence of SAEs did not appear to increase in subjects with hepatic impairment.

Renal impairment

No specific clinical studies have been conducted in patients with renal impairment. After administration of radiolabelled OCA in healthy volunteers, less than 3% of the dose was eliminated in urine suggesting minimal renal elimination. Renal elimination of total OCA (OCA, glyco-OCA and tauro-OCA) was less than 1% in subjects with hepatic impairment.

Based on these data, it is highly unlikely that renal impairment will affect the PK or safety profile of OCA and therefore no dose adjustment of OCA is required for renal impairment (747-113).

Pregnancy and Lactation

No clinical studies in pregnant or lactating women have been conducted. One pregnancy occurred during the 12-month, double-blind phase of Study 747-301. The subject was not taking any contraception at the time of the pregnancy, which was in the assessment of the Sponsor a major protocol violation.

Studies of reproductive and developmental toxicology in animals revealed no untoward effects of OCA. Based on the lack of specific effects in the battery of reproductive and developmental toxicity studies, and the large safety margin at the NOAEL dose for developmental toxicity in rat and rabbit, OCA would not be expected to cause foetal harm when administered during conception of pregnancy. Section 4.6 of the SmPC recommends as a precautionary measure to avoid use of obeticholic acid during pregnancy.

No specific nonclinical or clinical studies were conducted to evaluate the presence of OCA or conjugates in breast milk. The tauro-conjugate of OCA was observed, at low exposures, in rat pups nursing from dams dosed with OCA. The lack of effects in offspring from pre-/postnatal studies at up to 21-fold anticipated human exposure suggests that there are no specific concerns for lactation or breastfeeding of infants. Section 4.6 of the SmPC recommends that a decision should be made whether to discontinue breast-feeding or to discontinue/abstain from obeticholic acid therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Safety related to drug-drug interactions and other interactions

Five Phase 1 DDI studies involving repeated oral administrations of 10 mg and 25 mg OCA were performed to evaluate the potential of OCA at steady state concentrations to act as an inhibitor, inducer or substrate of certain metabolizing enzymes and transporters (midazolam (CYP3A4), caffeine (CYP1A2), warfarin (CYP2C9), rosuvastatin (BCRP, OATP1B1, OATP1B3), dextromethorphan (CYPD6), omeprazole (CYP2C19), and digoxin(P-gp). Based on the results of these studies, no inhibition to weak inhibition involving OCA and CYPs and transporters were observed and were not expected to cause clinically meaningful interactions, particularly in relation to safety.

However, the weak suppression of CYP1A2 (primarily at the 25 mg dose level) may produce clinically relevant increases in exposure for drugs that are metabolized by this CYP and have a narrow therapeutic window. This is outlined in the SmPC for the attention of the prescriber.

Across the DDI studies, no new safety signals were identified. There were no deaths or other significant TEAEs reported. One subject in Study 747-110 discontinued due to a TEAE (abdominal pain) and experienced 2 SAEs (cholecystitis acute and cholelithiasis) after discontinuation from the study. No safety signals suggesting an overexposure to OCA were observed during concomitant administration of OCA and omeprazole, supporting that gastric pH is not an important determinant in OCA absorption.

Intrinsic Factors

TEAE data from 306 PBC subjects treated with OCA and 134 (total of 440 PBC subjects) subjects treated with placebo in the double-blind, placebo-controlled studies were evaluated for possible subgroup differences.

Age at PBC Diagnosis

No substantial differences in the incidence of pruritus, fatigue, SAEs, CV events by age at PBC diagnosis were readily obvious. The duration of treatment in all 3 double-blind placebo controlled studies is considered too short and the number of subjects exposed too small to derive meaningful conclusions regarding the incidence of some of the events, e.g. cardiovascular events. Long term safety will be followed up as missing information as outlined in the risk management plan.

Gender

Male gender has been associated with a worse clinical prognosis for PBC. Overall very few male patients were included to allow a sound conclusion. In general, no clear indications of sex-related differences in the safety profile of OCA were observed.

BMI

There incidence of TEAEs by BMI subgroup was assessed and there was no difference in the overall incidence of TEAEs (94% for both BMI subgroups). There did not appear to be a dose-related effect on the incidence of TEAEs by BMI subgroup. In addition, there was no marked difference in the most commonly reported TEAEs when analyzed by BMI subgroup.

Race

The majority of subjects who participated in the double-blind studies were White subjects versus non-White subjects (296 subjects versus 10 subjects); 95% and 80% of subjects, respectively, experienced a TEAE. Due to the small number of Non-White subjects, conclusive interpretations of AEs by race cannot be made.

Disease Severity

Although no differences in safety profile were observed according to baseline bilirubin subgroups (≤ ULN vs.>ULN), bearing in mind the mild population included, more comprehensive data on the use in patients with moderate to severe hepatic impairment (Child-Pugh B and C) will be generated post authorisation.

Extrinsic factors

Region

In the double-blind period, the overall incidence of TEAEs by treatment group was similar between North America and Europe, with 95% and 93% of OCA-treated subjects experiencing a TEAE and comparable rates observed in the respective placebo groups. With the exception of nasopharyngitis, no regional differences in the incidence of common TEAEs in OCA-treated subjects were observed.

Incidence rates of cardiovascular disorders and dyslipidaemia disorders were comparable between regions. Hepatic disorders appeared to occur with slightly greater frequency with OCA treatment in North America (6%) compared to Europe (3%). The slightly higher event rate in North America was driven by events in the OCA 50 mg, which more North American (n = 40) subjects were exposed compared to Europe (n = 17). The incidence of treatment emergent SAEs did not show a regional difference or a distinct pattern of SAEs.

In summary, there was no significant regional variation in the safety profile of OCA. Hepatic disorders may have occurred with slightly greater incidence in North American subjects treated with OCA, but this was likely due to differential exposure to OCA 50 mg.

Discontinuation due to adverse events

Most subjects in the double-blind, placebo-controlled PBC studies completed their study. A total of 47 subjects (15%) treated with OCA withdrew from the study due to a TEAE while 4 subjects (3%) treated with placebo withdrew due to a TEAE.

Most TEAEs leading to discontinuation for OCA-treated subjects were in the SOC of "Skin and Subcutaneous Tissue Disorders" (36 subjects [12%]); 34 (11%) of these had a TEAE of pruritus that resulted in study discontinuation with most (n = 21) treated with OCA >10 mg.

In subjects treated with OCA 10 mg, the most frequently reported TEAE leading to study discontinuation was pruritus (n = 12). Of the 12 subjects with TEAEs of pruritus that resulted in study discontinuation, 7 occurred in Study 747-301 in the OCA 10 mg group. In this group, TEAEs of pruritus leading to discontinuation generally resolved within 2 months. In the OCA titration group, 1 subject withdrew due to a TEAE of pruritus after 221 days. The substantially lower incidence of subject discontinuations in the OCA titration group demonstrates the benefit of a titration regimen.

Other events that resulted in study discontinuation and were experienced by more than 1 OCA-treated subject were nausea (3 subjects [<1%]), ALT increased (2 subjects [<1%]), and oedema peripheral (2 subjects [<1%]). The highest rate of discontinuation was experienced by subjects treated with the 50 mg dose. Other than pruritus, no patterns were identified with respect to TEAEs leading to discontinuation.

Post marketing experience

At the time of submission of the dossier the product was not authorised in any country

2.5.1. Discussion on clinical safety

- ***Pivotal study 747-301***

Of the 217 randomised patients, 216 received at least one dose of the study treatments and 198 of them completed the 12-month DB period (70, 64 and 64 patients in the placebo, OCA titration and OCA 10 mg groups, respectively). The main reason for discontinuation was AE (n=15), followed by consent withdrawal (n=4).

Over 90% of patients on any of the treatment groups experienced at least one treatment emergent AE (TEAE), with over half of the TEAEs considered as treatment-related (52% in placebo, 60% in OCA titration group and 74% in the OCA 10 mg).

The most frequent TEAE across all treatment groups was pruritus, which is a symptom also known to be associated with PBC. Over half of OCA-treated patients experienced pruritus (56% and 68% in the OCA titration and OCA10mg groups, respectively), compared to 38% of the placebo-treated patients. Pruritus has been identified by the Applicant as an AE of Special Interest (AESI) and is further discussed at the end of this section.

Other TEAEs more frequently reported in OCA-treated patients than in placebo were fatigue, nasopharingitis, arthralgia and hypothyroidism.

It is noted that the frequencies of most GI disorders were similar for placebo and either OCA treatment group with the exception of dyspepsia, which was more frequently reported in placebo patients (8 vs. 4 [all in OCA titration group]).

Regarding lab abnormalities, no relevant haematological parameter changes were observed. For serum chemistry parameters, no relevant differences were observed across groups, with the exception of those parameters expected to be affected by OCA treatment.

In terms of severity, the majority of events were mild-moderate with a numerically more OCA patients reporting moderate to severe TEAEs.

AESIs

The Applicant selected AESIs as those TEAEs frequently reported and assessed as OCA-related (e.g. pruritus), those related to dose-limiting toxicities (e.g. hepatic disorders), lab changes (e.g. lipids, liver enzymes) or other TEAs generally associated with adverse outcomes (e.g. CV AEs). A comparison was made between OCA and placebo groups.

Pruritus

Pruritus is a common symptom associated with PBC and also is an OCA-induced, dose-related TEAE. This is an AE that could impact patient's quality of life and, in some hard to control cases, lead to an early LT due to being treatment-resistant.

Over half of the patients on any of the treatment groups reported on-going pruritus at baseline (64%, 53% and 60% in the placebo, OCA titration and OCA 10 mg groups, respectively). TEAEs of pruritus, defined as new on-set or increasing intensity pruritus, were more frequently reported in OCA-treated patients than in placebo-treated patients (38%, 56% and 70%, in the placebo, OCA titration and OCA 10 mg groups, respectively). Most of them required an intervention for pruritus (50%, 62% and 59% in the placebo, OCA titration and OCA 10mg groups, respectively).

Pruritus was the main reason for discontinuation in a total of 8 patients, 1 in the OCA titration group and 7 in the OCA 10 mg. Discontinuations due to pruritus occurred in approximately 10% of patients.

Regarding to time to onset, pruritus TEAEs occurred sooner in OCA 10 mg patients (mean time approximately 7 weeks), followed by OCA titration group patients (by 2 months) and placebo patients (within 3 months of the start of the study).

The incidence of pruritus seemed to be comparable between patients with on-going pruritus and those with new-onset pruritus. These AEs were mostly manageable with standard measures. Overall, these AEs were tolerated, as suggested by the low numbers of discontinuations due to pruritus.

In terms of severity, more OCA-treated patients reported a maximum severity of moderate/severe events, when compared with placebo treated patients (17%, 40%, and 49%, in the placebo, OCA titration and OCA 10 mg groups, respectively). Data regarding pruritus event days per subject-year (day 0 to month 12) showed a larger number of moderate-severe pruritus event days in OCA-treated patients, compared with placebo-treated patients, in which the majority of event days were mild.

When the occurrence of these TEAEs is broken down in two 6-month periods, some differences can be seen between the two OCA treatment groups. The number of severe pruritus event days per subject-year in OCA 10 mg was larger during the first 6 months and then decreased (from 41.05 to 21.02, respectively), while there was a slight increase in the number of severe pruritus event days per subject-year in OCA titration patients during the second 6-month period (from 7.99 to 10.17,

respectively), but remained at a lower frequency than that observed for OCA10mg patients during the first 6-month period.

Based on the titration subgroups, the percentage of patients that experienced pruritus during the 2nd 6-month period was similar between those who remained at 5mg and those that up-titrated to 10mg (58% vs. 55%). The incidence of pruritus for both titration subgroups was lower during this later period (both 33%), compared with the initial 6 months. Severity (in terms of severe pruritus event days) was lower in those patients that up-titrated than during the initial 6-month period of those from the OCA 10mg group (2.31 days vs. 41.05 days).

Patient reported outcomes, such as pruritus VAS or the 5-D pruritus questionnaire, seemed to indicate that patient's perception of pruritus severity improved with continued treatment (VAS), and the analysis of the 5-D pruritus questionnaire (by ANCOVA) did not show any significant differences across the different treatment arms at the end of the 12-month double-blind treatment period.

The SmPC lists pruritus as a very common adverse reaction and provides guidance on dose adjustment / treatment discontinuation for the management of pruritus.

Hepatic-related effects

The incidence of TEAEs in this group was low in general in the pivotal study. However, they seem to be dose-related, with more OCA-treated patients reporting them, compared to the placebo group.

Although increases in liver enzymes were not common in this study, most of the hepatic-related events reported (such as ascites, hepatic encephalopathy, oesophageal varices, and upper GI haemorrhage) seem to be disease progression-related, as the majority of them are frequent complications seen in later stages of the disease. In spite of the low numbers, this is an important and somewhat unexpected matter of concern, bearing in mind the mild population included in this study. The Applicant clarified that all Hepatic AEs occurred in patients with more advanced liver disease (as identified by the Applicant´s algorithm). These events will need to be further characterised in the currently on-going "confirmatory" study and/or by additional post-marketing data monitoring. The SmPC notes the occurrence of liver-related adverse reactions and provides guidance to HCPs on monitoring for possible liver injury.

Lipid-related effects and Cardiovascular TEAE

Lipid disorders are commonly seen in patients with PBC. Any relevant changes can be considered as relevant, due to the potential long-term implications in CV safety. OCA treatment has been associated with reductions in HLD-c levels and increases in LDL-c. These events mainly occurred in patients with pre-existing lipid disorders. Assessment of atherosclerotic CV-related events, evaluation of risk factors and measures taken to minimize risk will be reported in the 6 monthly PSURs. The long-term cardiovascular implications of changes in serum lipoproteins continue to be investigated in the ongoing LTSE studies and the long-term PBC outcomes study (747-302).

In general, the frequency of CV TEAEs was low and most of them were mild or moderate in severity. A total of 4 SAEs were reported by 2 patients: 1 SAE of chest pain and 1 SAE of sick sinus syndrome in one subject; two SAEs of congestive heart failure in another subject (one of them fatal).

<u>SAEs and deaths</u>

The overall number of SAEs was in general low, with higher number of patients reporting them in the OCA treatment groups (4%, 16% and 11% in the placebo, OCA titration and OCA 10mg groups, respectively). A dose-dependent relationship is not readily obvious for SAEs, probably due to the small numbers.

One death, due to worsening congestive heart failure, was reported in the pivotal trial, a male with various CV co-morbidities. The event was assessed by investigators as "unlikely related". This further stresses the relevance of characterising the effect of OCA on the lipid profile and in the elderly.

With regards to hepatic-related SAEs, a total of 3 patients (1 (1%) in placebo, 2 (3%) in the OCA titration group), reported a total of 8 SAEs. Most of these SAEs were consistent with potential disease progression events (e.g. hepatic encephalopathy). Further insight on long term safety and efficacy in PBC patients in more advanced disease stages and in the elderly will be provided within studies 747-302 and – 402 which are conditions to the marketing authorisation.

Discontinuations due to AEs

Overall, the incidence of treatment discontinuation was low, suggesting that OCA treatment is reasonably tolerated. The main reason for discontinuation was due to AEs, reported by a total of 15 patients. Of the patients in the OCA titration groups discontinuing due to AEs, none of them had up-titrated to 10mg. The most common TEAE leading to discontinuation was pruritus, reported in 8 patients, 1 patient in the OCA titration and 7 in the OCA 10mg group and none in the placebo group. Most of these pruritus TEAEs were severe in intensity.

The remaining TEAEs (rash, abdominal distension, diarrhoea, nausea, vomiting, contusion, and headache) occurred in one patient each, with two patients reporting a SAE (one fatal cardiac failure, one interstitial lung disease) that lead to discontinuation.

Pooled data from the DB, placebo-controlled and LTSE studies.

In the overall clinical program, a total of 1325 subjects were exposed to at least 1 dose of OCA, among which 306 were participating in double-blind (DB) studies. Of these, 201 were exposed to doses ≤10 mg. In the OCA10mg group, almost all patients (n= 123, 93%) were exposed for at least 1 month, with 49% of patients (64) exposed for at least 9 months. For OCA doses above 10mg, exposure past 1 month was limited due to the nature of the study designs (DB duration of 3 months) and the poor tolerance observed at higher doses.

The majority (>80%) of patients within each study completed the double-blind phase, with generally similar completion rates across the 3 studies. The most common reason for discontinuation was pruritus.

Pooled data largely supports the safety profile observed in the pivotal study. In general, OCA safety profile reported in the DB studies was comparable to that of the OL LTSE studies. Some dose-relationship trends can be observed, especially in terms of pruritus, which showed the highest incidence in the treatment groups that initiated treatment at 50 mg OCA (80%- 94%).

Patients on OCA experienced TEAEs more frequently than those on PBO (94% *vs.* 89%, p=0.05). Moreover, among TEAEs, those presented by OCA patients were more often severe than those presented by PBO (29% *vs.* 13%, p<0.01), and more frequently related to investigational product (77% *vs.* 53%, p<0.01). The majority of TEAEs were mild or moderate in severity.

Regarding hepatic-related TEAEs potentially, they were numerically more frequent at the 50mg dose, suggesting a dose-relationship. This includes those TEAEs related to hepatic decompensation. All patients who experienced liver adverse events had demonstrated signs and symptoms of advanced disease prior to initiating treatment with OCA. Hepatic-related TEAEs typically occurred between the first 1 to 3 months of treatment. Therefore the prescriber is advised in 4.4 of the SmPC to monitor patients during treatment for elevations in liver biochemical tests and for the development of liver-related adverse reactions and dose adjustments were included in the SmPC for patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (see also discussion on pharmacology).

Regarding SAEs during the double-blind phase studies, these were more frequent in OCA-treated patients (25 OCA-treated patients [8%] vs. 5 placebo-treated patients [4%]). Four of the OCA treatment-emergent SAEs (all occurred in the OCA 50 mg dose) were considered to be related to OCA. Two of the SAEs were hepatic (jaundice and PBC flare) and 1 GI (GI hemorrhage). This finding further stresses the relevance of characterising the effect of OCA on liver function within the defined conditions to the marketing authorisation, especially considering that the population included was at an early stage of the disease and that limited data is available on patients with a more advanced disease stage and/or liver impairment.

Special populations

Age

- *Paediatric patients*

A waiver was granted for all subsets of the paediatric PBC population from birth to less than 18 years of age, since PBC does not occur in the specified paediatric subsets.

- *Elderly patients*

Although there seems to be no relevant age-related differences in terms of TEAE incidence, the data in elderly and very elderly patients are limited. This is outlined in the SmPC. Further insight on long term safety and efficacy in PBC patients in more advanced disease stages and in the elderly will be provided within studies 747-302 and – 402 which are conditions to the marketing authorisation.

Liver impairment

Clinical studies in PBC patients with decompensated liver disease have not been conducted. Available are data from two clinical studies in subjects with various degrees of liver impairment due to other liver diseases: study 747-103, multiple-day dosing of OCA 10mg (duration 6-12 days); study 747-204, multiple day dosing of OCA 25 mg in patients with alcoholic cirrhotic portal hypertension. Data available from patients with moderate or severe liver impairment is very limited and particularly study 747- 402 will further characterize this profile.

Data from these studies and additional PK modelling indicate that OCA exposure increases with increasing severity of the liver impairment. In patients with moderate and severe hepatic impairment there was an increase in systemic exposure of OCA of approximately 4- fold (Cmax and AUC; LS mean) and approximately 10 to17-fold (Cmax and AUC; LS mean); respectively. Similar increased systemic exposure was observed in the study of subjects taking 10 mg or 25 mg of OCA in patients with alcoholic cirrhosis and portal hypertension (moderate to severe hepatic impairment) relative to healthy subjects. While higher plasma exposures are expected to occur in patients with hepatic impairment, only small increases in liver exposure are predicted. Data from the clinical hepatic impairment study and PK simulations performed by the Applicant show that total OCA exposure in the liver increased 1.1-fold, 1.5-fold and 1.7-fold for mild, moderate and severe hepatic impairment, respectively, relative to exposures in patients with normal hepatic function. It is agreed that a 2-fold increase in liver exposure, as predicted for the recommended 5 mg-10 mg dosing, is not likely to be sufficient to achieve the liver exposures associated with hepatotoxicity observed at higher doses (250 mg). In addition, PK simulations predict that liver exposures of OCA 10 mg twice weekly in patients with moderate and severe hepatic impairment would be approximately equivalent to a 5 mg and 6 mg once daily dose in patients with no hepatic impairment. This information is considered sufficient to support the proposed dose adaptations for patients with hepatic impairment as outlined in the SmPC.

Renal impairment

No specific clinical study has been conducted in patients with renal impairment. Urinary elimination of OCA and its metabolites is minimal, based on phase 1 data on healthy volunteers. Laboratory parameters

indicative of renal function did not show relevant changes throughout the pivotal study. Adequate information has been included in the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

Clinical follow-up is currently limited, i.e. max 5 years, in a limited number of patients particularly in the elderly and in advanced stages of the disease. Further characterisation of the safety profile in these patient populations will be provided within studies 747-302 and 747-402 which are conditions to the marketing authorisation.

2.5.2. Conclusions on the clinical safety

Overall, treatment with OCA appears well tolerated and with an acceptable safety profile in the studied PBC population. The main limitations are the limited safety database and the fact that an important proportion of the target population has not been studied, i.e. patients with a more advanced liver disease. This is considered an important drawback and deficiencies on whether the observed safety profile in a rather mild PBC population can be extrapolated to a more severe one will need to be addressed within the two PAES being conditions to the marketing authorisation.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

See conclusions on efficacy.

2.6. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risk	Pruritus
Important potential risks	Liver injury Atherosclerotic cardiovascular events secondary to changes in lipids
Missing information	Use in patients with other concomitant liver diseases
	Use in patients with moderate to severe hepatic impairment (Child-Pugh Class B and Child-Pugh Class C)
	Use in patients with hepatocellular carcinoma
	Use post liver transplantation
	Use in elderly and very elderly patients (≥65 years)
	Use during pregnancy and breast-feeding
	Long-term safety

Pharmacovigilance plan

There are no activities planned or ongoing.

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risk		
Pruritus	SmPC and PIL	None
Important potential risks		
Liver injury	SmPC and PIL	None
Atherosclerotic cardiovascular events secondary to changes in lipids	SmPC and PIL	None
Missing information		
Use in patients with other concomitant liver diseases	SmPC and PIL	None
Use in patients with moderate to severe hepatic impairment (Child-Pugh B and C)	SmPC and PIL	None
Use in patients with hepatocellular carcinoma (HCC)	SmPC and PIL	None
Use post liver transplantation	SmPC and PIL	None
Use in elderly (≥65 years) and very elderly (≥75 years) patients	SmPC and PIL	None
Use during pregnancy and breast-feeding	SmPC and PIL	None
Long-term safety	SmPC and PIL	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.6 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. New Active Substance

The applicant compared the structure of obeticholic acid with active substances contained in authorised medicinal products in the European Union and demonstrated that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers obeticholic acid to be a new active substance as it is not

a constituent of a medicinal product previously authorised within the European Union.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ocaliva (obeticholic acid) is included in the additional monitoring list as it is approved under a conditional marketing authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Primary biliary cirrhosis (PBC) is a rare, serious, life-threatening liver disease characterized by cholestasis with progressive impairment of bile flow in the liver that results in increased hepatocellular bile acid concentrations. Bile acids at elevated hepatocellular concentrations can be toxic to the liver. Such hepatocellular injury results in a local inflammatory response and is signalled early on by the secretion of alkaline phosphatase (ALP). In patients with an inadequate response to therapy, the disease frequently progresses to hepatic fibrosis and eventual cirrhosis, hepatic decompensation, and death unless a patient receives a liver transplant (Kuiper 2010).

3.1.2. Available therapies and unmet medical need

There are limited therapeutic options for PBC patients. Liver transplantation can significantly improve survival and pruritus in patients (Corpechot 2008, Lindor 2009). However, it is a complex, time-consuming operation with identified risks suitable only for patients with advanced liver disease, including perioperative and surgical complications, immunologic and infectious disorders, and various medical complications. Complications of liver transplant include bleeding, rejection, infection, and side effects from medications such as immunosuppressants. Furthermore, given the underlying autoimmunity that causes PBC, the disease can recur in a significant percentage of patients receiving liver transplants, with increasing likelihood over time (Silveira 2010, Lindor 2009).

Ursodeoxycholic acid (UDCA), a bile acid constituent, is the only medicine currently approved to treat PBC. UDCA improves biochemical indices such as ALP and bilirubin and delays histological progression

(Poupon 1997, Corpechot 2008). The results of clinical trials of appropriate dose and length of treatment, in combination with well-controlled epidemiologic analyses, provide strong evidence that treatment with UDCA increases progression-free survival, with significantly greater benefit for patients who demonstrate greater response as measured by decreases in ALP, bilirubin and ALT. Accordingly, UDCA treatment has been recommended as first line therapy for patients with PBC in both European (European Association for the Study of the Liver [EASL]) and American (American Association for the Study of Liver Diseases [AASLD]) treatment guidelines (Lindor 2009, EASL 2009).

While UDCA has a marked impact on clinical outcomes in PBC, up to 50% of UDCA-treated patients either fail to respond or have a suboptimal response as defined based on various liver biochemistry algorithms. These criteria included a decrease >40% in ALP from the baseline value or decrease to a normal level (Parés 2006); ALP <3x ULN, AST<2x ULN, and bilirubin <ULN (Corpechot 2008, Corpechot 2011); and normalization of abnormal concentrations of bilirubin, albumin, or both (Kuiper 2009).

The risk associated with non-response to UDCA is substantial. A cross-sectional study using the United Kingdom PBC patient cohort (UK-PBC) data indicates that this lack of response is significantly more common in patients who are young at disease onset or who are male, presumably reflecting an accelerated disease course (Carbone 2013). Fifty percent of patients in the UK-PBC study who had presented with PBC below the age of 50 were either in a state of UDCA non-response or had already undergone liver transplantation. There is an increased impact in those patients with a non-response to UDCA (in population terms) who develop the disease when younger given their expectations of normal lifespan. These patients are at significantly increased risk of an adverse outcome such as a liver transplant or end stage liver disease (Parés 2006, Kuiper 2009, Corpechot 2008, Kumagi 2010b, Corepchot 2011, Momah 2012). These findings have recently been confirmed by both the nationwide UK-PBC group (Mells 2011) and the Global PBC Study Group (Lammers 2014).

Furthermore, while UDCA at the recommended dosage (13 mg/kg/day to 15 mg/kg day) is generally well tolerated (Hempfling 2003, Axcan Pharma US, Inc.), there is a small subset of PBC patients who are unable to tolerate UDCA (primarily due to gastrointestinal symptoms) and thus are at an even greater risk of adverse outcome if unable to remain on therapy.

While research has been conducted on a number of other drugs (azathioprine, methotrexate, colchicine, D-penicillamine, cyclosporine A, chlorambucil, glucocorticosteroids), little to no consistent research supports the benefit of these compounds on PBC (Rudic 2012).

Based on the totality of evidence, there is a clear ongoing unmet medical need for second-line therapies in this serious, life-threatening disease, as well as other alternative therapies for the small percentage of patients with PBC who are unable to tolerate UDCA.

3.1.3. Main clinical studies

One single pivotal study has been presented to support the efficacy of obeticholic acid (OCA) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. The primary efficacy measure of the pivotal phase III trial was the percentage of subjects at Month 12 with ALP <1.67x ULN and total bilirubin ≤ULN and ALP decrease of ≥15% from Baseline.

3.2. Favourable effects

Results from the study at month 12 showed that a higher percentage of patients in the fixed OCA 10 mg group (n=34, 47%) achieved the primary endpoint (defined as the proportion of patients with ALP<1.67 ULN and ≥ 15% reduction in ALP and a total bilirubin ≤ ULN at month 12) compared to placebo (n=7, 10%), thus demonstrating superiority (p<0.0001). A higher percentage of patients (n=32, 46%) in the OCA titration group (key secondary endpoint) also achieved the composite endpoint, compared to placebo (p<0.0001). Of note, a similar proportion of patients ineligible for OCA up-titration at 6 months (who continued OCA treatment with the 5 mg dose) also met the primary composite endpoint at month 12 (approximately 50%).

Treatment effect on the primary composite endpoint was supported by additional efficacy analyses performed in the completer and EE populations.

Mean absolute and percentage change from baseline to 6 and 12 months in ALP, conjugated bilirubin, GGT, ALT, and AST showed statistically significant differences over placebo for both OCA treatment groups for most of the endpoints (except LS mean percentage change of bilirubin for OCA 10mg vs. placebo, at 6 months).

Responder analyses showed a higher percentage of patients in both OCA treatment groups achieved the ALP reduction, compared to placebo (p ≤ 0.0001) at both timepoints, 6 and 12 months. At 12 months, approximately one third of patients in each OCA treatment group achieved an ALP reduction of >40%, compared with 1% in the placebo group.

The percentage of subjects achieving the biochemical treatment response criteria (Paris I modified, Paris II, Mayo II, and Toronto II), were also higher in OCA-treated patients than in the placebo group.

In the monotherapy study (n=59), after 12 weeks of treatment, the mean percent change from baseline in ALP was -44.5% and -37.6% for the 10 mg and 50 mg OCA groups, respectively, in comparison to a 0.4% increase in the placebo group (p <0.0001).

Results from phase II trials are consistent with those of the pivotal study, which add robustness to the evidence provided.

3.3. Uncertainties and limitations about favourable effects

Data on treatment effect up to 30 month of treatment from initiation of the pivotal study is at present available for a limited proportion of patients. Although it is acknowledged that the use of clinical measures of treatment efficacy based on long-term hard end-point is largely unfeasible in a phase III trial in PBC patients, mainly due to time constrains, the choice of a biochemical surrogate challenges the interpretation of study results in terms of clinical benefit. Thus, the main uncertainty concerns to what extent changes in laboratory parameters correlate with clinical liver outcomes. Other important uncertainties are the lack of data in patients with a more advanced stage of the disease and the limited long-term data.

The results from the primary composite endpoint are mainly driven by changes in ALP, since the majority of patients entered with normal/near normal bilirubin values (<2 ULN) and remained normal throughout the study duration. Furthermore, despite that approximately one third of patients in OCA treated groups achieved an ALP reduction of >40% at 12 months (compared to 1% in placebo), few patients achieved ALP normal levels (6 in the OCA-treated groups vs. none in the placebo group). In clinical practice, the normalization of ALP levels with UDCA in early stages of the disease has been correlated with similar survival rates as the general population. Nevertheless, based on the experienced gained with UDCA, OCA

treatment resulted in changes in laboratory parameters that are indicative of a potential clinically relevant benefit.

3.4. Unfavourable effects

OCA has been evaluated in 1507 subjects (including PBC patients, healthy volunteers and other indications), who received at least one single dose. However, due to differences in dose strength and treatment duration, the main safety population is comprised by those patients from the pivotal study (n=216).

The most commonly reported adverse reactions were pruritus (63%) and fatigue (22%). Adverse reactions leading to discontinuation were 1% in the OCALIVA Titration group and 11% in the OCALIVA 10 mg group. Pruritus was the most frequently reported TEAE across all treatment groups (38%, 56% and 68% in the placebo, OCA titration and OCA10mg groups, respectively). However, the majority of pruritus occurred within the first month of treatment and tended to resolve over time with continued dosing. Pruritus was included as important identified risk into the RMP and Guidance on management and dose adjustment for severe pruritus was included into the SmPC which was considered acceptable by the CHMP.

3.5. Uncertainties and limitations about unfavourable effects

The safety population baseline demographics and disease characteristics were well balanced among study arms and overall can be considered a mild population at an early stage of the disease. Representation of patients with more advanced disease and/or various degree of liver impairment was scarce. In addition, since patients with total bilirubin ≥ 2x ULN, severe portal hypertension or hepatic failure were excluded from both the main studies, no information of treatment effect is available at present in patients with decompensated disease.

Hepatic effects related with disease progression (such as ascites, hepatic encephalopathy, oesophageal varices, and upper GI haemorrhage) seemed to be numerically higher in OCA-treated patients and the SmPC advises to monitor patients for elevation in liver enzymes and liver related adverse reactions.

None of the clinical hepatic AEs at doses ≤10 mg were considered related to study drug by the Investigators or the Sponsor. The nature of clinical hepatic-related events in patients with PBC receiving OCA was consistent with that reported in patients with late-stage chronic liver disease (ie, ascites, hepatic encephalopathy, oesophageal varices), and considered likely related to disease progression.

It is acknowledged by the CHMP that there is insufficient support to conclude on a causal association between liver injury and OCA at the proposed clinical doses. Therefore liver injury was qualified important potential risk in the RMP.

Even though the overall incidence was low further investigations in patients with moderate and advanced disease (ie, Child-Pugh Class B and C), will need to be provided by means of the confirmatory studies 747-302 supported by study 747-401 which is to be performed in patients in more advanced stages of the disease to exclude clinical relevance of this finding.

The SmPC has been revised to include details regarding serious hepatic events to help health care professionals manage their patients appropriately. Additionally, dosage recommendations for patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment have been included which was considered acceptable by the CHMP.

Lipid disorders were also reported in patients treated with OCA. Lipid disorders are commonly seen in PBC patients. A clear pattern for the changes could not be identified and these changes did not seem to be associated with the occurrence of CV AEs. Further characterization of the long-term safety of OCA with respect to changes in lipid levels and CVD in patients with PBC will become available by means of the conditions of the marketing authorization.

3.6. Effects Table

Table 33: Effects Table for OCA in the treatment of PBC (data cut-off: 31-August-2014).

Effect	Short Description	Unit	OCA fixed 10mg	OCA titration	Placebo	Uncertainties / Strength of evidence
Favourable Effects						
ALP<1.67 ULN and ≥15% reduction in ALP and a total bilirubin ≤ULN at month 12	Primary composite Endpoint	%	47%	N/A	10%	-Only biochemical data is available (ALP levels) - ALP normalisation with UCDA relays to better prognosis; it is unknown if the same can be extrapolated to OCA results - Very few patients on either OCA group normalised ALP levels -Relevance of OCA Anti-inflammatory effects is unknown
Composite endpoint	key secondary endpoint	%	N/A	46%	10%	
Responder analyses (12months) ALP≥40%	secondary endpoint	%	30%	34%	1%	
Unfavourable Effects						
Pruritus		Proportion	AE 70% G3/4 49% SAE N/A%	AE 56% G3/4 40% SAE N/A%	AE 38% G3/4 17% SAE N/A%	
Tolerability			AE 95% ≥1dose reduction/delay: N/A AE leading to discontinuations 11% G3/4 69%	AE 93% ≥1dose reduction/delay: N/A AE leading to discontinuations 7% G3/4 70%	AE 90% ≥1dose reduction/delay: N/A AE leading to discontinuations 3% G3/4 50%	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

PBC is a rare, progressive disorder characterised by progressive impairment of bile flow and resulting hepatic toxicity. Patients with PBC have limited treatment options, with UDCA being the only medicinal product current authorised for the treatment of PBC. Available data on UDCA treatments indicate a correlation between normalisation of ALP levels and progression-free survival. Up to 50% of patients do not satisfactorily respond to UDCA treatment or are unable to tolerate it; their prognosis is sombre, due to the lack of alternatives. So, for patients not achieving adequate control of the disease, despite treatment with UDCA or in the cases in which patients are not eligible to receive it, there is an unmet medical need. In this context, OCA treatment has demonstrated relevant ALP reductions in patients treated with a fix OCA dose of 10 mg or titrating from 5 mg up to 10 mg.

As for UDCA, it is reasonably likely that the results on biochemical parameters translate into benefit in terms of clinical outcome data, although this remains to be formally demonstrated by means of the post-authorisation follow up within this conditional marketing authorisation.

The safety profile appeared to be overall well tolerated and for most part manageable with supportive treatments (e.g. for pruritus) and/or dose adjustments. Toxicities were generally mild-moderate, and resulted in infrequent dose reductions, dose interruptions, or discontinuations. Also these AEs can be reasonably managed with implemented recommendations in the SmPC.

Therefore, at this stage OCA is presented as a suitable treatment option for those patients in need for further treatment to prevent or delay PBC progression.

3.7.2. Balance of benefits and risks

Overall, the beneficial effect of OCA is currently based on changes in biochemical parameters. Although very limited clinical data (such as histology or different measurements of parameters of fibrosis) are currently available sufficient correlation has been established between ALP levels and liver outcomes from previous clinical experience with UDCA.

Although not yet demonstrated by clinical outcome parameters, available data are sufficiently indicative of a clinically relevant benefit in the treatment of PBC in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

The existing evidence demonstrated the benefits of OCA to a degree that allows them to be assessed against the overall well tolerated and manageable safety profile in the studies conducted and the risks related to the absence of data.

In particular the lack of direct clinical evidence showing the extent of efficacy and safety also in the long term treatment and in more advanced liver disease stages will be addressed within the conditions of the marketing authorisation. This is considered acceptable due to the lack of treatment options in this second line indication of a severely debilitating disease. Furthermore the SmPC cautions adequately about availability of limited data in patients with hepatic impairment and provides reasonable dose adjustments.

The benefit risk of OCALIVA 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 is considered to be positive in the context of this CMA.

3.7.3. 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 during the procedure.

The product falls within the scope of Regulation (EC) No 507/2006 concerning conditional marketing authorizations, as it aims at the treatment of a seriously debilitating and life-threatening disease and is designated as an orphan medicinal product:

PBC is a rare, chronic, serious, life-threatening liver disease that progresses to hepatic fibrosis, cirrhosis, debilitating hepatic decompensation and death unless a patient receives a liver transplant (Kaplan 2005). Without therapeutic intervention, the combined effects of chronic cholestasis and bile-duct destruction ultimately lead to progressive liver impairment culminating in liver failure resulting in liver transplant or death. The 10-year survival of asymptomatic patients in 3 contemporary series ranged from 50% to 70%.

OCA for the treatment of PBC was granted Orphan Designation from the EMA COMP on 27 Jul 2010, as the prevalence of the disease was below the EMA and COMP's statutory threshold (no more than 5 in 10,000).

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is considered sufficiently likely that the applicant will be able to provide comprehensive data:

  Study 747-302 is a randomized, placebo-controlled, international study being conducted to confirm the clinical benefit associated with OCA treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints.

  Study 747-401 is a phase 4, double-blind, randomized, placebo-controlled, study evaluating the efficacy, safety, and pharmacokinetics of obeticholic acid in patients with primary biliary cholangitis and moderate to severe hepatic impairment.

  To assure timely completion of the studies the applicant is committed to conducting regular ongoing assessments of patient recruitment, retention and event rate accrual over the course of study conduct. The CHMP/Rapporteurs will be provided with annual updates of key study metrics, including enrolment updates and details on event accrual. The Applicant is further committed to notifying the CHMP/Rapporteurs immediately in the case of any unforeseen delays or issues with study conduct, or recommendations from the DMC to alter the conduct of the study. This was accepted by the CHMP.
- Unmet medical needs will be addressed: Ursodeoxycholic acid (UDCA) is the only medicine currently approved to treat PBC. Up to 50% of patients do not satisfactorily respond to UDCA treatment or are unable to tolerate it; their prognosis is sombre, due to the lack of alternatives. As discussed above available data are sufficiently indicative of a clinically relevant benefit in the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The positive benefit risk of OCALIVA and the lack of treatment options in this second line indication of a severely debilitating / life threatening disease outweighs the risk inherent in the fact that additional data are still required.

3.8. Conclusions

The overall B/R of OCALIVA is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of OCALIVA is favourable in the following indication:

OCALIVA is 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 CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Other conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Interventional study 747-302: Description: In order to confirm the efficacy and safety of OCALIVA, the MAH should conduct and submit the results of study 747-302, a confirmatory double-blind, randomised, placebo-controlled multicentre study investigating the clinical benefit associated with OCALIVA treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints. Rationale: to investigate the effect of OCA on clinical outcomes in subjects with PBC	Final report: 2023
Interventional study 747-401: Description: In order to confirm the efficacy and safety of OCALIVA, the MAH should conduct and submit the results of study 747-401, a double-blind, randomised, placebo-controlled study evaluating the efficacy, safety and pharmacokinetics of OCALIVA in patients with PBC and moderate to severe hepatic impairment. Rationale: to investigate the uncertainties related to the lack of data in a population with more advances liver disease	Final report: 2020

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that obeticholic acid is considered to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.