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RESEARCH**

APPLICATION NUMBER:

207999Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Review Completion Date	4-22-2016
Established Name	Obeticholic acid (INT-747)
(Proposed) Trade Name	OCALIVA
Applicant	Intercept Pharmaceuticals
Formulation(s)	Oral tablet
Dosing Regimen	5 mg, and 10 mg
Applicant Proposed Indication(s)/Population(s)	Primary Biliary Cholangitis/Cirrhosis
Recommendation on Regulatory Action	Recommend Approval
Recommended Indication(s)/Population(s) (if applicable)	Primary Biliary Cholangitis/Cirrhosis (PBC)

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Glossary

AC	Advisory committee
AE	Adverse event
BLA	Biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	Chemistry, manufacturing, and controls
COST ART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case report form
CRO	Contract research organization
CRT	Clinical review template
CSR	Clinical study report
CSS	Controlled Substance Staff
ECG	Electrocardiogram
eCTD	Electronic common technical document
ET ASU	Elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good clinical practice
GRMP	Good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	Integrated summary of effectiveness
ISS	Integrated summary of safety
ITT	Intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New drug application
NME	New molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PI	Prescribing information
PK	Pharmacokinetics
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PP	Per protocol
PPI	Patient package insert
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PSUR	Periodic Safety Update report
REMS	Risk evaluation and mitigation strategy
SAE	Serious adverse event
SAP	Statistical analysis plan

SGE Special government employee
 SOC Standard of care
 TEAE Treatment emergent adverse event

Abbreviation or Specialist Term	Explanation
AASLD	American Association for the Study of Liver Diseases
AMA	antimitochondrial antibody
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical/Therapeutic/Chemical
BAS	bile acid sequestrants
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
CA	cholic acid
CDCA	chenodeoxycholic acid
CRA	clinical research associate
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
DB	double-blind
DCA	deoxycholic acid
DEXA	dual-emission x-ray absorptiometry
DSMC	Data Safety Monitoring Committee
EASL	European Association for the Study of the Liver
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 Harmonization
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
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
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
UK	United Kingdom
ULN	upper limit(s) of normal
US	United States (of America)
USP	United States Pharmacopeia
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 Executive Summary

1.1 Product Introduction

Obeticholic acid (OCA) is a modified bile acid, derived from chenodeoxycholic acid (CDCA), with addition of single α -ethyl group in the 6-carbon position (6 α -ethyl-chenodeoxycholic acid or 6-ECDCA). The trade name proposed by the Applicant is OCALIVA which is acceptable to the FDA.

In January 2006, Intercept Pharmaceuticals Inc. submitted their first IND and since then the Applicant has had numerous interactions with FDA to come to an agreement on an endpoint for accelerated approval. The primary endpoint that was agreed upon by the Agency was a composite of alkaline phosphatase (ALP) and total bilirubin (TB) reduction. Intercept submitted the NDA filing on the basis of data from a single, pivotal phase 3 study (747-301) with supportive safety and efficacy data from two phase 2 trials (747-201 and 747-202). Designation of PBC (with inadequate response to UDCA) as a serious and life threatening disease with unmet medical need were the key considerations in these discussions. The Agency has since granted orphan designation (April 2008), fast track (May 2014) and priority review (August 2015) of obeticholic acid for the treatment of PBC. FDA generally requires that two adequate and well-controlled trials be conducted to provide substantial evidence of efficacy for drug approval. The adequacy of a single trial to support approval is determined by its ability to support the efficacy claim based on the strength of the results. If only one clinical trial is conducted, then internal consistency across study subsets, evidence of an effect on multiple endpoints, and statistically very persuasive efficacy results with much smaller alpha less than 0.05 is considered in the evaluation. The Agency has flexibility in acceptance of a single trial especially in rare diseases with unmet medical need. PBC is a rare disease with unmet medical need and as such, one phase 3 trial was acceptable to the Division. FDA agreed to file the submission with 1,507 total human OCA exposures, and ~400 PBC patients were exposed to OCA (290 PBC patients for >6 months) at the time of NDA submission. The ICH human exposure guidelines were met or exceeded.

1.2 Conclusions on the Substantial Evidence of Effectiveness

Ninety percent (90%) of patients enrolled in the pivotal trial had early stage PBC with normal total bilirubin and normal albumin levels at baseline. Although the primary endpoint was pre-specified as a reduction in both ALP and TB, due to the nature of the enrollment population, the primary endpoint was driven by ALP alone. In the phase 3 trial at month 12, a total of 46% patients in OCA titration arm and 47% patients in the OCA 10 mg arm compared to 10% patients in the placebo arm achieved the primary endpoint (predominantly due to reduction in ALP). The protocol did not control for multiplicity beyond the primary endpoints, therefore, the secondary endpoints were exploratory; however, the secondary endpoints were supportive of the primary efficacy outcome. Numerically higher number of patients had gamma-glutamyl transferase (GGT) reduction, a marker of cholestasis, and reduction of serum transaminase (ALT and AST). IgM is not a prognostic marker in PBC, but an increase in IgM is seen in most PBC patients. Numerically higher numbers of patients treated with OCA also showed IgM level reductions (but not normalization) relative to placebo treated patients.

ALP is a prognostic marker of PBC progression and has been shown to correlate with survival and transplant free survival based upon published literature by different hepatologist's across different centers globally. The majority of these publications had limited number of patients, utilized a single responder criteria for assessment across pooled populations (early and advanced stages), and used different responder criteria by different investigators leading to significant challenges in the interpretability of the data. As a result, a group of academicians collaborated and formed the PBC study group; the group collected and analyzed clinical and laboratory data on 4,845 patients across Europe and USA (retrospectively collected data). The UK PBC group collaborated and formed UK-PBC cohort collected data on ~6000 PBC patients and provided the analyses of their data to the Applicant which was submitted with this NDA. The PBC study group published results describing the role of ALP in predicting outcomes, however limitations in interpretation were also observed.

To support use of the Applicant's pre-specified ALP threshold for the pivotal OCA trial 747-301, both the PBC study group and UK-PBC cohort provided the analyses of data on a matched subset of patients similar to the clinical trial (early stage PBC) patients and were able to show that ALP is predictive of transplant free survival. Additionally, FDA conducted independent analyses of the PBC study group data utilizing the same matched subset of patients (early stage disease subset) as in the pivotal clinical trial and reproduced the observation that ALP is predictive of the clinical outcomes (Section 8.4). Based on the totality of evidence (primary and secondary endpoints), an accelerated approval of OCA is recommended pending the clinical benefit trial and the PMRs (assessing safety and efficacy of long term monotherapy use, safety of OCA use in advanced stage PBC disease and in decompensated cirrhosis patients).

1.3 Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

I recommend the approval of OCA for treatment of primary biliary cholangitis (PBC). The approvability of this application relied upon the acceptability of the surrogate endpoint of reduction in alkaline phosphatase (ALP) to be reasonably likely to predict clinical benefit. See discussion below in this summary and in Section 8.4.

Obeticholic acid (OCA) is a new molecular entity that is a modified bile acid, derived from chenodeoxycholic acid (CDCA), with addition of a single α -ethyl group in the 6-carbon position (6 α -ethyl-CDCA). OCA is a farnesoid X receptor (FXR) agonist. FXR activation inhibits bile acid synthesis and promotes bile flow (choleresis). The proposed indication for OCA for the treatment of primary biliary cirrhosis/cholangitis (PBC) (b) (4) with an inadequate response to ursodeoxycholic acid (UDCA) or (b) (4) intolerant to UDCA. Recommended dosing starts at OCA at 5 mg for 3 months. If there is an inadequate biochemical response in ALP or total bilirubin (TB) and there are no tolerability issues with OCA (i.e., no increase in pruritus or other adverse events), the dose should be uptitrated to OCA 10 mg. OCA does not target the basic immunopathogenesis of PBC; however, its choleric action has the potential to slow disease progression. This upstream effect of "choleresis" may be beneficial in potentially reducing the downstream consequences of the disease (damage by toxic bile salts) and related complications (portal hypertension, cirrhosis, liver failure).

PBC predominately affects women (women to men 10:1), between the ages of 40 and 60 years. PBC is a chronic, autoimmune, cholestatic, progressive disease, which in addition to liver damage also leads to fatigue, pruritus, and sicca syndrome. PBC can range from asymptomatic and slowly progressive to a symptomatic and rapidly evolving disease. Other extra-hepatic autoimmune diseases can also co-exist such as Sjogren's syndrome (34%), Hashimoto's thyroiditis (13%), Raynaud's syndrome (13%), Rheumatoid arthritis (8%), psoriasis (6%), or other autoimmune disease (33-55%). Non-cirrhotic patients treated with UDCA typically respond biochemically, however approximately 40% patients have an inadequate response to UDCA. Male sex is an independent predictor of poor response to UDCA. In addition, women <30 years have only a 50% likelihood of response to UDCA. If the disease is left untreated or inadequately responsive to UDCA (assessed biochemically), patients progress to cirrhosis and liver failure leading to liver transplant or death.

There is an unmet medical need in PBC patients who do not respond adequately to UDCA or are intolerant to UDCA. Given the long duration for clinical outcome trials to show clinical benefit, it is reasonable to consider accelerated approval of OCA for PBC using a surrogate endpoint. Without therapeutic alternatives, PBC is serious and life-threatening disease. The phase 3 trial was a one year trial in 216 patients with three arms: placebo, OCA 10mg and OCA titration (dose increased at month 6 from 5mg → 10 mg if patient had no tolerability issues and did not achieve primary endpoint). The primary efficacy endpoint for the phase 3 trial was a composite of ALP <1.67 X ULN and total bilirubin ≤ULN and at least ≥15% reduction in ALP. A total of 92% patients in phase 3 trial had normal total bilirubin; therefore the driving factor of the efficacy results was reduction in ALP.

Phase 3 results are as follows: At month 12, a total of 46% and 47% patients on OCA titration and OCA 10mg arm, respectively, achieved reduction in ALP >1.67 X ULN and at least ≥15% reduction in ALP, and these were statistically significant relative to placebo. Of the 18 patients who had elevated ALP and TB at baseline, 1 out of 4 patients in the titration arm, 2 out of 7 patients in OCA 10 mg and none out of 7 patients in placebo arm achieved the composite endpoint. The ALP reduction response is durable as seen in the long term safety extension trial data results submitted to a cutoff point of up to 30 months. Subgroup analyses (disease severity, age, gender) were not conducted due to small sample size.

The protocol did not control for multiplicity beyond the primary endpoints; therefore the secondary endpoints were considered exploratory. However, the secondary endpoints supported the primary outcome measure. A numerically high number of patients showed reduction in gamma-glutamyl transferase (GGT), which is a maker of cholestasis and achieved a lowering of serum transaminase (ALT). IgM is not a prognostic marker in PBC, but an increase in IgM is seen in almost all PBC patients. Numerically higher numbers of patients treated with OCA showed IgM level reductions (but not normalization) relative to placebo patients, in who no changes in IgM levels were observed. These secondary outcomes are supportive of the primary outcomes.

The overall OCA profile is safe. The main adverse events include dose dependent pruritus, dose dependent reduction in HDLc and fatigue. The most concerning safety adverse events were serious liver adverse events that were seen with higher OCA exposures.

Patients with severe pruritus at baseline were excluded. In the majority of patients, pruritus was managed with interventions such as alternative dosing schedules, treatment interruption, use of bile acid binding agents and anti-histamines. Treatment emergent severe pruritus was the main reason for discontinuations in the OCA 10 mg treatment arm. Fatigue was noted in OCA treated patients at a higher frequency compared to placebo.

Generally, patients with PBC have high HDLc levels (mean HDLc of the trial population was ~70-80 mg/dL). In the OCA clinical trials, dose dependent HDLc reductions were seen; at month 12, reductions from baseline in mean HDLc was observed in 21% of patients in OCA 10 mg arm, 15% in OCA titration arm and 3% in placebo arm. Almost 59 patients on OCA 10 mg and about 45 patients in OCA titration arm had some HDLc reductions, 5, 4, and 0 patients enrolled to OCA 10 mg, OCA titration arm and placebo arm had HDLc reduction more than 2 standard deviation (>44 mg/dL). A few patients had HDLc decline to as low as 7 mg/dL. The observed lipid profile changes are reversible with drug discontinuation.

Primarily at OCA doses of 25 mg and 50 mg (which are higher than the to-be-approved doses), liver biochemical test elevations and hepatic decompensation events were observed (new onset jaundice, ascites, and PBC flare). In the pivotal trial one patient receiving OCA 10 mg developed ascites, in the OCA titration arm one patient experienced 2 separate events of ascites and 2 separate events of hepatic encephalopathy; and another patient developed esophageal varices, while in the placebo arm one patient had one event of variceal bleeding. OCA and its conjugates glyco-OCA and tauro-OCA undergo extensive enterohepatic recirculation and have a long half-life. PK modeling showed that OCA 10 mg tablet once a day administration led to high OCA systemic and liver exposures in patients with moderately advanced (Child-Pugh B) and advanced (Child-Pugh C) cirrhosis. These high exposures could increase the risk of hepatic injury, as hepatic injury was seen in the nonclinical models at exposures that would occur in patients with advanced cirrhosis on OCA 10 mg daily. The data on cirrhotic patients is limited; 20 patients with Child Pugh A cirrhosis were enrolled in the clinical trial and no data in patients with Child Pugh B and C is available for assessment of safety and efficacy. The Applicant proposed no dose adjustment for hepatic impairment, however, the FDA review team recommended a dose reduction in patients with Child Pugh B and C cirrhosis in addition to close patient monitoring, which is also included in the labeling.

Nonclinical data demonstrated the hepatobiliary system to be the major system of toxicity. The NOAEL from the chronic toxicity study in rats and dogs were estimated to produce systemic exposures approximately 2.3 and 12 times those in humans at the maximum recommended human dose respectively, Section 4.4. The dosing regimen of 5 mg QD (proposed by the Applicant) would result in 9- and 17-fold increased steady state plasma concentrations (plasma C_{ss}, avg) and 1.7- and 2.3-fold increased steady state liver concentrations (liver C_{ss}, avg) in moderate and severe hepatic impairment compared to normal hepatic function, respectively. In the integrated analysis of safety there was a dose-response seen for hepatic decompensation events as well as biochemical changes possibly indicative of hepatic injury with higher hepatic OCA exposures.

ALP has previously not been used as a surrogate endpoint in PBC clinical efficacy trial for a drug approved by the FDA. The primary composite endpoint that was agreed upon by the FDA for this trial was ALP < 1.67 × ULN and TB ≤ ULN and a ≥ 15% ALP reduction. This composite endpoint was agreed upon on the basis of the findings of various publications that the Applicant submitted to the FDA to leverage the endpoint. The majority (92%) of patients enrolled in the phase 3 clinical trial had normal TB and normal albumin at baseline consistent with early stage disease (PBC staging per the Rotterdam Criteria). Given TB increases as the disease progresses to moderately advanced stage and/or advanced stages, the primary efficacy endpoint was driven mainly by ALP reduction alone in this study population of mostly early stage disease patients.

The acceptability of ALP being used as a surrogate for accelerated approval in this application was the central review issue. ALP is a non-specific enzyme and ALP can come from different sources, including bone, liver and intestines. Liver alkaline phosphatase constitutes 40-50% of normal serum alkaline phosphatase activity, and its activity increases in cholestatic liver disease. Liver alkaline phosphatase activity increases in the blood early in PBC. ALP is used both clinically for PBC diagnosis as well as for

routine monitoring. To address this issue, the Applicant submitted the analyses of the PBC study group data with the NDA submission. The PBC study group analyzed data on ~4,845 PBC patients (globally), correlated data with survival outcomes and concluded ALP (<1.67 X ULN) is a surrogate reasonably likely to predict the clinical outcomes (death, liver transplant) in early stage PBC. The UK-PBC cohort, which included ~6000 patients, showed that a reduction of ALP <1.67 X ULN correlated with improved survival of patients. Long term outcome data from the UK-PBC cohort showed persuasive results across subgroups and further substantiated that ALP is a surrogate that is reasonably likely to predict clinical outcomes. Additionally, FDA also performed analyses on the Global PBC datasets and found that ALP is reasonably likely to predict clinical outcomes.

In order to address the origin of ALP i.e., whether it originated from bone or liver, the Applicant performed ALP fractionation. The ALP fractionation was conducted only in 37 patients treated with OCA; the Applicant reported that blood samples for this analysis were not available for placebo patients. The baseline ALP fractionation results showed that about 80% ALP originated from liver; and at the end of month 12 the ALP reduction was predominantly due to decrease in the liver ALP fraction. The major limitation was that ALP fractionation performed in only 37 OCA treated patients and zero patients on placebo.

Another uncertainty remains whether ALP can predict outcomes in advanced stage disease; published literature currently supports TB to be a surrogate that predicts clinical outcomes in advanced disease. A knowledge gap exists in the literature about whether ALP reduction in advanced stage disease can be predictive of clinical outcomes similar to what was observed in the OCA trials for early stage disease. It is also not known if ALP remains elevated in patients in advanced disease or whether it starts to trend downward or whether ALP it normalizes.

There is always a potential risk with accelerated approval if the surrogate in question, ALP reduction, does not in actuality predict clinical outcomes, as patients would be exposed to the drug, OCA, and have the potential to experience adverse reactions, as well as the potential for financial and non-monetary costs of ineffective treatment. However, if ALP does predict outcomes in early stage disease, then the patients who do not respond to UDCA (40%) and continue to have disease progression will benefit from the treatment resulting in increased treatment options for patients who are intolerant to UDCA. There is adequate evidence to support that a reduction of ALP is reasonably likely to predict clinical benefit; however until the phase 4, confirmatory trial is completed the validity of ALP as a surrogate is unknown. At present, there is an ongoing confirmatory trial to demonstrate clinical benefit outcomes. In addition, there are no data on OCA in advanced stage disease or in patients with decompensated cirrhosis. The Applicant has agreed to a PMR to assess PK safety and efficacy in advanced stage disease patients. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Analysis of Condition</u></p>	<p>Primary biliary cholangitis/cirrhosis (PBC) is a chronic, slowly progressive (spanning over decades) autoimmune, cholestatic liver disease characterized by inflammatory destruction of interlobular and septal bile ducts.</p> <p>In the ursodeoxycholic acid (UDCA) treated patients the 5,10, 15 year survival is 90%, 78%, and 66% and if untreated the survival is 79%, 59% and 32% respectively.</p> <p>PBC predominately affects women; women to men ratio is 10:1, typical age of diagnosis is 40-60 years of age</p> <p>PBC is a rare disease with prevalence of 40.2/100,000 in US and 39.2/100,000 in Europe</p> <p>Exact pathogenesis is unknown; but thought to occur in genetically predisposed patients in the presence of environmental triggers. Features of both the adaptive and innate responses</p>	<p>PBC is a slowly progressive, serious and rare liver disease that affects primarily women with a typical age of onset of 40-60 years. Patients eventually progress to liver cirrhosis, liver failure, hepatocellular cancer and death or liver transplant. The phenotype is variable with some patients being fairly asymptomatic, and some patients experiencing severe and debilitating symptoms, such as severe pruritus, fatigue, and malnutrition. In addition, patients also frequently suffer from the symptoms of other co-existing autoimmune diseases.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>contribute to biliary pathology. The liver injury is mediated by inflammatory infiltration (plasma cells, lymphocytes, mononuclear cells etc.), that causes necrosis of small intrahepatic bile ducts leading to bile duct loss (ductopenia) and bile stasis. Bile salts are toxic and contribute to damage of bile ducts as well as hepatic parenchymal structures. The damage caused by the inflammatory infiltrate and bile stasis leads to fibrosis and cirrhosis. Bile salts are required in absorption of fat and fat soluble vitamins, decrease of bile flow to intestines causes malabsorption of nutrients and micronutrients.</p> <p>Cirrhosis is inevitable without treatment and eventually leads to portal hypertension which causes hemodynamic alterations such as increased portal pressures, portal-systemic shunting, splanchnic vasodilation and peripheral vasoconstriction, increased cardiac output etc. Therefore in advanced stages of disease in addition to the inflammation, bile duct loss and bile stasis mediated damage; progressive injury is accelerated by onset of portal hypertension and its complications (esophageal variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites etc.) which further hastens the process of liver failure.</p> <p>Other conditions such as osteopenia/osteoporosis leading to fractures, hyperlipidemia, and fat soluble vitamin deficiency are also common in patients with PBC.</p> <p>Fatigue and pruritus are the two most common symptoms in PBC patients and are quite disabling.</p>	
<p><u>Current Treatment Options</u></p>	<p>Ursodeoxycholic acid (UDCA) was approved by the FDA in 1997 for PBC. Currently UDCA is the only medical treatment available. Overall UDCA has a good safety profile. Non-cirrhotic PBC patients who achieve a biochemical response with UDCA have survival comparable to that of a healthy population. Most cirrhotic patients do not to achieve an adequate biochemical response with UDCA.</p> <p>About 40% patients achieve inadequate biochemical response with UDCA and continue to progress to cirrhosis and liver failure. ALP and TB are the two important components in assessing response that have been utilized in various retrospective clinical studies. A small percentage (<5%) of patients do not tolerate UDCA mostly secondary to GI symptoms or hair loss.</p> <p>Patients who do not respond to UDCA and continue to progress and develop liver failure or hepatocellular cancer requiring liver transplantation (LTx) if eligible or succumb to death. PBC is one of the top 6 indications for LTx in US.</p> <p>Even with liver transplantation, PBC recurrences are noted. Although the progression of PBC in recipient liver is very slow, there is reportedly up to 10-43% incidence of PBC recurrence at 15 years post-transplant.</p>	<p>There is an unmet medical need in patients with PBC who are:</p> <ul style="list-style-type: none"> Intolerant to UDCA Have an inadequate response to UDCA Patients with advanced stage disease who are unlikely to respond to UDCA <p>The treatment armamentarium would greatly benefit from novel safe and effective therapies for these patients.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	<p style="text-align: right;">(b) (4)</p> <p>The efficacy of OCA was established in one phase 3 trial; the phase 3 trial was adequately designed and well-controlled. The safety and efficacy of monotherapy was assessed in two additional phase 2 trials. The database encompassed a total of 440 patients enrolled across all 3 trials, as well as supportive data from multiple nonclinical and phase 1 trials. The trials varied in treatment duration and dose.</p> <p>Patients were enrolled on basis of elevated ALP while the overwhelming majority of patients had normal total bilirubin and normal albumin and thus were considered early stage disease by the Rotterdam criteria (early stage - normal total bilirubin and albumin, moderately advanced stage - either TB abnormal, advanced stage – both abnormal).</p> <p>Notably, a 3 month phase 2 trial assessed efficacy of OCA monotherapy and the biochemical response of ALP reduction was also observed, similar to phase 3 trials results, relative to placebo arm.</p> <p>The phase 3 trial was a one year trial in 216 patients with three arms, placebo, 10mg and titration from 5mg to 10 mg. The primary efficacy endpoint for the phase 3 trial was a composite of ALP <1.67 X ULN and total bilirubin ≤ULN and at least ≥15% reduction in ALP. However, since 92% patients in phase 3 trial had total bilirubin within normal reference range, the main driver of the efficacy results was reduction in ALP.</p> <p>Phase 3 results are as follows: At month 12, a total of 46% and 47% patients on OCA titration and OCA 10 mg arm respectively achieved reduction in ALP >1.67 XULN and at least ≥15% reduction in ALP, and these were statistically significant relative to placebo. Of the 18 patients who had elevated ALP and TB at baseline, 1 out of 4 patients in the titration arm, 2 out of 7 patients in OCA 10 mg and none out of 7 patients in placebo arm achieved the composite endpoint. The ALP reduction response is durable as seen in the long term safety extension trial in data submitted to a cutoff point of up to 30 months. Subgroup analyses (disease severity, age, gender) were not conducted due to small sample size.</p> <p>The trials demonstrated reduction in ALP, which was seen as early as 2 weeks and the response was durable and sustained at 3 months in both phase 2 trials and at 12 months in the phase 3 trial. The Global PBC study group published results by conducting retrospective analyses on 4,845 PBC patients and found ALP and TB, as a composite endpoint, prognosticates death and liver transplantation.</p> <p>FDA conducted additional analyses of the Global PBC data and identified a subset of patients that matched the trial population (baseline ALP >1.67 X ULN, UDCA concomitant usage, and early stage disease as per Rotterdam criteria). Using these same matching criteria resulted in</p>	<p>If ALP is on the causal pathway of PBC, the reduction in ALP would equate to slowing down the progression of disease and thereby allowing patients to live with their native liver for a longer duration. This will help avoid the complications of liver transplantation and commitment to lifelong immunosuppression. There are no treatment options for patients who fail UDCA; therefore, OCA is a therapeutic option in patients who fail UDCA.</p> <p>Limitation of data: The phase 3 trial enrolled 90% of patients with early stage disease. The remaining 10% of patients enrolled had moderately advanced disease; therefore data are limited. There are no data in advanced liver disease patients (as defined by Rotterdam criteria) or in patients with decompensated cirrhosis; therefore, the benefits and harm in this population with OCA use are unknown.</p> <p>Although dose recommendation for OCA use in patients with advanced stages of PBC have been proposed by the FDA, these may not be adequate for all patients with variable ranges of hepatic impairment. Therefore, additional safety data are required for this population.</p> <p>The confirmatory trial is ongoing and until the results are analyzed the clinical benefit outcomes of ALP to support its use as a surrogate are yet to be established.</p> <p>There is a sub-group of patients in whom pruritus worsens secondary to OCA treatment and cannot be managed by anti-histamines, and bile acid sequestrants. These patients may not be able to tolerate the drug and will not benefit from OCA treatment.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>181 patients identified in the phase 3 trial. The following thresholds were identified as if the baseline ALP $\geq 2 \times$ ULN, then patients were designated as responders when they achieved both ALP $< 2.0 \times$ ULN and decrease $\geq 40\%$ AND if the patients' baseline ALP were $\geq 1.67 \times$ ULN then they were designated as responders if they achieved both ALP $< 1.67 \times$ ULN and a decrease $\geq 15\%$. For the FDA derived thresholds, the C-statistics (0.68-0.70) and Hazard ratio were (2.54-2.68), which was better when compared with C-statistics of 0.64-0.68 and HR of 1.82-2.42 for the pre-specified threshold. FDA modified exploratory analyses of ALP reduction was statistically significant for the OCA treated group (43% and 38% for OCA 10 mg and OCA titration group respectively) compared to 5% response in placebo arm.</p> <p>An Advisory Committee meeting was held on April 7th 2016 to query whether ALP was an appropriate surrogate that is reasonably likely to predict clinical benefit. The AC members voted unanimously (17-0) in favor of OCA approval on the surrogate basis of ALP reduction. Based on the biological plausibility of ALP as a surrogate in PBC, the AC committee considered ALP a diagnostic biomarker, as well as a marker for monitoring progression of the disease.</p> <p>The secondary endpoints were TB, GGT, AST and ALT. The total bilirubin also reduced albeit this was seen in only a few patients treated with OCA. A statistically significant number of patients treated with OCA achieved GGT reduction, which is supportive evidence for reduction in cholestasis. Aminotransferases (ALT and AST) reduction was also statistically significant in the OCA treated group and is supportive of reduction of hepatocellular damage. Additionally, there was reduction (but not normalization) of IgM in the OCA treatment groups, which was statistically significant compared with placebo group. IgM is specifically elevated in PBC.</p>	
Risk	<p>The safety database for OCA includes all patients from two phase 2 and one phase 3 trial. Additional safety database reviewed included trials conducted in healthy volunteers (PK/PD trials) and non-alcoholic steatohepatitis (NASH) trials. The safety profile demonstrated for OCA was consistent across phase 2 and 3 trials.</p> <p>Dose dependent increase in pruritus as well as severe pruritus was observed. Incidence of pruritus was 38% in placebo, 56% in OCA titration arm and 68% in OCA 10 mg arm. Incidence of severe pruritus was 7% in placebo, 19% in OCA titration arm and 23% in OCA 10 mg arm. There were 7 discontinuations due to pruritus in OCA 10 mg arm and one discontinuation in OCA titration arm compared to zero in the placebo arm. The incidence of pruritus was higher in patients with baseline ALP $> 3 \times$ ULN.</p> <p>Dose dependent increase in the incidence of fatigue was also seen: 14% placebo patients, 16% patients in titration arm and 23% patients in OCA 10 mg arm experienced fatigue.</p>	<p>Overall the safety of OCA use is well characterized in early stage PBC population.</p> <p>There were no major/serious safety concerns (i.e., death or life threatening adverse events).</p> <p>Pruritus and fatigue appear to be worsened in some patients taking OCA and could limit use in some patients.</p> <p>Reduction in HDLc may occur over time and may increase the risk for cardiovascular events.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Dose dependent HDLc reductions were seen. At month 12, reductions from baseline in mean HDLc was observed in 21% in OCA 10 mg arm, 15% in OCA titration arm and 3% in placebo arm.</p> <p>Pruritus and dyslipidemia were reversible with OCA discontinuation.</p> <p>The majority of patients were female and white. Differences in the incidence of the adverse events were not discernable across different sub-populations (age, gender, race, baseline UDCA use, baseline total bilirubin) as the small sample size and imbalance across treatment groups precludes a meaningful interpretation.</p> <p>Drug-drug interactions were limited (Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates).</p> <p>Nonclinical data indicated that OCA can induce liver injury at high doses (OCA 100 mg). In the healthy human trials liver biochemical abnormalities were noted at OCA 100 mg dose. At doses of 25 mg and 50 mg (which are higher than the to-be-approved doses of 5 and 10mg), higher rates of hepatic decompensation events were observed (new onset jaundice, ascites, and PBC flare) as well as biochemical changes possibly indicative of hepatic injury.</p> <p>OCA undergoes enterohepatic circulation and it and its conjugates have a very long half-life. PK modeling showed that OCA 10 mg tablet once a day administration leads to very high OCA systemic and liver exposures in patients with moderately advanced (Child-Pugh B) and advanced (Child-Pugh C) cirrhosis. These high exposures could cause an increased risk of hepatic injury. There is lack of clinical data in patients with advanced cirrhosis as only 20 patients with Child Pugh A cirrhosis were enrolled in the clinical trial.</p> <p>ALP may be a better marker of progression of disease and response to treatment in early phases of PBC. As the disease progresses the ALP levels may gradually decrease as bilirubin increases making it an inadequate marker for trials in patients with advanced disease.</p>	<p>Data of longer duration of OCA use are required to understand the implications of cardiovascular events with HDLc lowering.</p> <p>OCA can result in liver injury at high exposures as seen in nonclinical studies and in early phase trials with higher doses.</p> <p>Patients with impaired hepatic function can have much higher exposures and a reduced dose has been recommended for these patients. Additional data is needed in patients with hepatic impairment.</p>
<p><u>Risk Management</u></p>	<p>Higher rates of hepatic adverse events were seen at higher OCA doses. The maximum efficacy is seen at OCA 10 mg after which the efficacy response plateaus.</p> <p>Treating physicians will be able to monitor patients' response to treatment based on liver biochemical changes.</p> <p>The safety and efficacy of OCA have not been studied in patients with advanced liver disease and limited data are available for patients with moderately advanced liver disease. The dose</p>	<p>The prescribing information recommends:</p> <ul style="list-style-type: none"> • OCA dose of 10 mg which is not to exceed 10 mg. • Ongoing assessment of liver biochemical tests and HDLc. • Dose adjustment in patients with hepatic impairments and in instances of disease progression; these dose adjustments must be

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>adjustment proposed by FDA is based on modeling and simulation in Child Pugh A, B and C hepatic impairment (based on data gathered in other liver diseases). This dose adjustment may or may not be sufficient to accommodate for later stages of hepatic impairment in PBC patients. PMR placebo-controlled studies will be required in patients with advanced stage liver disease (per Rotterdam criteria) and patients with decompensated cirrhosis.</p> <p>Long term safety data with OCA use as monotherapy are lacking.</p> <p>The safety of OCA has not been established in pregnant women.</p>	<p>done on an ongoing basis.</p> <ul style="list-style-type: none"> • Close monitoring during dose adjustments. <p>PMR to gather additional data from a placebo-controlled OCA as monotherapy trial.</p>

2 Therapeutic Context

2.1 Analysis of Condition

Primary Biliary Cholangitis/Cirrhosis (PBC) is an autoimmune, chronic cholestatic liver disorder with a progressive clinical course extending over many decades. PBC is characterized by non-suppurative destruction of the small intralobular bile ducts (lymphocytic inflammation), which is a unique feature. Loss of the intralobular bile duct (ductopenia) leads to progressive impairment of bile flow in the liver resulting in increased hepatocellular bile concentrations. Bile acids at elevated concentrations can be toxic to the liver.

Exact pathogenesis is unknown; but thought to occur in genetically predisposed patients in the presence of environmental triggers. Features of both the adaptive and innate responses contribute to biliary pathology. The liver injury is mediated by inflammatory infiltration (plasma cells, lymphocytes, mononuclear cells etc.), that causes necrosis of small intrahepatic bile ducts leading to bile duct loss (ductopenia) and bile stasis. Bile salts are toxic and contribute to damage of bile ducts as well as hepatic parenchymal structures. The damage caused by the inflammatory infiltrate and bile stasis leads to fibrosis and cirrhosis. Bile salts are required in absorption of fat and fat soluble vitamins, decrease of bile flow to intestines causes malabsorption of nutrients and micronutrients. Cirrhosis is inevitable without treatment and eventually leads to portal hypertension which causes hemodynamic alterations such as increased portal pressures, portal-systemic shunting, splanchnic vasodilation and peripheral vasoconstriction, increased cardiac output etc. Therefore in advanced stages of disease in addition to the inflammation, bile duct loss and bile stasis mediated damage; progressive injury is accelerated by onset of portal hypertension and its complications (esophageal variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites etc.) which further hastens the process of liver failure.

Ursodeoxycholic acid (UDCA) is the only approved treatment. Approximately, 60% of patients respond to UDCA and have a close to normal life expectancy. Without treatment or secondary to inadequate response to UDCA patients, the disease progresses at a variable rate to liver failure^{1, 2} leading to death or liver failure. PBC is the 6th leading indication for liver transplantation in the US. PBC recurrence is seen after liver transplantation.

PBC is a rare liver disease. Based on well-defined case findings, the incidence and prevalence rates for PBC in Europe, North America, 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.

Autoimmune diseases are commonly observed in patients with PBC³. More than 80% of patients have been reported to exhibit features of at least one non-hepatic autoimmune disease (~55%) sometime during the clinical course of the disease. Sicca syndrome (dry eyes and dry mouth) is seen in up to 70% of PBC patients. Other autoimmune conditions observed with PBC are Sjogren's syndrome (~34%), Raynaud's syndrome (13%), Hashimoto's thyroiditis (13%), rheumatoid arthritis (8%), Scleroderma or CREST¹ (~2%), and inflammatory bowel disease (~1%).

PBC disproportionately affects women (women: men ~ 10:1). The typical age of diagnosis is between 40 and 60 years of age. Recent data suggest that those who are young at onset (diagnosed before 50 years of age) or male have a worse prognosis⁴. Racial and ethnic differences in PBC patients have not been consistently identified.

Antimitochondrial antibodies (AMA) directed against the E2 subunit of the pyruvate dehydrogenase complex are a sensitive serological hallmark of PBC. AMA is the serological hallmark of disease. AMA is a highly disease-specific autoantibody found in 90-95% of patients and less than 1% of controls. AMA is present even before biochemical abnormalities are seen. Currently, the diagnosis is made when two of the following three criteria are

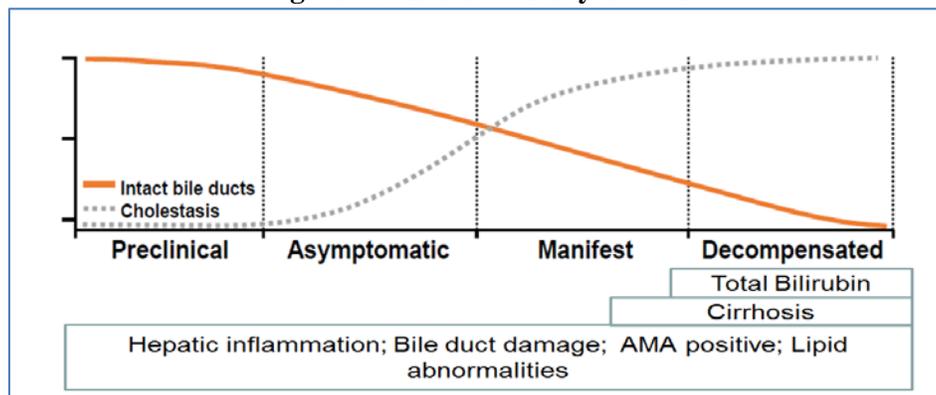
¹ CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome) is a limited type of scleroderma.

met⁵:

1. Biochemical evidence of cholestasis with elevation of ALP activity (for more than 6 months)
2. Presence of AMA, which present in ~95% of patients and is detectable years before the clinical signs appear
3. Histologic evidence of chronic non-suppurative cholangitis of small and medium size bile ducts if a liver biopsy is performed.

PBC disease progression varies widely across patients, with some patients progressing to decompensation over a period of a few 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. Diagnosis is suspected based on cholestatic serum liver tests and confirmed with AMA testing. In 95% of patients AMA is present, which is diagnostic of PBC. About 5-10% patients are AMA negative, in these cases a liver biopsy can substantiate the diagnosis. Liver biopsy is also utilized if diagnosis of PBC is questionable, if the alkaline phosphatase activity is ≥ 1.5 times normal and AST > 5 time normal. Liver biopsy may be recommended in AMA-negative patients and to exclude other concomitant diseases such as autoimmune hepatitis and non-alcoholic steatohepatitis.

Figure 1: Natural History of PBC



Source: Figure modified, adopted from Applicant AC slide presentation

Clinical Symptoms in PBC:

1. **Fatigue:** is the most common but a non-specific symptom, has been found in up to 78% of patients. Fatigue is associated with excessive day time somnolence. Fatigue does not correlate with the severity, histological stage or duration of PBC. Fatigue is associated with lower overall health-related outcomes.
2. **Pruritus:** is more specific to PBC and occurs in 20%-70% of patients. Pruritus can be local or diffuse, is worse at night, often exacerbated by contact with certain fabrics (wool), heat etc. Pruritus is localized to soles of feet, palms of hands, with most of the intense itching occurring in late evening. Pruritus typically diminishes as disease progresses and disappears when patients develop cirrhosis and liver failure. Ethology for pruritus is unknown; however, the current thinking is that pruritus is due to the following suspected pruritogens: bile salts, endogenous opioids, histamine, serotonin, progesterone/estrogen, and autotaxin/lysophosphatidic acid.
3. **Osteoporosis:** occurs in up to a third of patients. The relative risk of developing osteoporosis in PBC compared to age-matched healthy population is 4.4%. 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. Vitamin D metabolism is normal in patients with PBC except for those with jaundice and clinically advanced disease. Fractures occur at higher rates than the general population in patients with PBC.
4. **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. Jaundice is a late finding. As the disease advances, there is development of portal hypertension and its complications such as esophageal varices, ascites, hepatocellular carcinoma (HCC), and hepatic encephalopathy etc.

5. **Hyperlipidemia:** is seen in PBC, with disproportionately elevated high density lipoprotein cholesterol. Patients with PBC are not at increased risk of death from atherosclerosis^{6,7}. However, recent meta-analyses demonstrated statistically significant increased risk of cardiac atherosclerosis disease among patients with PBC; however evaluation of publication bias was not accounted in this meta-analysis review.

Xanthelasma and xanthoma may be present. Overlap syndrome with autoimmune hepatitis can also be found. The survival of individuals who develop esophageal varices is poor with a 5-year survival rate of 63%. Mean survival once total bilirubin reaches 2 mg/dL is 4 years, declining to 2 years when bilirubin reaches 6 mg/dL⁸. The risk for HCC is increased in advanced PBC and is also associated with decreased survival. Without therapeutic intervention the disease progresses to liver impairment leading to liver failure resulting in liver transplant or death. Complications of liver transplant include death, primary graft failure, graft rejection at any time post transplantation, infections, and side effects of immunosuppressants. PBC recurrence is seen in about 23%, 35% and 43% of recipient liver at 5, 10 and 15 years respectively at follow up.

Stages of disease: There is no unified definition of stages of the PBC in the literature. The disease stage can be classified as early stage, or advanced stage on basis of:

1. Histology [Utilizing with Ludwig/Scheuer PBC Stage 4 (cirrhosis) or Ishak score 6 (cirrhosis)].

Liver biopsy data are limited in PBC. In clinical setting, the diagnosis of PBC is made with AMA, a liver biopsy is typically not performed; moreover, the disease progresses very slowly, a liver biopsy is not performed in for patient follow up. From the available data, it seems that cirrhosis is considered advanced stage disease by most clinicians. However, the caveat being that a patient can be in stage 4 (Ludwig/Scheuer classification) or stage 6 (Ishak score) fibrosis i.e., Child Pugh A and may remain in this stage for many years or even a decade without experiencing any clinical significant event (decompensation events).

2. Biochemical markers (total bilirubin and albumin)

A Rotterdam criterion is utilized mostly in European countries; and this classification criterion is not widely used in the US. Other biochemical markers such as AST, ALT, and ALP are also utilized.

Table 1: Rotterdam Criteria

Stage	Criteria
Early	normal total bilirubin and normal albumin
Moderately Advanced	either abnormal total bilirubin or abnormal albumin
Advanced	abnormal total bilirubin and abnormal albumin

Source: Adapted from Kuiper et.al, 2009 "Improved Prognosis of Patients with Primary Biliary Cirrhosis That Have a Biochemical Response to Ursodeoxycholic Acid" Gastroenterology 2009

The advantage of utilizing the Rotterdam criteria includes ease of assessing disease stage in PBC patients, and without a need for invasive testing. Also, a rise in TB is a very sensitive marker in PBC for assessment of the disease progression. The limitations include the lack of further granularity of staging once a patient is in the advanced stage of disease. Additionally, in theory, the presence of ascites confounds the interpretation of albumin levels. One problem that exists with this classification is patients in compensated cirrhosis can have normal TB and normal albumin, therefore the correlation between the

3. Onset of symptoms of portal hypertension and its complications.

Once portal hypertension ensues and patient can experience events such as ascites, elevations of TB, esophageal variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, the patient is now in the decompensated cirrhosis stage which is associated with a very high mortality and morbidity and portends proximity to death or need for transplant. Notably, in PBC portal hypertension symptoms can occur even in the absence of cirrhosis.

Prognostic markers: Gender and age were found to predict prognosis in PBC. Presence of symptoms, specifically

fatigue and pruritus are used more for risk stratification, but a correlation with survival or prognosis has not been established.

Biochemical prognostic markers for PBC: ALP and TB are the two surrogate markers that have been studied by various groups. In addition, aminotransferases (AST, ALT), gamma-GT, and albumin have also been proposed as biochemical predictors of decompensation and mortality.

Risk scores for prognostication: Have been described and analyzed both retrospectively and prospectively. A few of them are mentioned here.

1. Mayo Risk score: Mayo Risk Score was calculated as follow: $R = 0.871 \times \log_e(\text{bilirubin [mg/dL]}) + 2.53 \times \log_e(\text{albumin [gm/dL]}) + 0.039 \times \text{age [yrs]} + 2.38 \times \log_e(\text{prothrombin time [sec]}) + 0.859 \times \text{edema}$. Patients with an MRS ≥ 4.5 have a high risk of UDCA therapy failure

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Source: Adapted from Lammers et.al., 2014

2. GLOBE Risk score 2014

$((0.044378 * \text{age at start of UDCA therapy} + 0.93982 * \text{LN}(\text{bilirubin times the upper limit of normal (ULN) at 1 year follow-up})) + (0.335648 * \text{LN}(\text{alkaline phosphatase times the ULN at 1 year follow-up})) - 2.266708 * \text{albumin level times the lower limit of normal (LLN) at 1 year follow-up} - 0.002581 * \text{platelet count per } 10^9/\text{L at 1 year follow-up})$.

The Globe score utilizes: a complex mathematical model that utilizing age at start of UDCA, ALP, TB, albumin and platelet count in modeling for prediction of survival.

3. UK PBC Risk Scores 2015

$1 - \text{baseline survival function}^{\exp(.0287854 * (\text{alp} \times \ln - 1.722136304) - .0422873 * (((\text{alt} \times \ln / 10)^{-1}) - 8.675729006) + 1.4199 * (\ln(\text{bil} \times \ln / 10) + 2.709607778) - 1.960303 * (\text{alb} \times \ln - 1.17673001) - .4161954 * (\text{plt} \times \ln - 1.873564875))}$.

Another complex mathematical model that utilizes biochemical parameter: ALP, AST, ALT, TB, albumin and platelets and predicts survival.

Since the approval of this application hinges on ALP, a brief discussion of ALP is presented. In addition, a brief description of total bilirubin and conjugated bilirubin is also presented.

Alkaline Phosphatase

ALP is a zinc metalloenzymes which hydrolyzes organic phosphatase in alkaline medium. In humans, there are four distinct but related ALPs:

1. Intestinal,
2. Placental,
3. Placenta-like,
4. And liver/bone/kidney (tissue-nonspecific ALP).

The genes of the first three are located together on chromosome 2, whereas the tissue-nonspecific ALP form is located on chromosome 1. In pregnancy, there is a slow increase in ALP values during the first 6 months, followed by a larger increase and reaching up to three or four times the usual values. This increase is mainly caused by the placental isoenzyme. Abnormal ALP levels may also be a sign of metastatic cancer of the liver, bronchogenic

carcinoma, lymphoma or infiltrative diseases such as sarcoidosis.²

ALP is bound to the canalicular membrane, and is present on the surface of cholangiocytes. The function of ALP is to catalyze the hydrolysis of phosphate esters, most notably, ATP in the hepatobiliary canalicular space. ALP is an important regulator of canalicular pH, ATP concentrations and secretion of HCO₃⁻ rich alkaline bile.

Primarily bile acids increase in PBC and cause the damage seen in cholestatic liver disease. Bile acids have membrane solubilizing features and increase the permeability of intercellular tight junctions, thereby increasing detachment of membrane bound ALP and enhancing the passage of the enzyme into sinusoidal blood. This redirection of ALP to the circulation and speculated of decreased ALP in the canalicular space which is thought to be detrimental.

In healthy adults, liver and bone account for more than 80% of circulating ALP. In PBC, ALP and GGT can both be mildly or markedly elevated. Increased ALP is found in both intra- and extrahepatic cholestasis, but the diagnostic sensitivity, in cholestatic disease is 80% to 100%. Elevated ALP does not differentiate between intra- and extrahepatic cholestasis,

ALP is a marker of cholestatic conditions. Fibrates selectively decrease liver-ALP (L-ALP) activity in blood and anti-epileptics have inductive properties and increase Liver-ALP. These effects (of drug-induced increase or decrease in ALP) are confined to the liver isoenzyme. Importantly, high immunoglobulin concentrations can markedly enhance serum ALP activity.

Reviewer Comment: During the literature review, it was noted in several publications that patients older than 60 (especially women) have higher ALP (up to 1.5 times normal) than younger adults (Poupon 2015). This laboratory variability was not accounted for and the same absolute cut-off value of ALP was used for all ages³. This concern was discussed with Applicant during the review process however; the Applicant responded that there were currently no data available to suggest the validity of the difference in ALP levels in patients older than 60 years. Additionally, in discussions with hepatology experts during the AC meeting, there was consensus that these differences have not been noted to be true in their clinical practices. Therefore, the Division agreed to accept the ULN for ALP to be the same for all ages.

ALP is elevated in many inflammatory conditions⁹. Smokers have 10% higher ALP levels than nonsmokers⁴. ALP levels also fluctuate approximately 6% from week to week in healthy individuals⁵. Normal ALP variability in healthy individuals and smokers has been accounted for in the trial by using a change in ALP of at least $\geq 15\%$ reduction.

The ALP assay variability is less than 10%. However, the intra-patient variability was not known at the time of NDA submission. During this trial, the Applicant performed analyses of intra-patient variability, which is discussed in Section 6.3.11.1.

Total and Conjugated Bilirubin

Bilirubin is the breakdown product of heme from cells, such as red blood cells (RBCs), cytochrome P450 and myoglobin. Almost 80% of heme is derived from hemoglobin breakdown in RBCs. In the liver, bilirubin is

² <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC545762/>

³ http://ac.els-cdn.com/0009898175900716/1-s2.0-0009898175900716-main.pdf?_tid=77d0c700-4433-11e5-8d9e-00000aacb361&acdnat=1439742534_5e287b1cdb171dbb14fb9b49533baf4c

⁴ Frost-Pineda K1, Liang Q, Liu J, Rimmer L, Jin Y, Feng S, Kapur S, Mendes P, Roethig H, Sarkar M. Nicotine Tob Res. 2011 Mar;13(3):182-93

⁵ <http://www.exeterlaboratory.com/test/alkaline-phosphatase/>

solubilized by UDP-glucuronosyl transferase which conjugates bilirubin to glucuronic acid. The soluble bilirubin is then actively transported from the hepatocyte into canalicular bile by an ATP-dependent transport process which is the rate limiting step in hepatic bilirubin excretion.

Conjugated bilirubin (i.e., direct bilirubin) is usually present in small amounts in the serum of healthy individuals due to the rapidity of bile secretion. Levels increase when the liver starts losing its excretory capacity, thus elevations in circulating direct bilirubin indicate liver damage. Conjugated hyperbilirubinemia is commonly caused by bile duct obstruction.

Elevated conjugated bilirubin with concomitantly elevated aminotransferases can be seen in acute viral hepatitis, autoimmune hepatitis, ischemic liver injury, drug toxicity, toxic liver injury, among other causes. PBC patients can also present late in their disease course with direct hyperbilirubinemia, along with elevated ALP and GGT and normal or only mildly elevated aminotransferases.

Total bilirubin has more often been reported in the published literature. In the clinical management of PBC, total bilirubin is and reflects the severity of ductopenia. Increasing bilirubin is indicative of advancing disease state and the potential onset of cirrhosis and increased risk for its complications.

This reviewer thinks that the total bilirubin is a good measure of hepatic function, with some exceptions including when serum albumin is altered or if a patient has hemolysis or has Gilbert's syndrome etc... Serum conjugated bilirubin is the fraction of conjugated bilirubin (CB) which is 'spilled over' and could be secreted in the biliary ductal system as a result of bile duct damage. Not all the 'spilled over' conjugated bilirubin may be detected in the serum, given the changes in local hepatic micro-environment and local homeostasis, such as cirrhosis; regenerative nodules, etc., which regulate the release of CB into the bloodstream. The serum CB levels indicate ductal damage; however, CB lacks the precision in accurately estimating disease burden or disease stage.

2.2 Analysis of Current Treatment Options

Ursodeoxycholic acid (UDCA) is administered as a dose of 13-15 mg/kg/day and is the only FDA approved therapy for PBC. Liver biochemical test improvements are observed in 90% of patients treated with UDCA in 6-9 months. About 20% patients will have normalization of biochemistries after 2 years. However, UDCA therapy has not been reported to improve fatigue, pruritus, associated bone disease or autoimmune features as associated with PBC.

The UDCA efficacy trial in patients with PBC that led to the approval is summarized below (NDA 020675: Approved 10 December 1997).

A U.S., multicenter, randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy of ursodeoxycholic acid at a dose of 13 to 15 mg/kg/day, administered in 3 or 4 divided doses in 180 biopsy-confirmed PBC patients. The primary efficacy parameter was incidence and time to treatment failure, a composite endpoint defined as: death, liver transplant, histologic progression by two stages or to cirrhosis, development of varices, ascites, or encephalopathy, doubling of bilirubin, marked worsening of fatigue or pruritus, drug intolerance or voluntary withdrawal. Secondary endpoints included changes in biochemical markers, development or progression of selected signs or symptoms, and histologic changes. Patients were followed up to 4 years in a double-blind fashion, and were then switched to an open-label, active drug, long-term extension study.

Results: After two years of double-blind treatment, the incidence of treatment failure was significantly ($p < 0.01$) reduced in the URSO 250 mg arm (20 of 86 (23%)) as compared to the placebo arm (40 of 86 (47%)). Time to treatment failure, which excluded doubling of serum bilirubin and voluntary withdrawal, was also significantly ($p < 0.001$) delayed in the URSO 250 treated arm ($n = 86$, 803.8 ± 24.9 d vs. 641.1 ± 24.4 d for the placebo arm ($n = 86$ on average) regardless of either histologic stage or baseline bilirubin levels (> 1.8 or < 1.8 mg/dl). However, the reviewer notes, the major driving factor of the therapeutic gain was doubling of TB which was statistically significant ($p = 0.01$). All other components of the primary endpoint moved in a favorable direction and supported the TB results.

The second study [submitted as supportive trial in NDA 20-675] was conducted in Toronto. In this randomized, placebo controlled, double-blind trial, 222 patients were stratified according to the presence or absence of symptoms

at baseline. Patients were followed for 2 years in a double-blind fashion. UDCA 250-mg tablets were administered at a dose of 14 mg/kg/day, given as a single daily dose. The primary efficacy endpoint was the proportion of patients showing an increase in baseline bilirubin greater than 50%. Secondary endpoints were defined as change in symptoms and biochemical markers, liver histology; and time to death or liver transplant.

Results: At two years, a statistically significant ($p < 0.001$) difference between the two treatments ($n = 106$ for the URSO 250 arm and $n = 106$ for the placebo arm), was demonstrated in the following: reduction in the proportion of patients exhibiting a more than 50% increase in serum bilirubin; median percent decrease in bilirubin (-17.12% for the URSO 250 arm vs. +20.00% for the placebo arm), transaminases (-40.54% for the URSO 250 arm vs. +5.71% for the placebo arm) and alkaline phosphatase (-47.61% for the URSO 250 arm vs. -5.69% for the placebo arm); incidence of treatment failure; and time to treatment failure. The definition of treatment failure included: discontinuing the study for any reason; a total serum bilirubin level greater than or equal to 1.5 mg/dl or increasing to a level equal to or greater than two times the baseline level; and the development of ascites or encephalopathy. Clinical benefit end points were not evaluated.

Table 2: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product Name	Year of Approval	Dosing/ Administration	Indication	Important Safety and Tolerability Issues
Ursodeoxycholic acid (UDCA)	10 th December 1997	13-15 mg/kg/day in two to four divided doses	Primary biliary cirrhosis	>1% adverse event: Nausea, dyspepsia, vomiting, abdominal pain, diarrhea, headaches, cough, pruritus, alopecia and rash

Source: Reviewer Generated from the Urso® Label

Numerous other drugs have been tested in clinical trials but none have been found beneficial, and are therefore not listed in Table 2. These include chlorambucil, penicillamine, cyclosporine, corticosteroids, azathioprine, methotrexate, colchicine, and malotilate. Doubling the dose of UDCA and the addition of colchicine, methotrexate, or silymarin have not been found to be beneficial over and beyond the benefit achieved with UDCA alone.

(b) (4)

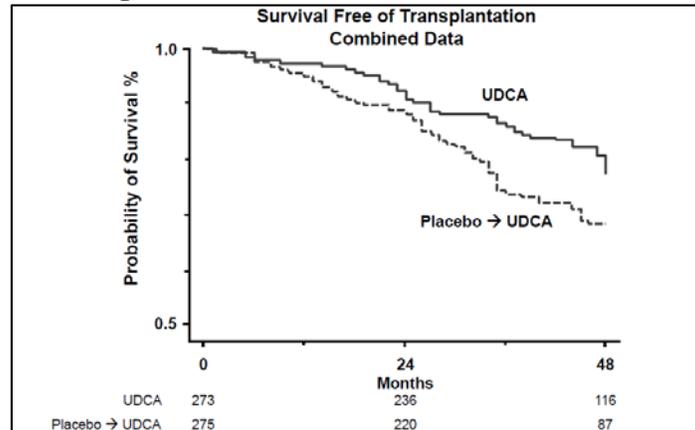
Controversies about UDCA's Clinical Benefit:

Many trials have suggested UDCA delays the histological progression of the disease, and improves the long term survival^{10, 11, 12, 13, 14, 15}. Subsequently, many trials and meta analyses were published but unable to show the clinical benefit; however, most were flawed due to short duration (<2 years) of patient follow up and usage of inadequate UDCA dose.

A 'pooled' analysis on individual patient data was conducted by Poupon et.al., 1997, from the 3 largest placebo controlled double blind studies (Toronto ($n = 222$), Mayo ($n = 180$) and Paris ($n = 146$)). This analysis also included some longer follow-up (up to 4 years) data from US, French and Canadian data that was generated from the placebo controlled clinical trials for UDCA approval⁶ (Poupon 1997). The re-evaluation showed an improvement in survival with UDCA after 4 years of treatment (Figure 2: UDCA Use and Clinical Benefit).

⁶ Poupon RE, Lindor KD, Cauch-Dudek K, et al. Combined Analysis of Randomized Controlled Trials of Ursodeoxycholic Acid in Primary Biliary Cirrhosis. Gastroenterology. 1997; 113:884-890

Figure 2: UDCA Use and Clinical Benefit

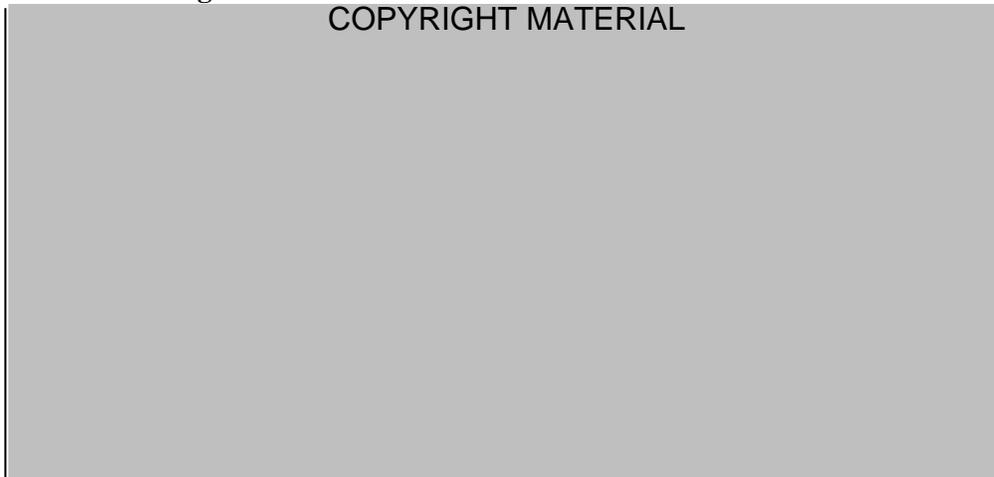


Source: Adopted from the Applicant's AC slide deck presentation (4-7-2016)

Foot note: For the "Placebo → UDCA" group, patients randomized to placebo in 2 of the 3 pooled studies were treated with placebo for 2 years and then given the option to receive UDCA for an additional 2 years.

Figure 3: Survival in Patients Treated With UDCA

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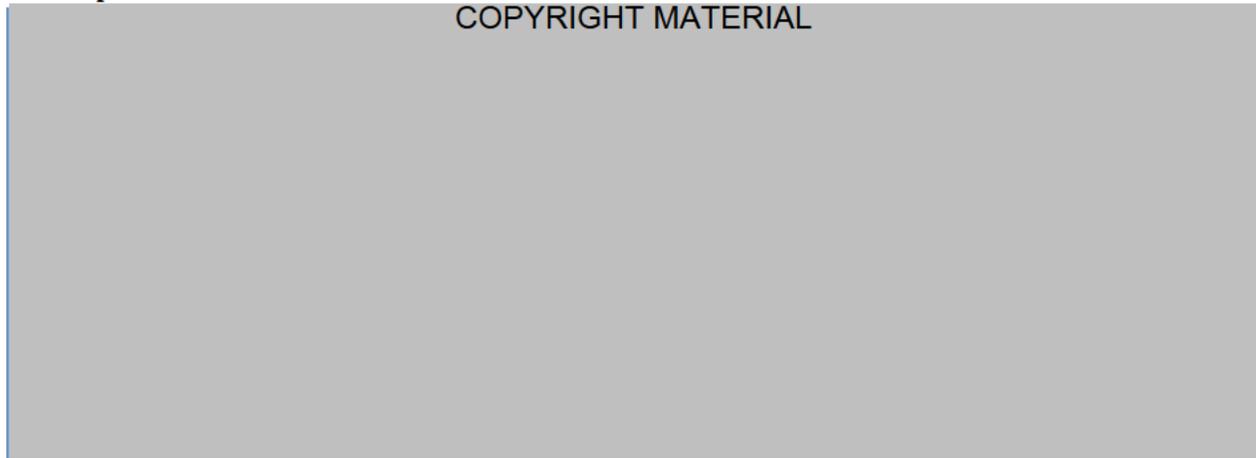


Source: Poupon RE, Bonnand AM, Chretien Y, et al. Ten-year survival in ursodeoxycholic acid-treated patients with primary biliary cirrhosis. *Hepatology* 1999; 29(6):1668-1671

Poupon et al., 1999 reported (Figure 3: Survival in Patients Treated With UDCA) in a ten year follow up about 40% patients do not respond to UDCA, especially the patient who are in more advanced stage disease. Furthermore, while UDCA at the recommended dosage (13 mg/kg/day to 15 mg/kg day) is generally well tolerated, there is a small subset of PBC (~5 %-expert opinion) patients who are unable to tolerate UDCA (primarily due to gastrointestinal symptoms) and are at greater risk of adverse outcome if unable to remain on therapy.

The above presented findings were replicated in various retrospective analyses as assessed by different investigators, i.e., UDCA treatment provided survival benefit. However, various investigators utilized different responder criteria, i.e., ALP and/or TB and/or AST thresholds reduction criteria required at one year after treatment with UDCA to predict clinical outcomes, The UDCA responders showed a normal life expectancy whereas UDCA non-responders reached an adverse clinical endpoint sooner (endpoints: liver related death, liver transplantation, complications of cirrhosis or histological evidence of cirrhosis).

Figure 4: Early PBC as defined by Normal Bilirubin and Normal Albumin and Survival rates on a 15 year follow up



Source: Corpechot, 2011 Journal of Hepatology

This reviewer chooses to discuss this publication as the population in this cohort is similar to the population enrolled in trial 747-301. The Barcelona, Paris, Rotterdam, and Toronto criteria were assessed in this publication.

All patients (N=165) were treated with UDCA for 12 months, and patients were treated with UDCA in early stages of disease as defined by biochemically (normal TB and normal albumin) or histologically early stage (Stage 1 and 2 of disease). The graph on the left hand side (Figure 4) patients categorized on the basis of histological staging and UDCA biochemical responders according to Paris II criteria (see Table 1) were shown to have a better survival. The right side graph depicts the survival in UDCA biochemical responders versus non-responders in the patients with early stage disease (normal bilirubin and normal albumin) over a 15 year follow up. The main messages of this publication were:

1. There is no consensus on definition and magnitude of biochemical response in PBC for analyzing responders. The rate of biochemical response ranged from 63% to 87% depending on the chosen criteria. The rate of adverse outcome in non-responders varied from 4% to 27% according to the definition of the biochemical response.
2. The severity of disease stage needs to be accounted while choosing a responder criterion.
3. Even the non-responders benefitted with UDCA treatment; the 10 year survival was about 77% compared to pre-UDCA era survival of about 59% and a 15 year survival in UDCA treated patients was about 70% compared to 32% in pre-UDCA era (as shown by PBC study group).

Reviewer comment:

In conclusion the totality of the data shows, UDCA improves the survival rates in early stage disease PBC patients who achieve an adequate biochemical response. In advanced stages of disease (cirrhosis), most patients do not respond adequately to UDCA therapy. However, even inadequate responders benefitted with UDCA treatment with improved survival over non-UDCA treated patients (Corpechot 2005).

Responder Criteria to Assess Clinical Outcomes in PBC Patients

Various responder criteria utilizing ALP, TB and other liver biochemical parameters were proposed over the years correlating with the clinical outcomes. The risk scores have been described earlier in the review.

⁷ Corpechot, C, Carrat, F, Bahr, A, Chrétien, Y, Poupon, RE, and Poupon, R. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. *Gastroenterology*. 2005; 128: 297–303

Table 3: Biochemical Response Criteria for Risk Stratification in UDCA Treated Patients (Responder Criteria)

Criteria	Definition of biochemical response	Evaluation time point	Number of patients
Mayo criterion, 1999	ALP < 2.0xULN	6 months	180
Barcelona criterion, 2006	> 40% decrease of ALP or normalization	1 year	192
Paris-1 criterion, 2008	ALP < 3.0xULN, AST < 2.0xULN and total bilirubin ≤ 1mg/dL	1 year	292
Rotterdam criterion, 2009	Normalization of abnormal bilirubin and/or albumin	1 year	375
Toronto criterion, 2010²²	ALP ≤ 1.67xULN	2 years	69
Toronto criterion, 2010	ALP < 1.76x ULN	10 years	69
Toronto criterion, 2011	ALP < 1.76x ULN AND TB < ULN	8.2	683
Paris-2 criterion,* 2011	ALP ≤ 1.5xULN, AST ≤ 1.5xULN and bilirubin ≤ 1mg/dL	1 year	165
Ehim criterion,** 2011	≥ 70% decrease of γ-GT	6 month	138
Momah/Lindor (New Mayo) criterion, 2011	ALP ≤ 1.67xULN and bilirubin ≤ 1mg/dL	1 year	73
Rotterdam Criteria	Albumin ≥ LLN and Bilirubin ≤ ULN	9.7 years (1-17.3 years)	375

Source: Adapted from Lammers WJ, Kowdley KV, van Buuren HR Predicting outcome in primary biliary cirrhosis. Ann Hepatol. 2014 Jul-Aug; 13(4):316-26.

*early disease patients only; **Japanese patients

Reviewers comment: Various responder criteria (Table 3) to assess correlation between biochemical markers globally are shown. The PBC patients of different disease stage severity (early, moderately advanced and advanced stages) were analyzed together utilizing a single responder criterion in most analyses. The duration of the trials was also variable in these observational studies.

Lack of consensus on responder criteria: Literature published until 2010 showed UDCA responders had better survival outcomes compared to UDCA non responders, however which responder criteria performed the best was still unclear and there was no consensus among hepatology experts on a single responder criteria.

Given these limitations of the evidence to show survival benefit of UDCA, the Global PBC study group was formed by academic investigators to conduct a more rigorous patient-level meta-analysis with the goal of evaluating potential surrogate endpoints that would be reasonably likely to predict clinical benefit for patients with PBC.

The Global PBC Study Group Data

Refer to Min Min, PhD statistical review of the Global PBC dataset and Section 8.4 in this review.

The Global PBC study is a retrospective and/or prospective database that analyzed the data on 4,845 PBC patients across 14 major PBC centers in the US and Europe to obtain natural history data and assess the prognostic value of biomarkers (specifically ALP and TB) in patients with PBC.

Lammers et.al., 2014, published their retrospective trial and presented clinical and biochemical characteristics in 4,845 PBC patients, of which 4119 [85%] were treated with UDCA at a median dosage of 12.3 mg/kg/day (interquartile range 9.4–14.6 mg/kg/day). During follow up 1,118 patient reached clinical endpoint; 389 underwent liver transplantation and 729 died; 358 (49%) died of liver-related causes, 245 patients (34%) died of other causes, and the cause of death was unknown for 126 patients (17%). Transplant free survival was statistically significant between the UDCA treated versus untreated patients ($P < 0.0001$)¹⁶.

At 1 year after study enrollment, levels of alkaline phosphatase that were 2.0 times the upper limit of normal (ULN) best predicted patient outcome (C statistic, 0.71) but not significantly better than other thresholds. Of patients with alkaline phosphatase levels 2.0 times the ULN, 84% survived for 10 years compared with 62% of those with levels >2.0 times the ULN ($P < 0.0001$). One year after study enrollment, a bilirubin level 1.0 times the ULN best predicted patient transplant-free survival (C statistic, 0.79). The conclusion of the PBC Study Report was that combining alkaline phosphatase and total bilirubin increased the ability to predict patient survival.

The limitations of the Global PBC data include

1. *Different severity of patient population were analyzed using same criteria,*
2. *Missing data (significant number of patients),*
3. *Different laboratories utilized for biochemical analyte assessment and,*
4. *Different clinical practice patterns in different parts of the globe.*

UK-PBC Cohort

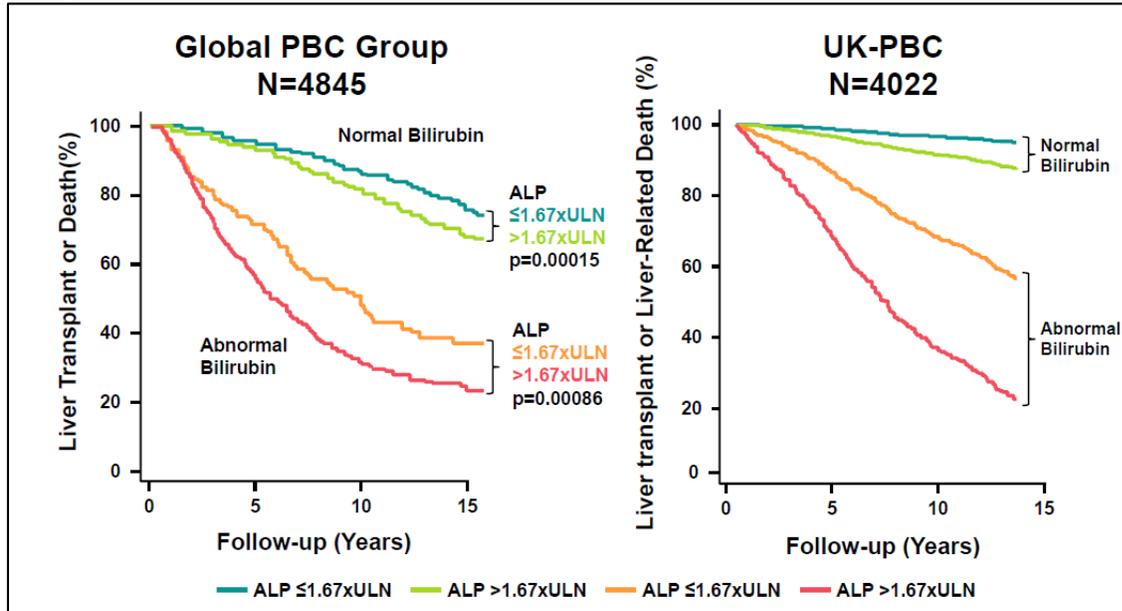
UK-PBC cohort began in 2007. PBC Foundation recruited patients via the UK-PBC consortium, a research network consisting of 150 hospitals in UK and all 7 UK transplant centers and captured ~25% of the UK population. These are prospectively collected data sets and notably death due to liver related deaths were collected separately (unlike Global PBC data base where data on death as “liver related” death was not captured).

For the UK-PBC cohort the follow-up time ranged from 11 days to 39.4 years (median follow-up was 6.56; IQR, 3.26-11.14 years). During the follow up period, 537 (13.35%) patients reached a clinical endpoint: 479 (11.91%) patients underwent liver transplant and 58 (1.44%) patients died from liver-related causes (44 from liver failure, 11 from HCC and 3 from variceal hemorrhage). Transplant-free survival rates are considerably higher in UDCA-treated versus untreated patients as summarized below Analysis from UK-PBC Cohort was presented in the NDA submission by the Applicant showing similar results.

The main conclusion of the UK PBC study group was

- Higher levels of either ALP ($>1.67 \times \text{ULN}$) or bilirubin ($>\text{ULN}$) were each individually associated with reduced liver transplant-free survival,
- The association of high ALP ($>1.67 \times \text{ULN}$) and poor outcome is independent of the bilirubin level, follow-up time, gender, age at diagnosis, histological stage and UDCA treatment,
- ALP values have predictive significance in addition to bilirubin and,
- Assessment of the combined primary endpoint (ALP $\leq 1.67 \times \text{ULN}$ and TB $\leq \text{ULN}$) significantly correlates with improved liver event-free survival in PBC.

Figure 5: ALP value and ALP+TB values and Predictive Significance in UK PBC and Global PBC Study Group



Source: Copied and electronically reproduced from Applicants NDA submission (Independent Corroboration of Clinical Utility of Surrogate Endpoints in PBC (page 25 of 31))

Figure 5 shows ALP with normal bilirubin and ALP+TB both were predictors of transplant free survival. The analyses were calculated utilizing ALP <1.67 x ULN as threshold. Although, when TB was added to ALP the predictive capability was better.

Table 4: Transplant-Free Survival Rates in the UK-PBC and Global PBC Groups

	Transplant-free Survival Rates ¹					
	UK-PBC Cohort			Global PBC Group		
	5 years	10 years	15 years	5 years	10 years	15 years
Total Cohort	93.5	84.2	76.1	88%	77%	63%
UDCA-treated	95.9	88.4	81.7	90%	78%	66%
UDCA-Untreated	85.1	69.8	57.9	79%	59%	32%

¹ For the UK-PBC cohort, transplant free survival is based on the occurrence of liver transplant or liver related death. For the Global PBC study group, Transplant free survival is based on the occurrence of liver transplant and all-cause mortality.

Reviewer Summary: The UK-PBC analysis results were also submitted with this NDA submission by the Applicant and were reviewed to assess the adequacy to support the use of ALP and TB as a surrogate. The analyses of the UK PBC data were similar to the Global PBC Study group analyses. The reviewer notes that UK PBC cohort results have not been published. The PBC Study group independently analyzed their dataset and Applicant was not allowed to access the raw datasets although the Applicant was provided with the PBC study group analyses. Therefore the PBC cohort submitted parts of data-sets to the FDA in a DMF file for independent analysis. The FDA did not have access to the UK PBC cohort data. Refer to Section 8.48.4.

Global PBC database and UK PBC database show ALP is a prognostic and a surrogate in early stages of PBC that predicts clinical outcomes. As PBC progresses the biomarkers that are predictive of outcomes change. In early stage disease ALP is probably the most sensitive biomarker, whereas as patients progress, TB becomes more important.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

This is a new molecular entity and is not currently marketed in the United States or internationally.

For the purpose of this review the drug will be referred to as Obeticholic Acid (OCA). The Applicant has used OCA synonymously with 6 α -ethylchenodeoxycholic acid (6-ECDCA) and INT-747.

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3.2 Summary of Presubmission/Submission Regulatory Activity

Due to the rarity of PBC and its slow progression, it is challenging to conduct clinical trials that assess clinical outcomes. Therefore FDA has provided feedback to the applicant regarding the possibility of pursuing a Subpart H (accelerated approval) for OCA in the treatment of PBC. The applicant proposed the use of absolute and percent change in alkaline phosphatase (ALP) levels as a potential primary endpoint; however, FDA did not agree that ALP alone could be considered an acceptable endpoint to support marketing approval because of the lack of a clear link between changes in ALP (and other biomarkers as well) and long term outcomes in patients with PBC. FDA suggested that the applicant could use biochemical endpoints only if these biomarkers could be supported by a review of the literature and demonstrate that they are reasonably likely to predict clinical benefit.

Based on this advice, the Applicant helped establish, and subsequently collaborated with, the Global PBC Study Group project to investigate the potential link between biochemical variables, in particular ALP and bilirubin, and clinical outcomes. The Global PBC Study Group is a multi-national, multi-center registry study that followed nearly 5,000 adult PBC patients until they achieved a clinical outcome of death or liver transplant. The group's principle investigators are located at the Erasmus MC University Medical Center in Rotterdam, Netherlands.

FDA reviewed the case report forms (CRFs) that were to be used for collecting the data for the Global PBC study group. FDA identified some deficiencies in the CRFs, and provided recommendations on elements that should be considered while collecting data for the CRF. FDA also stated that because of heterogeneity of disease severity, stratification of analyses by disease severity will be helpful; that a potential surrogate must be correlated with endpoints and clinical outcomes such as transplant free survival.

The applicant proposed conducting one pivotal phase 3 trial, Trial 747-301, using the primary endpoint of achievement of ALP < 1.67x ULN, total bilirubin \leq ULN, and ALP decrease of \geq 15% from baseline at Month 12. While the trial 747-301 had begun the results of Global PBC study group were still not know or published.

IND 63,307 was submitted on 27 January 2006, received Orphan drug designation on 9th April 2008; fast track designation in the treatment of PBC on May 27, 2014; Rolling review was granted on 18 November 2014. Presubmission regulatory activities related to this submission included approximately 5 formal face-to-face meetings

between the Applicant and FDA from November 2004 to November 2014). In addition, there were a number of teleconferences and written correspondences exchanged during the development program. The Phase 3 protocol were developed in communication with the FDA and are consistent with the overall recommendations of the PBC Study Group analyses of data, including the general study design, patient population, and primary efficacy endpoint. In order to support global registration, the Applicant included an evaluation of efficacy at 12 month (FDA recommendation).

Table A detailed account of meetings and agreements is provided in the Appendix presenting the event of NDA pre-Submission regulatory history.

3.3 Foreign Regulatory Actions and Marketing History

OCA is not marketed or approved in any other country at this time.

3.4 Financial Disclosures

The statements on financial disclosures (Form FDA 3454) were reviewed. A total of 107 investigators who participated in the two phase 2 trials and one phase 3 trial (Trial 747-201, 747-202 and 747-301) certified that they had no financial arrangements as defined in 21 CFR 54.2. All investigators who participated in these trials responded to the Applicant's request to complete the Form FDA 3454 (Please see Appendix 14.1).

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) performed site investigations (4 domestic and 2 international sites; sites were chosen from trials 747-201, 747-202, and 747-301) and found that the confirmatory efficacy studies were conducted adequately overall, and the data generated by the sites appear acceptable in support of the indication.

Overall assessment of findings and recommendations:

Six clinical investigator sites and the Applicant were inspected for this application. The classification for the routine Applicant inspection for this new molecular entity is pending. Four of the inspections have a final classification of NAI. The isolated instances of dosing error are not considered systemic or systematic. The violations cited for the VAI classifications at the Applicant and at the clinical sites of Drs. Schiffman and Kowdley sites are considered minor.

Findings Classification: No deviation from regulations (DARRTs review 1-8-2016, 1-20-2016, 1-12-2016, 4-11-2016). For further details reader is directed to read review placed in DARRTs by Dr. Susan Leibenhaut for this application.

4.2 Product Quality

A Review by the OPQ (office of Product Quality) has been reviewed. For details the reader is referred to the review in DARRTs by Hitesh Shroff. The recommendations are as follows:

Recommendation and Conclusion on Approvability:

- The applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.
- The Office of Facility and Process has made a final overall manufacturing Inspection “Approval” recommendation for the facilities involved in this application.
- The claim for the Categorical Exclusion for the Environmental Assessment is granted.
- However, the label/labeling issues have *not* been completely resolved as of the date the review was entered in DARRTS.

4.3 Clinical Microbiology

Not issues noted.

4.4 Nonclinical Pharmacology/Toxicology

This is a summary of the nonclinical reviewer Tracy Behrsing PhD review. Dr. Behrsing’s reviewed the package for OCA that included pharmacology, pharmacokinetics/ ADME/toxicokinetics, single-dose and repeat-dose toxicology, genetic toxicology, carcinogenicity, reproductive and development toxicology, and special toxicity studies.

Like endogenous bile acids, OCA is conjugated with the amino acids taurine and glycine. With the exception of the rabbit, OCA is primarily metabolized to the taurine conjugate with minimal or no metabolism to glyco-OCA in nonclinical species (mouse, rat, and dog). In contrast, both the taurine and glycine conjugates are major metabolites in humans, and exposures to the conjugates exceed those to the parent compound. Based on EC50 values, the glycine and taurine conjugates of OCA have potencies at FXR which are similar to the parent compound; and thus, these are considered to be active metabolites.

In repeat-dose oral toxicity studies in rodents and non-rodents, the hepatobiliary system was identified as the primary target system of toxicity. In the 26-week oral toxicity study in rats, treatment with OCA produced changes in clinical chemistry parameters (e.g., increases in ALT, AST, and ALP), increased liver weights, and bile duct hyperplasia with hepatocellular hypertrophy. Clinical signs such as yellow skin were observed in high dose animals (60 mg/kg/day). In the 9-month oral toxicity study in dogs, OCA produced clinical signs of toxicity that could be associated with liver function (yellow discoloration of the skin, mucous membranes, and eyes) and elevated ALT levels.

While there were no microscopic changes in the liver in the 9-month toxicity study, histopathological changes were noted in the liver and gallbladder in a shorter duration study in dogs. Increased liver enzymes were also observed in humans at higher doses than 10 mg, proposed for the current indication. Additional primary target organs in the 26-week toxicity study in rats were the large intestine (sub-acute inflammation) and bone marrow (increased cellularity).

Overall, the estimated systemic exposures to total OCA equivalents (i.e., OCA and its taurine and glycine conjugates) at the NOAELs in the 26-week and 9-month toxicity studies in rats and dogs, respectively, exceed those in humans at the maximum recommended human dose (MRHD) of 10 mg proposed for the current indication. The NOAEL from the 26-week toxicity study in rats (6 mg/kg/day) was estimated to produce systemic exposures approximately 2.3 times those in humans at the MRHD. The NOAEL from the 9-month repeat-dose toxicity study in dogs (15 mg/kg/day) was estimated to produce systemic exposures approximately 12 times those in humans at the MRHD.

In a 2-year oral carcinogenicity study in CrI:CD1 mice, there were no drug-related neoplastic findings at OCA doses up to 25 mg/kg/day. In an oral carcinogenicity study in CrI:CD(SD) rats of up to 2 years in duration, 20 mg/kg/day OCA caused an increase in the incidence of benign granulosa cell tumors in the ovaries and benign granular cell tumors in the cervix and vagina of female rats. There were no drug-related neoplastic findings in male rats at OCA doses up to 20 mg/kg/day.

OCA was not genotoxic in the Ames test, a human peripheral blood lymphocyte chromosomal aberration test, and a mouse micronucleus test. The glycine conjugate of obeticholic acid was also not genotoxic in an Ames test and human peripheral blood lymphocyte chromosome aberration test. The taurine conjugate of obeticholic acid was not genotoxic in an Ames test, and was negative in a human peripheral blood lymphocyte chromosomal aberration test in the presence of metabolic activation; whereas, the findings of the chromosomal aberration assay in the absence of metabolic activation were inconclusive.

In an oral fertility and early embryonic development study, treatment of male and female rats with up to 50 mg/kg/day OCA did not affect fertility or early embryonic development. The NOAELs for male and female systemic toxicity in this study were 50 and 25 mg/kg/day, respectively. In an embryo/fetal development study in rats, 75 mg/kg/day OCA caused decreased fetal body weights and increased numbers of early or late resorptions and nonviable fetuses. In maternal animals, this dose produced mortality, decreased body weight, body weight gain, and food consumption, and abortion.

Therefore, the developmental toxicity observed at this dose may be secondary to maternal toxicity. The NOAEL for maternal toxicity and embryo-fetal development in this study was 25 mg/kg/day. In an embryo/fetal development study in rabbits, the NOAEL for maternal and developmental toxicity was 20 mg/kg/day OCA (the highest dose tested). Finally, in a pre- and postnatal development study in rats, there was no evidence of any adverse effect on pre- and postnatal development at oral doses of OCA up to 40 mg/kg/day (the highest dose tested).

MO Comment:

Notably the NOAEL for exposures in dogs is 12 times those in humans and that the primary signal is in the hepatobiliary system. While the modeling for the systemic exposures done for patients with moderately advanced and advanced hepatic impairment show exposures up to 17 times that of healthy patients (see clinical pharmacology review for details of modeling and simulations). Therefore this corroborates that lower doses should be recommended for patients with hepatic impairment and it is important to monitor these patients closely and adjust dose or discontinue treatment for evidence of liver injury.

4.5 Clinical Pharmacology

The key issues that Clinical Pharmacology addressed are summarized. Reader is referred to Clinical Pharmacology combined review by Dr. Elizabeth Shang, Dr. Shen Li, Dr. Yuching Yang, Dr. Ping Zhao and Dr. Dhananjay Marathe in DARRTs. Key relative elements are described below:

Major active metabolites (glyco-OCA and tauro-OCA) in human plasma are amino acid conjugates. After oral administration of 25 mg [¹⁴C]-OCA, about 87% is excreted in feces. Urinary excretion is less than 3%.

1. Adequacy of the assay methods used for ALP and total bilirubin to measure the changes of these primary surrogate endpoints in Phase 3 trial

The assay methods used to measure ALP and bilirubin in the Phase 3 trial are adequate. ALP and total bilirubin are routine clinical lab tests. The Applicant used commercially available assay kits for ALP and total bilirubin. In addition, the Applicant used three labs instead of using one central lab for measuring these endpoints. These labs are accredited by their respective national authorities. In US, it is CLIA-certified. One of the three labs was used as a reference lab as it had better precision and accuracy. The measurements in the other two labs were harmonized to the reference lab by applying harmonization factors. The majority (~92%) of patients enrolled in phase 3 study had normal bilirubin at baseline and at the end of the treatment. Thus, the difference between corrected and uncorrected values is less critical. For ALP, the difference between corrected and uncorrected values is < 10%. Only 10 measurements had difference > 10% with the highest of 20%. The Applicant also conducted primary efficacy

analysis with uncorrected values and found that the conclusion remained the same. Thus, using commercially available assay kits for ALP and total bilirubin in this NDA is acceptable. It is recommended that the Applicant use uncorrected values of ALP and total bilirubin for the primary efficacy analysis as some of the total bilirubin data were not corrected in the database

2. Appropriateness of the proposed starting dose of 5 mg QD with titration to 10 mg QD at 3 months for overall population

On basis of the dose dependent increase in incidences of pruritus and better tolerability profile with time with a lower starting dose, Applicant's proposal to start dosing at 5 mg QD (once daily) is appropriate. Although, patients in the phase 3 trial were up-titrated at 6 months, the proposal of up-titration of dose at 3 months is supported by the clinical data that showed that the trend of reduction in ALP saturated at 3 months upon 5 mg once daily dosing and there was minimal further decrease in ALP from 3 months to 6 months and beyond with the same dose at the population level. Further, the median time to onset of severe pruritus was <2 weeks and all of the discontinuations due to pruritus in the 10 mg QD arm occurred within the first three months. Thus, the duration of 3 months will give fair idea of tolerability of starting dose and identification of patients with tolerability. The increase in dose from 5 mg to 10 mg QD resulted in additional responders from month 6 to month 12. Also there were some patients who were responders at month 6, but became non-responders by month 12, possibly due to disease progression, with continued dosing of 5 mg QD. These patients might also benefit from up-titration to 10 mg QD. The physicians should continue to evaluate biochemical response (reduction in ALP) longitudinally and utilize the up-titration rule at ≥ 3 months from the treatment initiation.

3. Requirement of dose adjustments for patients with hepatic impairment.

The hepatic impairment (moderate and severe) resulted in several fold (4- to 17- fold) increase in plasma exposures of OCA as compared to healthy volunteers in the dedicated study with a single 10 mg dose, the following dosing schema is recommended: Given the signal of dose-response for pruritus in PBC patients FDA proposed an alternative dosing regimen of 5 mg QW (once weekly) as the starting dose to target comparable initial plasma exposures to patients with no or mild hepatic impairment. This could be followed by subsequent dose up-titrations based on efficacy and tolerability to 5 mg BIW (twice weekly) followed by further increase to 10 mg BIW (twice weekly) in order to mitigate the potential risk of early discontinuations and gain requisite efficacy. It is worth noting that the Applicant had proposed no dose adjustment for hepatic impairment citing that despite higher systemic plasma exposure levels of OCA in patients with hepatic impairment, liver exposure was predicted to be similar (~2-fold) to healthy controls based on their physiologic pharmacokinetic model.

4. Evidence of efficacy for approval of OCA as a monotherapy in adult patients unable to tolerate UDCA?

There is evidence of activity of OCA to support its approval in a monotherapy setting for adult patients unable to tolerate UDCA. Evidence for monotherapy was evaluated based on the response at 3 months in a pooled dataset consisting of two Phase 2 studies and the Phase 3 study. The pooled data showed good responder rate (38%) for monotherapy at 3 months and this responder rate was comparable to that achieved with combination therapy with UDCA. Also there was marked reduction in ALP biomarker with monotherapy and this change was statistically significant ($p < 0.0001$) (Figure 14). Based on this evidence, use of OCA as a monotherapy for patients who are unable to tolerate UDCA seems reasonable.

5. Consideration for discontinuation of OCALIVA for lack of efficacy.

The consideration could be given for discontinuation of OCALIVA for the patients who do not show response of reduction in alkaline phosphatase if the benefit-risk is unfavorable. Currently there is not enough evidence to show how the long term efficacy of transplant-free survival and overall survival would transpire for patients who do not show response of reduction in alkaline phosphatase with OCALIVA. This uncertainty in long term efficacy should be weighed against the possible unfavorable lipid profile (decrease in HDL) and its relation to possible cardiovascular risk due to continued treatment with OCALIVA. Based on the evidence from Phase 3 study, the reviewers propose that the physicians could consider possible discontinuation of drug if there is a lack of clinically

meaningful response (reduction in ALP) after the patient is on a stable dose of OCALIVA for ≥ 6 months. There is currently an ongoing Phase 3b confirmatory trial with continued dosing of OCALIVA for patients with PBC and with composite efficacy endpoint consisting of death, liver transplant, MELD (Model for End-stage Liver Disease) score >15 , hospitalization for variceal bleeding, encephalopathy, spontaneous bacterial peritonitis, uncontrolled ascites, and hepatocellular carcinoma. The protocol for this extension trial does not stipulate discontinuation based on lack of efficacy. The evidence from this study could be taken into consideration to possibly weigh the anti-fibrotic beneficial effect of OCALIVA in order to consider continuation of therapy in the absence of ALP response. This issue was discussed at the GIDAC (Advisory Committee) meeting and a consensus was not reached.

6. Potential for OCA to affect the pharmacokinetics of drugs that are CYP1A2 substrates

There appears to be potential for OCA to increase the systemic exposure to drugs that are CYP1A2 substrates based on the in vitro and in vivo findings. Although in vitro studies did not show CYP1A2 inhibition, down regulation of CYP1A2 expression by OCA was suggested. Further, in an in vivo study, the effect of 10 mg OCA on CYP1A2 substrate caffeine showed that systemic exposure to caffeine increased by 42% while the exposure of metabolite paraxanthine was unaltered. Similarly, the systemic exposure to caffeine increased by 65% following 25 mg OCA without change in systemic exposure to paraxanthine. Unaltered paraxanthine exposure could be due to the fact that this metabolite is partially metabolized by CYP1A2. Based on the overall findings, there appears to be potential for OCA to modulate CYP1A2 expression and affect the systemic exposure to co-administered drugs that are CYP1A2 substrates. These findings will be reflected in the label.

4.5.1 Mechanism of Action

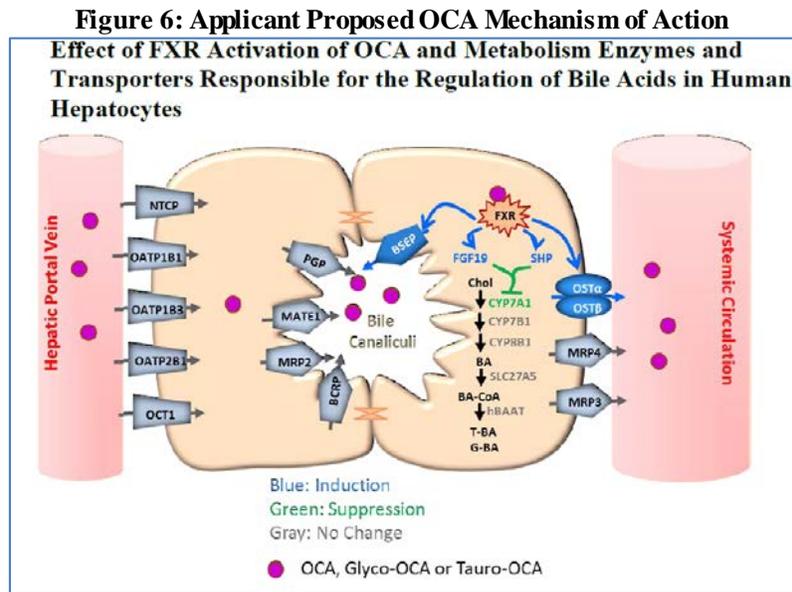
OCA is a selective and potent agonist for the farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine (also expressed in kidney, adrenal glands, and adipose tissue). OCA is derived from chenodeoxycholic acid (CDCA), with addition of single α -ethyl arm in the 6-carbon position. UDCA is an epimer of CDCA. While structurally similar to CDCA or OCA, UDCA has no significant FXR agonist effects, UDCA acts through post-translational mechanisms.

Mechanism of action:

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- α -hydroxylase (CYP7A1) expression and bile acid synthesis

Reduction of bile acid synthesis complemented by the effects of OCA to increase expression of bile acid transporters promotes choleresis. 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 reduced the toxic burden of hepatic bile acid (choleresis) accumulation in cholestasis.



Source: Copied and electronically reproduced from the Applicant submission from the clinical summary -page 14 of 86

4.5.2 Pharmacodynamics

The pharmacodynamic action of OCA that were noted in the trials with OCA include

1. Increase in FGF19
2. Decrease in endogenous bile acids production,
3. Decrease in C4

These effects have been described in detail in the clinical review, Section 6.

4.5.3 Pharmacokinetics

Like bile acids, OCA and its conjugates also undergo extensive enterohepatic recirculation.

Therefore, the PK profiles exhibit multiple peaks within a day following once daily dosing as meals affect the bile secretion into the intestine.

Total OCA (sum of OCA, glyco- and tauro-OCA) is used in exposure-response analysis for efficacy as OCA and these conjugates have similar potency in FXR activation.

Absorption

Following multiple oral doses of OCA 10 mg once daily, peak plasma concentrations (C_{max}) of OCA occurring at a median time (T_{max}) of approximately 1.5 hours. Median T_{max} for glyco-OCA and tauro-OCA is 10 hours. Systemic exposures (AUC_{0-24h}) to OCA, glyco-OCA and tauro-OCA are 2.1-, 6.4-, and 9.4-fold higher, respectively, compared to single dose administration.

Food does not have a clinically relevant effect on the PK of 10 mg OCA.

Distribution

OCA and its conjugates are highly bound to human plasma proteins (>99.0%). After intravenous (IV) administration of 0.1 mg OCA, the volume of distribution of OCA was 618L.

Liver concentration is predicted to be much higher (~20-fold) than the plasma concentration in healthy patients based upon a PBPK model.

Metabolism and Elimination

Module 2.7.2 of the Applicant's submission states: Following repeated daily doses for 14 days, apparent steady-state condition of OCA was achieved after approximately 9 days. There was minimal accumulation of OCA after repeat dosing; however, there was significant overall accumulation of glyco-OCA and tauro-OCA. OCA is primarily eliminated in feces. Based on population PK modeling, the half-life of total OCA is predicted to be approximately 4 days suggesting that the majority of OCA will be washed out after 2 weeks.

The clinical Pharmacology reviewer noted the effective half-life of OCA is about 24 hours.

Systemic total OCA levels are higher with increasing severity of hepatic impairment, relative to healthy volunteers. Increased exposure of systemic OCA and its conjugates with increasing severity of hepatic impairment was proportional to the increases in endogenous bile acids exposure.

4.6 Devices and Companion Diagnostic Issues

Not applicable

4.7 Consumer Study Reviews

Not applicable for this product as of this time.

5 Sources of Clinical Data and Review Strategy

5.1 Table of Clinical Studies

Studies to support Efficacy: 747-301

Studies to support safety: 747-201, 747-202-, 747-301

Table 5: Clinical Studies to Support Safety and Efficacy of OCA in PBC

Study	747-201 (OCA)	747-202 (OCA+UDCA)	747-301 Pivotal trial (OCA±UDCA)
Total number of patients (n) enrolled/number of patients who completed the trial	59/48	165/136	216/198
Treatment	Placebo 10 mg 50 mg	Placebo 10 mg 25 mg 50 mg	Placebo 5mg 10 mg
Study Design	Phase 2, Double blind (DB), placebo controlled study; monotherapy	Phase 2, DB, placebo controlled study; in combination with standard of care (UDCA)	Phase 3, DB, placebo controlled study; in combination with standard of care (UDCA) or as a monotherapy if UDCA is not tolerated
Duration	3 months	3 months	12 months
Age range	34- 73 years	35- 73 years	29- 86 years

Patient inclusion criteria	ALP between 1.5 X ULN and 10 X ULN	ALP \geq 1.67xULN and/or 1.0xULN < TB < 2.0xULN
Primary Endpoint	Percent change in ALP from baseline to month 3	ALP < 1.67 x ULN and \geq 15% reduction in ALP and, TB \leq ULN at month 12

Source: Reviewer Generated from the data submitted to the NDA

To support the approval of this NDA, the Applicant conducted an array of clinical pharmacology related studies including 16 in vitro studies using human biomaterials. The phase 1 studies evaluated OCA pharmacokinetics (PK) and short term safety, pharmacodynamics (PD), clinical DDIs, QT prolongation potential (thorough QT study), absolute bioavailability, relative bioavailability, hepatic impairment, food-effect, and agent altering gastric pH on OCA PK.

5.2 Review Strategy

For this NDA submission, a single phase 3 clinical trial 747-301 was reviewed for safety and efficacy. The two supportive, controlled, phase 2 clinical trials, 747-201 and 747-202 were also reviewed for safety and efficacy. Details of the study design and conduct for each trial are contained in Section 6, and study results are discussed in Section 7 (efficacy) and 8 (safety). The 120 safety update was reviewed for summarizing the safety.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1 Clinical Trial 747-201

A phase 2 study of INT-747 (6-ECDCA) monotherapy in patients with primary biliary cirrhosis

6.1.1 747-201-Study Design

Overview and Objective

This 12 week, phase 2 trial was reviewed to understand the role of OCA as a monotherapy in patients, safety with PBC. The main aim of this trial was to analyze the ALP reduction response with OCA as monotherapy and to assess the safety profile of OCA as a monotherapy. This trial is dose finding trial. The major limitations of this trial includes: sample size is small (a total of 59 patients were enrolled in the trial with only 48 patients completing the trial) and trial duration was 12 weeks long. For this trial, the Applicant intended to enroll 120 patients; however, they were only able to enroll 59 patients. The enrollment was stopped prematurely because it was difficult finding patients who were not on UDCA treatment.

Doses were selected on basis of Phase 1 trials in healthy volunteers where single and multiple doses of 50 mg were observed to be safe for use. A 3 month time period was chosen by Applicant, as an appropriate timeframe over which initial assessment of the safety of OCA, and pharmacological effect of OCA on the key biochemical endpoints in PBC patients could be obtained.

Nine disease prognostic risk criteria that were previously reported on in the literature were analyzed in the trial are tabulated in Table 6, and have been discussed in the efficacy result section.

Table 6: Disease Prognostic Risk Criteria

Disease Prognostic Risk Criteria		Baseline Criteria (Positive Criteria) as Defined in SAP	End of Study (Responder Criteria) as defined in SAP
As Defined in 747-201 SAP	Names per Recent Published Literature, if Different (or Approximation)		
Paris ^a (Corpechot, 2008)	Paris I (Corpechot 2008)	ALP >3x ULN OR AST >2x ULN OR Total Bilirubin >1 mg/dL	ALP ≤3x ULN AND AST ≤2x ULN AND Total Bilirubin ≤1 mg/dL
Toronto 2 (Kumagi 2010)	Toronto I ^b (Kumagi 2010)	ALP ≥1.67x ULN	ALP <1.67x ULN
Toronto 1 (Kumagi 2010)	Toronto II ^b (Kumagi 2010)	ALP ≥1.76x ULN	ALP <1.76x ULN
New Toronto 1 (Meaney 2010)	Toronto III ^b (Meaney 2011)	ALP ≥1.76x ULN OR Total Bilirubin ≥ULN	ALP <1.76x ULN AND Total Bilirubin <ULN
New Toronto 2 (Meaney 2010)	Toronto IV ^c (Meaney 2010)	ALP ≥1.67x ULN OR Total Bilirubin ≥ULN	ALP <1.67x ULN AND Total Bilirubin <ULN
New Mayo (Momah 2010)	Mayo II ^d (Momah 2012)	ALP ≥2x ULN OR Total Bilirubin ≥ULN	ALP ≤1.67x ULN AND Total Bilirubin <ULN
Barcelona (Pares 2006)	NA	None	ALP >40% decrease OR Normal ALP Values (women ≤117 U/L; male ≤129 U/L)
Rotterdam (Kuiper 2009)	NA	<u>Early</u> : Normal Total Bilirubin and Albumin <u>Moderately advanced</u> : Abnormal Total Bilirubin or Albumin <u>Advanced</u> : Both Abnormal Total Bilirubin and Albumin	NA
NA	Mayo II plus 15% ALP Reduction ^e (Momah 2012, Lammers 2014, Study 747-301)	ALP ≥1.67x ULN OR Total Bilirubin >ULN	ALP <1.67x ULN AND total bilirubin ≤ULN, AND ALP decrease of ≥15% from Baseline

Source: Copied and electronically reproduced from Applicant's Protocol 747-201
 NA = not applicable

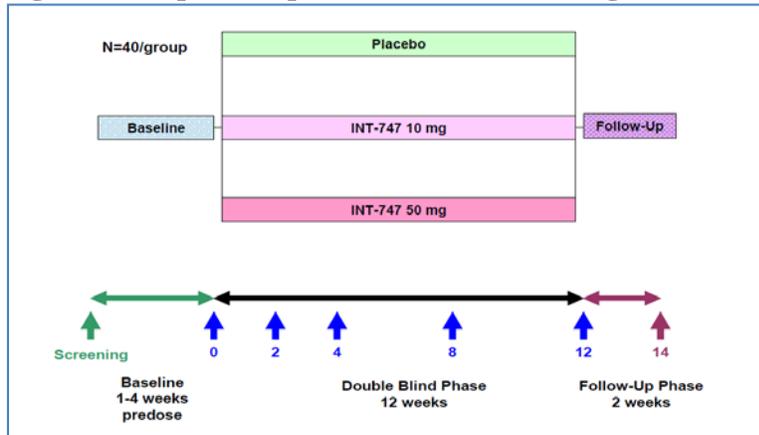
Study 747-201 is a double-blind, placebo controlled, 85 days, multicenter (18 centers in 6 countries) trial, enrolling 60 early disease PBC patients (93%) as defined by Rotterdam criteria⁸, out of which 59 patients were randomized 1:1:1 in parallel arm to study OCA 10 mg, OCA 50 mg OCA, and placebo and administered for 12 weeks (85 days). The study was completed by 48 patients and PK data is available for 34 patients. All patients returned to the study

⁸ As defined by the Rotterdam criteria: Normal/Early: Normal Total Bilirubin and Albumin; Moderately advanced: Abnormal Total Bilirubin or Albumin; Advanced: Abnormal Total Bilirubin and Albumin

site for 4 visits (Day 15, Day 29, Day 57, and Day 85) for evaluations of efficacy, safety, tolerability, and compliance with investigational product. There was a 2-week follow-up period i.e., on day 99.

Population enrolled: Of the 59 patients 93% patients had elevated ALP; 81% patients had positive AMA titers. 80% patients had a historical liver biopsy interpretation; however, staging of biopsy prior to enrolled was not performed. Randomization was centrally managed to ensure balance among treatment groups.

Figure 7: Graphical representation of Trial design



Source: Electronically copied and reproduced from Applicant submission 747-201 CSR Version 7.1 Submitted 26 April 2012

Study Endpoints

Primary efficacy endpoint:

Percent change (%) in serum ALP from baseline to end of study (EOS) or Day 85.

The baseline value was the mean of the pretreatment screening and day 0 evaluations. The EOS value was Day 85/ET or the last observed ALP value on treatment.

Secondary efficacy endpoints:

- 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 patients 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)
- Safety (study duration, dose and compliance, reason for withdrawal, treatment-emergent adverse events, vital signs, physical exams, concomitant medications, clinical laboratory assessments, 12 lead electrocardiograms).
- Safety parameters of special interest: (pruritus, hepatic adverse events, changes in lipids and cardiovascular events)

Other efficacy endpoints:

1. Absolute and percent changes in serum albumin values
2. Percentage of patients at Day 85/ET with ALP values within normal limits (\leq ULN), $<1.5x$ ULN, $<1.67x$ ULN, $<1.76x$ ULN, $<2x$ ULN, $<3x$ ULN

3. Percentage of patients with a decrease in ALP from Baseline to Day 85/ET of at least 10%, 15%, 20%, 40%, and 60%
4. Tertile ALP categories: Change in ALP values from Baseline to Day 85/ET as categorized by Baseline ALP tertile categories
5. SF-36 Quality of Life Questionnaire (QOL): Change from Baseline to Day 85/ET for scale scores and summary measures
6. PBC-40 QOL Questionnaire: Change from Baseline to Day 29, Day 57, and Day 85/ET for each domain
7. Enhanced liver fibrosis (ELF) score and change in levels of its components, hyaluronic acid, aminoterminal peptide of pro-collagen III, and tissue inhibitor of matrix metalloproteinase-1 from Baseline to Day 85/ET
8. Biomarkers of hepatic inflammation and fibrosis: Absolute and percent changes in levels of C-reactive protein, non-esterified fatty acid, tumor necrosis factor alpha, tumor necrosis factor beta, bile acids, glutathione, immunoglobulin M, and osteopontin from Baseline to Day 85/ET
9. Bile acid analysis: Absolute and percent changes in the levels of total endogenous bile acids and OCA plasma concentrations, and its conjugates, from Baseline to Day 85/ET
10. Absolute and percent change in Fibroblast growth factor-19 (FGF-19) levels from Baseline to Day 85/ET

Post-Hoc Analysis included in 747-201 CSR

- Absolute and percent changes in the levels of 7 α -hydroxycholest-4-en-3-one (C4) from Baseline to Day 85/ET.
- Percentage of patients who met the disease prognostic risk criteria defined as ALP < 1.67x ULN and total bilirubin \leq ULN, and ALP decrease of \geq 15% from Baseline (i.e., Mayo II plus 15% ALP Reduction)

Inclusion criteria:

1. Screening ALP value between 1.5 and 10 X ULN (remaining Inclusion criteria are similar to trial 747-202, please see section 6.2.1 for details)

Exclusion Criteria:

1. Conjugated bilirubin > 2 X ULN; ALT or AST > 5X ULN and serum creatinine > 133 μ mol/L (1.5 mg/dL) (remaining exclusion criteria are similar to trial 747-202, please see section 6.2.1 for other exclusion criteria)

Mandatory Discontinuation criteria:

1. ALT or AST > 3 \times average predose value (average of screening and baseline) and > upper limit of normal (ULN).
2. Conjugated (direct) bilirubin > 2 \times average predose value (average of screening and baseline), and > 25.7 μ mol/L (1.5 mg/dL).
3. Women who are pregnant during the trial period.
4. The emergence of clinical or laboratory AEs believed by the Investigator to justify patient discontinuation from the study.
5. Noncompliance, major violations, or if patient met exclusion criteria.

Figure 8: Schedule of Assessment for Trial 747-201

	Visit
--	-------

	Screening -4 to -1 Weeks ^a	Day 0 (Baseline)	Day 15	Day 29 ^b	Day 57 ^b	Day 85 /ET ^b	Follow - Up Day 99
Study Procedures							
Informed consent	X						
Medical history	X						
Inclusion/exclusion criteria	X	X					
Physical exam	X ^c					X ^c	
Electrocardiogram	X					X	
PBC-40 QOL and 5-D questionnaires	X	X	X ⁱ	X	X	X	
SF-36 QOL Questionnaire		X				X	
Pruritus VAS questionnaire		X	X	X	X	X	
Transient Elastography ^h		X				X	
Prior and concomitant medications	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X
Dispense investigational product		X		X	X		
Investigational product accountability				X	X	X	
Investigational product administration		X ^d	X	X	X		
Clinical Laboratory Evaluations							
Serum chemistry ^e	X	X	X	X	X	X	X
Hematology ^e	X	X	X	X	X	X	X
Liver panel ^e		X				X	
Serum Bile Acids ^e		X	X	X		X	
Pharmacokinetics ^f		X	X	X	X	X ^f	
Urinalysis	X					X	
Urine-based β -hCG pregnancy test	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	

Source: Electronically copied and reproduced from Applicant submission 747-201 CSR

Footnotes:

1. Screening evaluations can occur between Day -28 and Day -7, relative to Day 0.
2. Acceptable variation for actual study visits is +/- 3 days from nominally scheduled day for Day 29, 57, and 85 visits. However, every effort should be made to maintain the nominal visit schedules of patients as predicated by the occurrence of the Day 0 visit.

3. Physical examination at screening includes patient height and weight and on Day 85 includes patient weight.
4. Study drug administration on Day 1 (the following morning), approximately 30 minutes before breakfast, with water or on Day 0 while at the study site, approximately 30 minutes before breakfast, with water.
5. 8-hour fasting requirement applies only to Day 0 and Day 85 clinical laboratory evaluations.
6. A blood sample for pharmacokinetic analysis should be drawn shortly before the next dose from every patient on Days 0, 15, 29, 57, and 85 as well as from those who discontinue the study due to ALT/AST and/or bilirubin increases (see Section 4.7.1).
7. Urine based β -hCG pregnancy test must be performed in females of childbearing potential. If positive, a confirmatory blood test must be performed at the site. If the blood test is also positive, the patient must be discontinued from the study.
8. TE will be conducted at selected centers, using the Fibroscan® transient elastography (TE) device (Echosens, Paris, France).
9. The 5D questionnaire should be completed at Day 15.

Reviewer Comment: Although mentioned in the Schedule of assessment, the Applicant did not present the data on Fibroscan in the clinical study review 747-201.

Statistical Analysis Plan

Determination of sample size:

However, due to difficulties with patient recruitment into the study, the final enrollment was approximately 20 patients per group. Overall, a sample size of 20 patients per group resulted in 49% power to detect an effect size of 0.6466 for the difference in the primary efficacy endpoint (change in serum ALP) between treatment arms and placebo using a Wilcoxon-Mann-Whitney rank-sum test with a 0.05, 2-sided significance level. The informative value of subgroup analyses was also expected to be restricted by the reduced sample size.

The percent (%) change from Baseline to EOS was described with summary statistics. The primary efficacy endpoint was analyzed using the 2-sided Wilcoxon-Mann-Whitney test at the 5% level of significance. A hierarchical testing strategy was utilized to account for multiple comparisons. The statistical significance was to be evaluated in order as follows: if statistical significance at $\alpha = 0.05$ was observed for the OCA 10 mg group versus placebo, then the statistical significance at $\alpha = 0.05$ for the OCA 50 mg versus placebo was to be performed. If no statistical significance was observed at $\alpha = 0.05$ at the first step, then the subsequent comparisons were not considered statistically significant, regardless of the p-value.

Reviewer Comment:

All statistical testing, including secondary and exploratory endpoints, and post-hoc analyses were descriptive and exploratory. No statistical testing was done on subgroup analyses, or planned for sensitivity analysis of the primary endpoint.

Analysis Populations

The following analysis populations were used for efficacy, pharmacokinetic (PK), and safety analyses:

1. Intent-to-treat (ITT) Population included all patients randomized who received at least 1 dose of investigational product based on the treatment group assignment. The patients were analyzed by the treatment group to which they were randomly assigned (intent to treat principle). The ITT Population (N = 59) was used for the summary of all baseline characteristics, and all summaries and analyses of efficacy data (this definition is modified from that defined in SAP).
2. The Completer Population included all randomized patients who received at least 1 dose of investigational product based on the treatment group assignment and participated through the end of the 3-month, double-blind treatment period (i.e., Day 85). The Completer Population (N = 48) was used for the analyses of secondary and other efficacy data except for QOL and ELF score or its components.
3. The Safety Population included all randomized patients who received at least 1 dose of investigational product based on the treatment group assignment and had at least 1 post-treatment safety assessment. The Safety Population (N = 59) was used for the analysis of all safety data and was identical to the ITT population.
4. The PK Population included patients who provided either a Day 0 or Day 85/ET blood sample, and the Day 85/ET blood sample was collected at trough (i.e., approximately 24 hours after the prior investigational product dose). The PK population (N = 34) was used for analysis of PK data.

Protocol Amendments

The reviewer notes, were six amendments and 2 addendums submitted by the Applicant for this protocol. The reviewer has summarized briefly the key amendments, for details the reader is referred to read the Applicant submission in global submit review module 5.3.5.1- “747-201-Ph 2 A Study of INT-747 (6-ECDCA) Monotherapy in Patients with Primary Biliary Cirrhosis.”

Most amendments were to address safety. The reviewer has summarized these changes:

The safety issues were: mandatory study discontinuation on basis of liver biochemical test changes (AST/ALT and bilirubin); days of the blood samples collection for trough drug and metabolite concentrations (day 0, day 29, day 57 and day 85 and if any patient discontinues due to elevation of liver biochemical tests), and secondary endpoint data collection such as VAS, 5 D questionnaire, allow enrolling patient up to 75 years of age, update nonclinical experience, contraceptive requirements to minimize risk for teratogenicity. The addendums addressed safety monitoring by adding the patient clinic visit on day 8 (for patients recruited in UK) and on day 15 (patients in US). Some of these addendums and amendments were to fulfill the regulatory requirements as recommended by the FDA, EMA and ethics review committee few other changes were submitted by the Applicant.

Data Quality and Integrity: Applicant's Assurance

The Applicant reports this study was performed in accordance with Good Clinical Practices, including the archiving of essential documents.

Compliance with Good Clinical Practices

The Applicant provided attestation that the trial was conducted in accordance to the Declaration of Helsinki and US regulations covering the protection of human patients, Institutional Review Boards and the obligations of clinical investigators in accordance with Good Clinical Practice (GCP).

747-201-Study Results

Demographics:

Table 7: Patient Disposition: Analysis Populations

	Placebo	OCA 10 mg	OCA 50 mg	Total
	Number of Patients, n (%) ^a			
Enrolled (Randomized at Day 0)	23 (100)	20 (100)	16 (100)	59 (100)
Safety Population	23 (100)	20 (100)	16 (100)	59 (100)
ITT Population	23 (100)	20 (100)	16 (100)	59 (100)
Completer Population	23 (100)	16 (80)	9 (56)	48 (81)
PK Population	17 (74)	11 (55)	6 (38)	34 (58)

Source: Electronically copied and reproduced from Applicant submission 747-201 CSR (page 57 of 1264)

As noted above it was difficult for the Applicant to enroll patients who were UDCA non responders or intolerant to UDCA, therefore only 59 patients were enrolled in the trial. The distribution of patients enrolled in trial by country was as follows: America: 29%; Canada: 15%; Europe: 56%.

Table 8: Patient Disposition: Enrolled/Randomized Population (N = 60), ITT Population (N = 59)

	Placebo	OCA 10 mg	OCA 50 mg	Total
Primary Reason for Discontinuation				
Withdrew Consent	0 (0)	1 (5)	0 (0)	1 (2)
Major Protocol Violation	0 (0)	0 (0)	1 (6)	1 (2)
Withdrew Due to AE Pruritus	0 (0)	3 (15)	6 (38)	9 (15)

Source: Electronically copied and reproduced from Applicant submission 747-201 CSR (page 55 of 1264)

Reviewer Comment: Notably, 9 patients out of 16 patients enrolled in OCA 50 mg dose completed the trial, and 44% discontinued from trial. Most patients who discontinued from the trial did so in <30 days of receiving the first dose.

Demographic and Baseline Characteristics (747-201)

In trial 747-201, 85% females and 15% males were enrolled 95% were white the mean age at enrollment was 54.8 years and mean BMI was 27.6 kg/m².

Initially the Applicant utilized different ULN for albumin; however, when asked to reanalyze using the values that are used in current clinical practice the number of patient in each stage changes. The reviewer has presented the new disease stage table for all three trials. The classification for all the trials of diseases stage has been performed utilizing the following threshold.

1. Total bilirubin (TB) ULN: 19.32 µmol/L (females), 25.48 µmol/L (males);
2. Albumin LLN 35 g/L (females and males).

Table 9: Baseline disease stage based on Rotterdam Criteria for patients in trial 747-201

Rotterdam Criteria	Placebo (N=23)	OCA 10 mg (N=20)	OCA 50 mg (N=16)
Early Disease: Normal albumin, normal total bilirubin,	20 (87%)	11 (55%)	15 (94%)
Moderately Advanced Disease: Either low albumin or high total bilirubin	3 (13%)	9 (45%)	1 (6%)
Patients with low albumin	1 (33%)	5 (56%)	0
Patients with high total bilirubin	2 (67%)	4 (44%)	1 (100%)
Advanced Disease: Both low albumin and high total bilirubin	0	0	0

Source: Applicants submission to NDA Sequence 0057 (58)

Table 10: Baseline Liver Parameters: ITT Population (N = 59) for trial 747-201

	Placebo (N = 23)	OCA 10 mg (N = 20)	OCA 50 mg (N = 16)	Analyte Normal Range (or ULN)
ALP (U/L)				≤117 U/L (females), ≤129 U/L (males)
Mean (SD)	408.4 (223.0)	461.6 (298.7)	431.1 (177.2)	

Min, Max	141.5, 875.5	183.0, 1285.5	172.5, 834.5	
Conjugated (direct) Bilirubin (µmol/L)				≤7 µmol/L
Mean (SD)	3.9 (3.0)	5.5 (4.0)	3.9 (2.1)	
Min, Max	0.9, 13.7	1.2, 14.1	0.9, 9.1	
GGT (U/L)				≤50 U/L (Female), ≤73 U/L (Male)
Mean (SD)	466 (321)	653 (370)	455 (418)	
Min, Max	111, 1392	162, 1393	141, 1918	
ALT (U/L)				≤67 UL
Mean (SD)	83 (60)	86 (44)	71 (38)	
Min, Max	24, 273	38, 192	18, 154	
AST(U/L)				≤50 UL
Mean (SD)	71 (39)	67 (33)	66 (29)	
Min, Max	21, 157	31, 148	24, 123	

Source: Electronically copied and reproduced from Applicant submission 747-201 CSR (page 60 of 1264)

Reviewer Comment: About 45% patients enrolled to OCA 10 mg treatment arm had moderately advanced disease in comparison to 6% (only one patient) enrolled to OCA 50 mg and 13% in placebo treatment arm. However, the rates of patient discontinuation were almost 50% in patients dosed with OCA 50 mg.

As noted in Table 9 mean ALP of patients were higher in trial 747-201 compared to other trials (747-202 and 747-301); with a mean ALP was 431 and ALP in concentration in ULN was 3.7x ULN. Mean conjugated bilirubin was in normal reference range in majority of patients. Mean GGT was elevated across all treatment groups but was higher in OCA 10mg 653 U/L, compared with the placebo and OCA 50 mg groups 466 U/L and 455 U/L respectively. Mean ALT and mean AST were <2X ULN and were well balanced all across treatment arms.

Mean albumin was within normal range in all except 6 patients (1 enrolled to placebo arm and 5 enrolled to OCA 10 mg arm). TB was normal in all but 7 patients (2 enrolled to placebo arm, 4 enrolled to OCA 10mg arm and 1 enrolled to OCA 50mg arm). PT and INR were normal in all patients.

PBC Criteria for Diagnosis:

1. 93% patients had elevated ALP
2. 81% had positive AMA titers
3. 80% patients had a positive liver biopsy, however, the stages were not provided in CSR.

Compliance to treatment:

Patient compliance was assessed at each visit and confirmed by drug accountability (i.e., counting of returned capsules). Compliance was similar across all 3 treatment groups and for each study visit (95.5% to 100.3%). Compliance was 99.0%, 99.6%, and 98.4% for Day 29, Day 57, and Day 85/ET, respectively.

Protocol Deviations

There were 46 patients with 68 protocol deviations. Most protocol deviations occurred in the deviation categories “laboratory” (20 deviations, 12 patients), “inclusion/exclusion criteria” (16 deviations, 13 patients), and “visit schedule” (14 deviations, 8 patients).

Reviewer Comment:

Other than major protocol deviation in one patient enrolled to OCA 50 mg arm, rest of the protocol deviations did not affect the safety or efficacy of the trial.

There was one patient enrolled in trial who had serum creatinine 1.79 mg/dL but since the drug is not excreted via kidneys this was acceptable. A second patient had TB >2 ULN and the reviewer agrees with the investigator granted waiver for allowing the patient in trial, as the patient was stable clinically as per the narrative submitted by the Applicant.

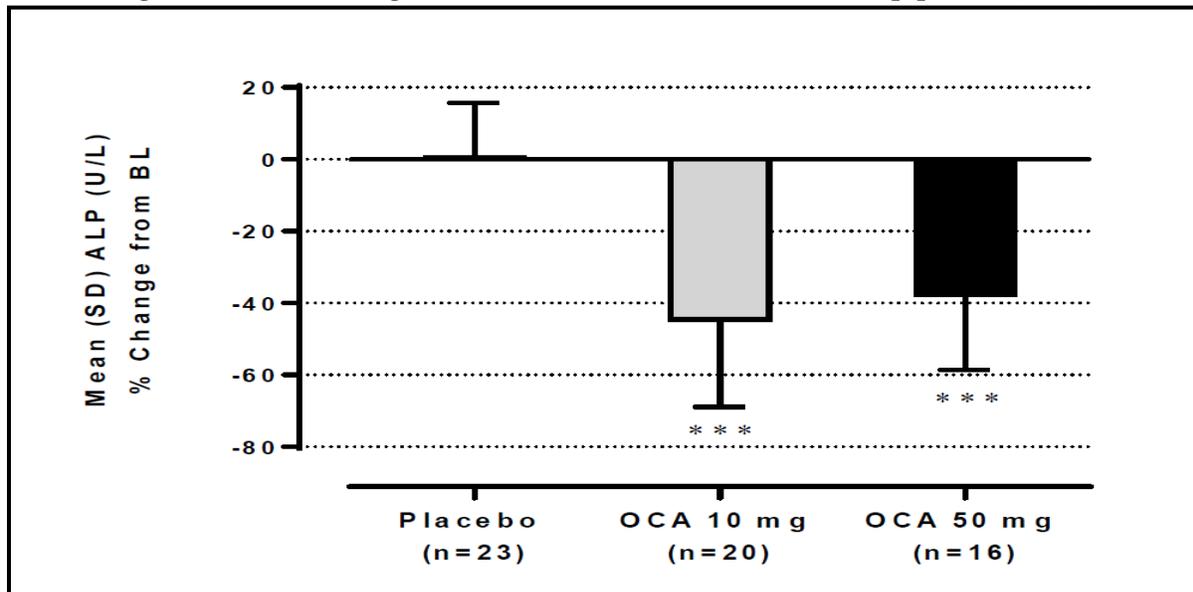
Patient 23-004-802 in the OCA 50 mg treatment group had a deviation on Day 57 (conjugated bilirubin level was 2x ULN), which should have resulted in a mandatory discontinuation. A waiver was granted for this deviation. The reviewer checked the laboratory data "adsl" and found there were no clinically significant changes in the liver biochemical parameters. I agree with the waiver granted.

6.1.1.1 Primary efficacy endpoint

The percent change in ALP levels from Baseline to end of treatment (EOT) in the OCA 10 mg and OCA 50 mg treatment arms was statistically significant (p <0.0001 for both OCA arms versus placebo).

The effect of OCA treatment on serum ALP levels were seen at week 2 and the response was durable for the entire duration of the trial. There was no apparent difference in the magnitude of improvement between the 2 OCA doses.

Figure 9 -Percent Change in ALP levels from baseline to EOS: ITT population (N=59)



Source: Electronically copied and reproduced from Applicant submission 747-201 CSR (page 65 of 1264) BL= Baseline Wilcoxon-Mann-Whitney p-value compared to placebo indicated in the figure is ***p <0.0001.

Reviewer Comment: Figure 9 and Table 10 shows the placebo arm did not show ALP reduction, whereas both the OCA treatment groups show similar response of ALP reduction at month 3. The absolute reduction of ALP was greater in comparisons to other trials. Please see integrated summary of effectiveness for comparison of OCA monotherapy and OCA=UDCA concomitant use.

Table 11: Percent Change in ALP Levels (U/L) from baseline to EOS: ITT Population (N = 59)

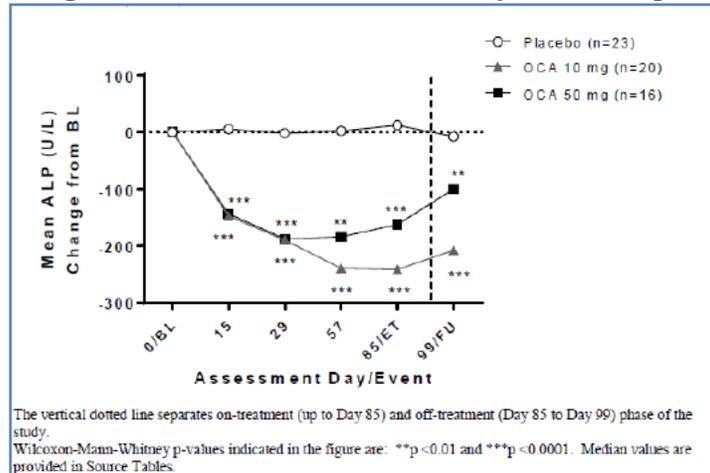
Percent Change	Placebo (n = 23)	OCA 10 mg (n = 20)	OCA 50 mg (n = 16)

Mean (SD)	0.4 (15.3)	-44.5 (24.4)	-37.6 (21.0)
Median	-0.8	-53.9	-37.2
p-value	NA	<0.0001	<0.0001

Source: Electronically copied and reproduced from Applicant submission 747-201 CSR (page 65 of 1264)

6.1.1.2 Secondary efficacy endpoints

Figure 10 Change in ALP Levels from Baseline to Day 99/Follow-Up: IIT population



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Reviewer's comment:

There was minimal reduction in ALP in patient enrolled to the placebo arm, whereas higher number of patients achieved a statistically significant reduction in ALP dosed with OCA 10 mg and OCA 50 mg arm at day 85/ET. Table 10, the dose exposure and ALP response is statistically significant as analyzed by the Applicant using different responder criteria (i.e., OCA showed ALP reduction with almost all responder criteria used by the Applicant, with the exception of normalization of ALP [$\leq 1 \times \text{ULN}$] in the OCA 50 mg arm).

Table 12: Percentage of patients who met responder criteria at day 85/ET: IIT Population

Responder Criteria	Placebo (n = 23)	OCA 10 mg (n = 20)	OCA 50 mg (n = 16)	Responder Criteria (Description) ^a
Paris I				ALP $\leq 3 \times \text{ULN}$ and AST $\leq 2 \times \text{ULN}$ and Total bilirubin $\leq 1 \text{ mg/dL}$
n (%)	11 (48)	13 (65)	11 (69)	
Toronto I				ALP $< 1.67 \times \text{ULN}$
n (%)	2 (9)	10 (50)	8 (50)	
Toronto II				ALP $< 1.76 \times \text{ULN}$
n (%)	4 (17)	10 (50)	9 (56)	
Toronto III				ALP $< 1.76 \times \text{ULN}$ and Total bilirubin $< \text{ULN}$
n (%)	4 (17)	9 (45)	9 (56)	

Toronto IV				ALP <1.67x ULN and Total bilirubin < ULN
n (%)	2 (9)	9 (45)	8 (50)	
Mayo II				ALP <1.67 ULN and Total Bilirubin <1 mg/dL
n (%)	2 (9)	9 (45)	8 (50)	
Barcelona (Pares)				ALP >40% decrease or normal ALP values (females: ≤117 U/L; male: ≤129 U/L)
n (%)	0 (0)	14 (70)	7 (44)	

Source: Electronically copied and reproduced from the Applicant submission 747-201 CSR page 72-1264

Reviewer Comment: Numerically higher number of patients dosed with OCA achieved a biochemical response, relative to placebo when analyzed by the various responder criteria as shown in Table 10.

Table 13: Percentage of Patients at Day 85/ET by Percent ALP Reduction from Baseline Categories: ITT Population (N = 59)

Criteria (% ALP Reduction from Baseline)	Patients Meeting Response Criteria		
	Placebo (n = 23)	OCA 10 mg (n = 20)	OCA 50 mg (n = 16)
	n (%)	n (%)	n (%)
10%	3 (13)	17 (85)	13 (81)
15%	2 (9)	17 (85)	12 (75)
20%	2 (9)	17 (85)	11 (69)
40%	0 (0)	14 (70)	7 (44)
60%	0 (0)	6 (30)	2 (13)
≤ULN	0(0)	5 (25%)	0 (0)

Source: Electronically copied and reproduced from the Applicant submission 747-201 CSR page 74-1264

A 40% ALP reduction was achieved in

- 14 (70%) patients dosed with OCA 10 mg,
- 7 (44%) patients dosed with OCA 50 mg,
- zero patients in placebo arm

A 60% reduction in ALP was achieved by

1. 6 (30%) patients dosed with OCA 10 mg and
2. 2 (13%) patients dosed with OCA 50 mg
3. 0 (0%) in placebo arm

Normalization of ALP was achieved in

- 5(25%) patients dosed with OCA 10 mg
- zero patients in OCA 50 mg and
- Zero patient in the placebo arm.

Reviewer Comment: Numerically higher number of patients achieved ALP reduction in OCA treated arm relative to placebo at each percent ALP reduction. However, OCA 10 mg dose seems to perform better compared with OCA 50 mg dose.

Table 14: Percentage of patients who met responder criteria based on Mayo II plus 15% ALP reduction at Day 85/ET: ITT analysis

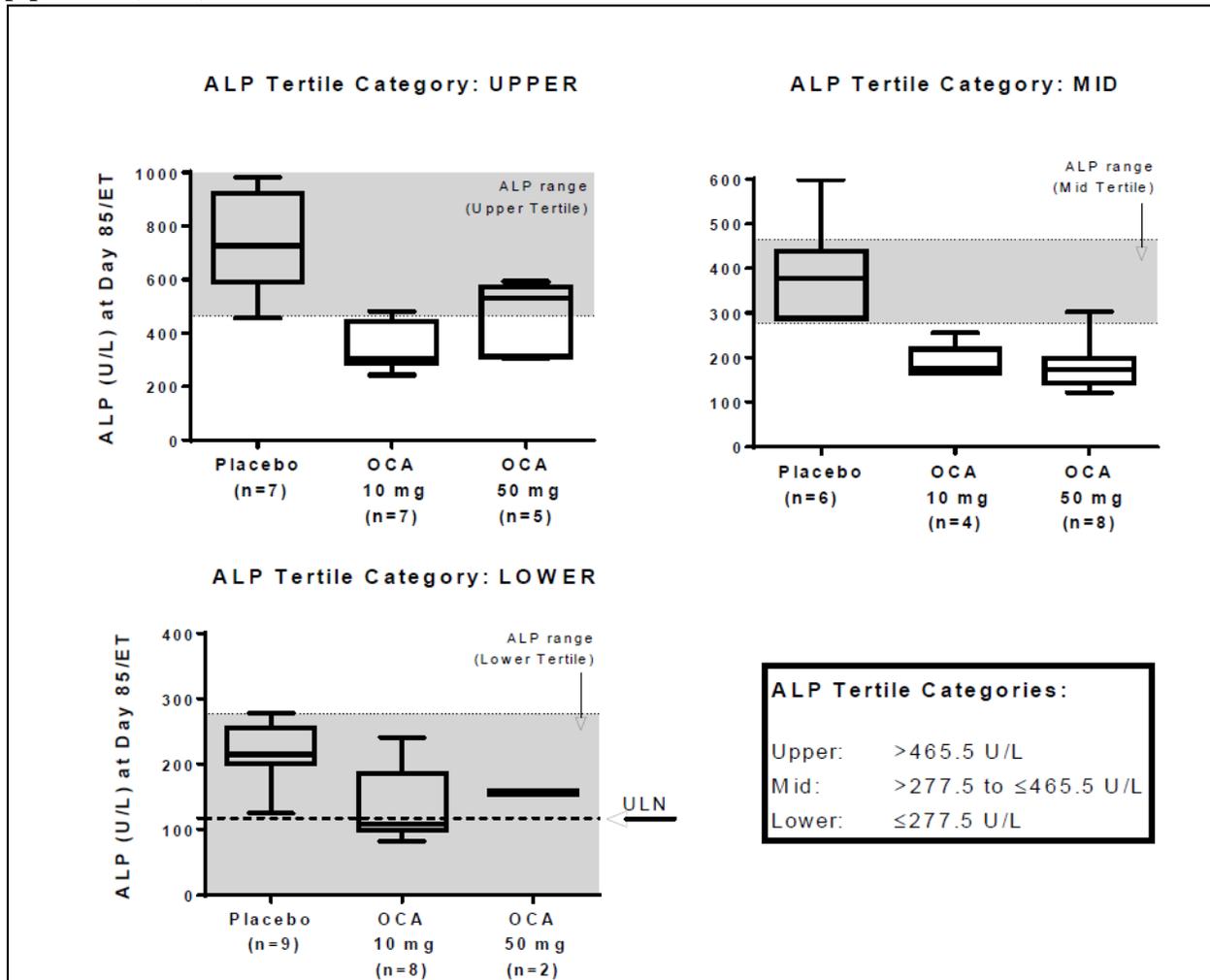
	Placebo	OCA 10 mg	OCA 50 mg
Patients meeting baseline criteria: ALP \geq 1.67x ULN or total bilirubin >ULN.	21	16	14
Patients meeting responder criteria: ALP <1.67x ULN and total bilirubin \leq ULN, and ALP decrease of \geq 15% from baseline.	1 (5)	7 (44)	7 (50)

Source: Adapted from the Applicant submission with modifications 747-201 CSR page 73-1266

Reviewer Comment: Table 13 shows numerically higher number of patients achieved the Phase 3 composite end point criteria. OCA exposure related response in ALP reduction is seen in the patients who received OCA as monotherapy.

Baseline ALP Tertile Categories

Figure 11: ALP Levels at Day 85/ET for Patients Categorized by Baseline ALP Tertile Categories: ITT population (N=59)



Source: Electronically copied and reproduced from the Applicant submission CSR 747-201 page 75 of 1264

The box and whisker plots represent median, IQR, minimum and maximum ALP values. The p-values were not determined per the SAP.

The baseline tertile categories were:

- Lower (≤ 277.5 U/L),
- Mid (> 277.5 to ≤ 465.5 U/L) and,
- Upper (> 465.5 U/L).

The ALP reduction response at Day 85/ET was assessed by categorizing the patients by the magnitude of at baseline and evaluating ALP change at Day 85/ET.

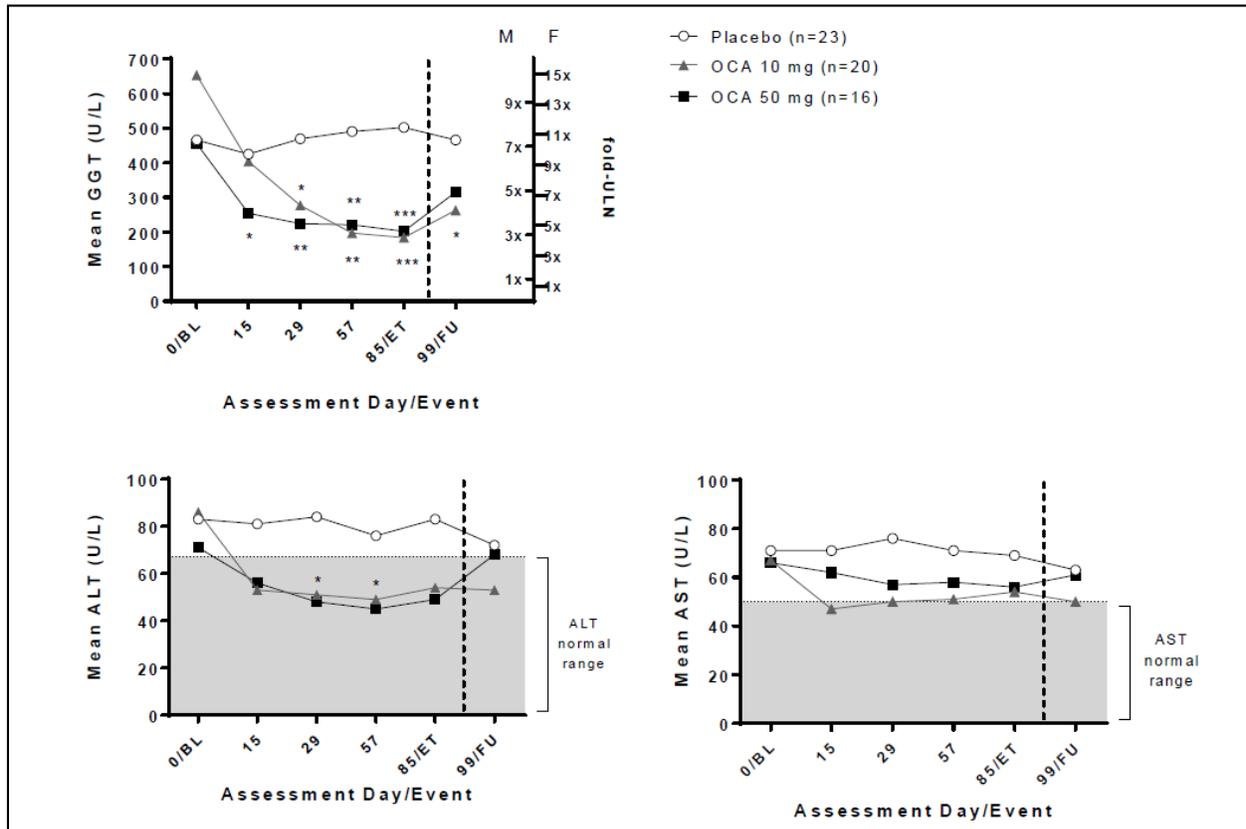
Reviewer Comment: One disadvantage was that the sample size was small in each tertile, therefore the interpretation of the results may or may not be generalizable to PBC population at large.

OCA 10 mg dose performed better in the patients who had baseline ALP in upper and mid tertile compared to placebo arm. In the lower tertile, the response was no better than placebo patients. This finding is in contrast with

747-301 trial finding where most patients who were biochemical responders were in the lower ALP tertile. However, the tertile categories are not similar in the two trials. The mean ALP in Trial 747-201 was 3.5-3.9 X ULN and the mean ALP in trial 747-301 was 2.72 X ULN. These findings suggest the patients with higher ALP responded well to OCA monotherapy.

Liver Enzyme Panel: GGT, ALT, and AST

Figure 12- GGT, ALT, and AST Levels from Baseline to Day 99/follow-up: ITT population (N=59)



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The letters “M” and “F” on the right Y-axis in GGT panel represents GGT fold-ULN for the male and female population reference ranges, respectively. The ULN of GGT reference ranges for male and female populations are 73 U/L and 50 U/L, respectively. The shaded area represents normal analyte ranges: (a) AST: ≤50 U/L, and (b) ALT: ≤ 67 U/L. Wilcoxon-Mann-Whitney p-values indicated in the figure are: *p < 0.05, **p < 0.01, and ***p < 0.001.

Reviewer Comments: GGT reduction was seen in patients treated with OCA 10mg and OCA 50mg relative to placebo treated patients and this reduction was statistically significant.

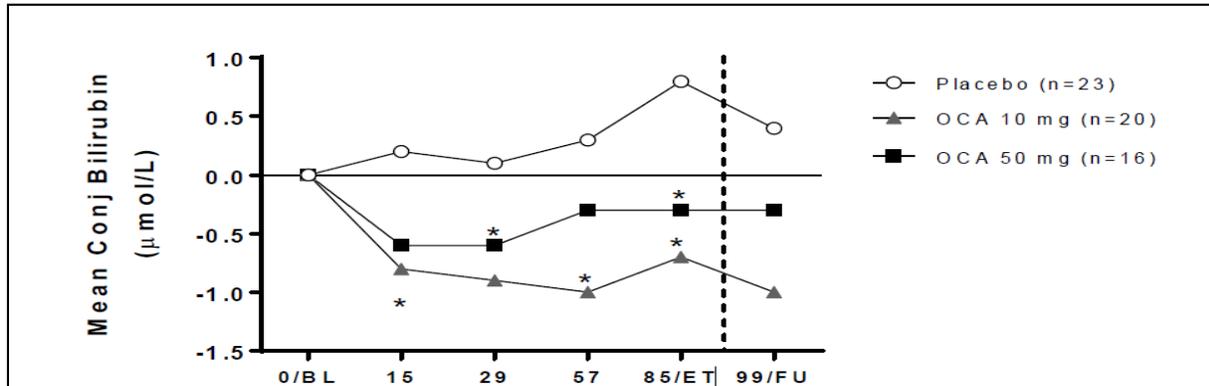
GGT:

Elevated GGT indicates biliary ductal damage, although the correlation of GGT and ALP is not very high (the correlation between GGT and ALP is 0.5 to 0.6 in different trials); but both parameters indicate damage to bile duct. There are limited data most publication were conducted prior to mid-80s and were performed in indications other than PBC. I think GGT is released from cholangiocytes (small and large bile ducts) and its assessment is valuable for cholestatic injury. It is a marker for bile duct injury in PBC. Limitations that I think are important to remember are: the intra-patient variability of the GGT is not known, and it is not known in end stage liver disease

GGT reduces/start trending down spontaneously. GGT reduction that occurs with OCA use in conjunction with ALP reduction is supportive of the primary endpoint and may indicate reduction of cholestasis. The GGT reduction was durable for the duration of the trial.

Similarly, there is a decline in ALT and AST in the 85 day duration trial. This reduction is supportive of the primary efficacy endpoint. Changes in AST were statistically not significant between the treatment arms.

Figure 13-Conjugated (Direct) Bilirubin Levels From Baseline to Day 99/Follow-Up: ITT Population (N = 59)



Source: Copied and electronically reproduced from Applicant submission Source: CSR 747-201- page 83-1264
 Wilcoxon-Mann-Whitney p-value (pairwise comparison) compared to placebo indicated in the figure is *p < 0.05.

Reviewer Comment: Conjugated bilirubin (CB) value changes are very small and the magnitude of change appears larger due to use of micromol/L SI unit usage. For example, the mean absolute change in conjugated bilirubin was -0.7 µmol/L from baseline value to day 85/ET which is ~ 0.04 mg/dL in OCA 10 mg arm, and in OCA 50 mg arm the mean absolute change was -0.3 µmol/L (0.0175 mg/dL) from baseline to the day 85/ET. Most patients in the OCA 10 mg arm had a CB reduction of 0.17 µmol/L, from baseline to the day 85/ET i.e., 0.009 mg/dL. The assay accuracy and precision in detecting a minor change might be technically difficult, although not impossible, assuming there was no hemolysis of sample and there was no lipemia (lipids > 300 mg/dL) or other interference in conduct of CB. Additionally, when TB is normal the CB readings are not accurate especially when change post therapy was small. Therefore, this reviewer does not agree that conjugated bilirubin is adequate to support the improvement of PBC as suggested by the Applicant. Additionally, intra-patient variability and the fluctuations in the conjugated bilirubin over 3 month period are knowledge gaps. The reduction may indicate choleretic effects of OCA. Absolute change in the conjugated bilirubin from baseline to end of treatment or day 85 was not statistically significant in OCA 50 mg arm compared with placebo; however, when the comparison was made between OCA 10 mg arm and placebo statistically significant difference was noted.

Table 15: 747-201 Patients with elevated total bilirubin at baseline and Day 85/ET for safety population

Treatment Group	Patient ID	Baseline ^a		Day 85/ET		Change from Baseline ^a	
		Total Bilirubin (µmol/L)	Alkaline Phosphatase (U/L)	Total Bilirubin (µmol/L)	Alkaline Phosphatase (U/L)	Total Bilirubin (µmol/L)	Alkaline Phosphatase (U/L)
Placebo	002003	24.80 H	661.0 H	23.90 H	720.0 H	-0.90	59.0
	018003	32.50 H	247.0 H	47.90 H	278.0 H	15.40	31.0
10 mg OCA	002002	24.75 H	1285.5 H	13.70	442.0 H	-11.05	-843.5

	015002	21.35 H	947.5 H	18.80	481.0 H	-2.55	-466.5
	020002	42.65 H	654.0 H	45.50 H	244.0 H	2.85	-410.0
	020004	26.85 H	366.5 H	13.50	255.0 H	-13.35	-111.5
50 mg OCA	018004	20.50 H	603.5 H	22.20 H	593.0 H	1.70	-10.5

Source: Applicant's submission to NDA Sequence 0056(57)

^a Baseline is the average of all visit values prior to first dose in double-blind phase. If results from only one evaluation are available, the available data from this evaluation is used as the baseline value. Baseline is from individual trial data.

Reviewer Comment: Of the patients with elevated TB at baseline and treated with OCA 10 mg, numerically more number of patients achieved TB reduction (3 out of 4 patients achieved reduction and normalization). However, the sample size is small to make any interpretation. At OCA 50 mg dose one patient had elevated TB who did not achieve any reduction, in fact the TB increased, but again interpretation cannot be made on n=1.

Table 16: 747-201 Patients with low albumin baseline and changes at Day 85/ET

Treatment Group	Patient ID	Baseline				Day 85/ET				Change from Baseline			
		Albumin (g/L)	Total Bilirubin (μmol/L)	Direct Bilirubin (μmol/L)	Alkaline Phosphate (U/L)	Albumin (g/L)	Total Bilirubin (μmol/L)	Direct Bilirubin (μmol/L)	Alkaline Phosphate (U/L)	Albumin (g/L)	Total Bilirubin (μmol/L)	Direct Bilirubin (μmol/L)	Alkaline Phosphate (U/L)
Placebo	054001	34.4	4.55	2.10	277.5 H	30.4 L	4.80	0.90	275.0 H	-4.0	0.25	-1.20	-2.5
10 mg OCA	010004	34.0	6.80	1.70	220.0 H	36.0	6.80	1.70	82.0	2.0	0.00	0.00	-138.0
	023006	33.9	17.20	12.50 H	553.5 H	31.8 L	15.00	10.80 H	419.0 H	-2.1	-2.20	-1.70	-134.5
	051004	32.1	9.05	3.50 H	233.0 H	31.8 L	6.20	2.60	105.0	-0.3	-2.85	-0.90	-128.0
	051005	33.8	8.85	3.65 H	591.0 H	36.7	19.80 H	11.80 H	289.0 H	2.8	10.95	8.15	-302.0
	056001	33.3	7.80	3.75 H	284.0 H				204.0 H				-80.0

Source: Applicants submission to NDA 20799 Sequence 0057(58)

Table 15 shows changes in albumin with OCA use are less pronounced in either direction (positive or negative). In trial 747-201 five patients were dosed with OCA 10 mg had low albumin. No conclusions about effects of OCA on albumin can be made with these data.

Serum IgM

Table 17: IgM Changes from Baseline to EOT

	Placebo (n = 23)	OCA 10 mg	OCA 50 mg
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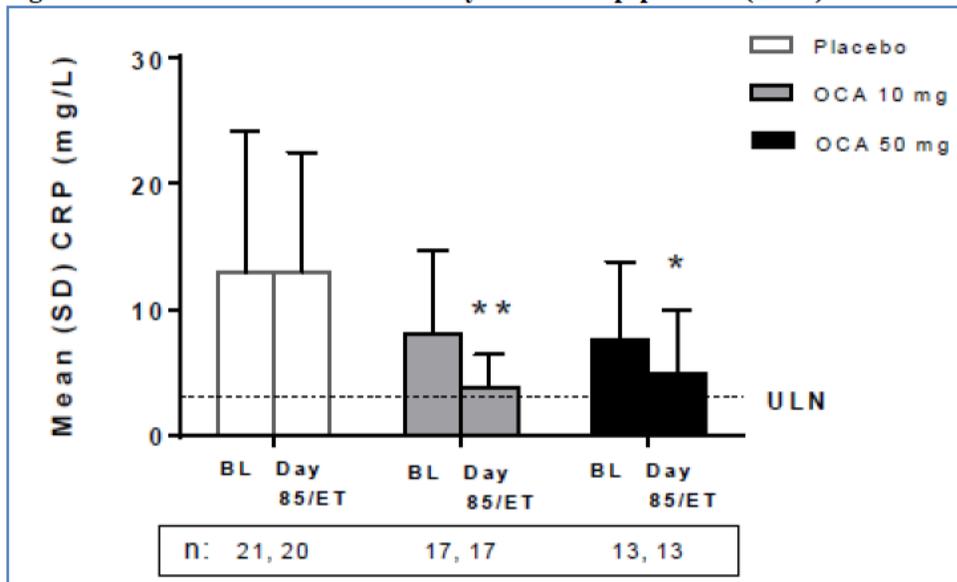
IgM (g/L)	Normal Range :0.4-2.3 g/L		
n at Baseline, and n at Day 85/ET	17, 16	14, 13	11, 12
Baseline (Mean [SD])	3.94 (2.11)	3.23 (1.95)	4.44 (2.10)
Baseline (Median)	303	270	383
Day 85/ET (Mean [SD])	3.79 (2.60)	2.92 (1.66)	3.91 (3.78)
Day 85/ET (Median)	3.23	2.65	2.80
N	13	11	9
Mean (SD)	0.10 (0.78)	-0.70 (0.83)	-1.15 (0.90)
N	13	11	9
Mean (SD)	1.20 (24.58)	-18.48 (15.97)	-27.82 (17.30)

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Reviewer Comment: Mean IgM levels were reduced from baseline to Day 85/ET in both OCA treatment arms compared to placebo; however, patients on the placebo arm had higher mean IgM levels at baseline compared to both OCA treatment arm. Although no treatment groups achieved normalization, reductions were seen in OCA treated patients. These reductions are supportive of primary efficacy endpoint.

CRP: The baseline mean (SD) CRP levels were 13.0 (11.1) mg/L in placebo, and 8.0 (6.6) mg/L and 7.5 (6.3) mg/L in OCA 10 mg and OCA 50 mg treatment arms, respectively. There was a large degree of variability within treatment arms, and 2x higher baseline CRP levels in the placebo arm compared to OCA treatment arms.

Figure 14: CRP levels at baseline and Day 85/Et: ITT population (N=59)



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Reviewer Comment: CRP is a non-specific inflammatory marker, may occur due to co-existing autoimmune disease, CRP could be high due to other autoimmune disease or due to PBC. Since the patients had stable medical disease and reduction of CRP occurred in temporal relation with OCA use, the reviewer thinks the decline in CRP is related to decrease in inflammation due to PBC related inflammation in liver. This supports the primary endpoint; however, neither OCA treated arms achieved CRP normalization. The reviewer also notes there was an imbalance in the baseline values in the three arms; however, no reduction in placebo arm was seen compared to OCA treated patients. Additionally, when the raw values were analyzed in the dataset “adlb” the reviewer noted the differences were driven predominately by few patients in both the OCA 10 mg arm and OCA 50 mg arm.

TNF- α and TNF- β :

TNF α : Reductions in TNF α were seen however, normalization was not seen in any treatment group. The clinical benefit of reducing these levels is relevant.

TNF- β : The levels increased across all treatment arms instead of decreasing.

Bile acids and OCA Pharmacokinetics: Mean baseline levels of bile acids in all treatment arms were comparable to the ULN; the mean (SD) bile acid levels were 10.5 (7.4) $\mu\text{mol/L}$ for placebo arm (n=6); 9.3 (2.9) $\mu\text{mol/L}$ in OCA 10 mg arm (n=7) and 13.2 (9.5) $\mu\text{mol/L}$ in OCA 50 mg arm (n=4). No statistical differences were observed from baseline to Day 85/ET in the absolute change or percent change of bile acids.

The mean (SD) levels of endogenous bile acids at baseline were 9.449 (10.665) $\mu\text{mol/L}$ in the placebo arm; 11.465 (10.250) $\mu\text{mol/L}$ in OCA 10 mg arm and 9.748 (9.456) $\mu\text{mol/L}$ in OCA 50 mg treatment arm. The mean levels of endogenous bile acids decreased by 10% from Baseline to Day 85/ET in the OCA 10 mg arm compared to a 52% increase in the placebo arm.

The level of bile acid analytes and change from baseline to Day 85 in ITT population (N=59, however there was missing data due to several patients not completing the assessments in the datasets):

Reviewer Comment:

The data interpretation is restricted by assessment in limited number of patients and, short duration of the trial.

Liver Fibrosis:

ELF score, a composite marker of liver fibrosis derived from 3 serum markers, including HA, P3NP, and TIMP-1. No statistically significant changes were observed from baseline to Day 85/ET in any treatment arms.

Reviewer Comment:

This reviewer points that clinical significance of ELF score is unknown. This is not well studied biomarker and clinical benefit with this biomarker is not established.

Disease-Specific and Quality of Life Assessments:

The SF-36 is a 36-item survey that measures 8 domains of health. It yields scale scores for each of these 8 health domains, and 2 summary measures of physical and mental health: the Physical Component Summary and Mental Component Summary. *No statistically significant changes were noted from baseline to Day 85/ET.*

PBC-40

The PBC-40 is a disease-specific QOL questionnaire, which consists of 5 domains, including general symptoms, itch, fatigue, cognitive function, and emotional/social. PBC-40 is not validated questionnaire, but has been used in clinical trials with PBC. Key findings are as follows:

1. **Pruritus**

Significant increases in pruritus were observed for both OCA dose levels ($p = 0.0008$ for OCA 10 mg, and $p = 0.0027$ for OCA 50 mg arms) in comparison to change in placebo on Day 29.

The itch scores for OCA 10 mg were also significantly increased on Day 57 ($p = 0.0176$), whereas for OCA 50 mg, the score was significantly increased on Day 85/ET ($p = 0.0172$).

Mean changes in the itch domain appeared to be dose-related: The change in itch score from Baseline to Day 85/ET was 2.8 and 4.2 for the OCA 10 mg and OCA 50 mg arms, respectively, whereas the change in score in the placebo arm was 0.2.

2. **Fatigue**: patients in all treatment arm experienced fatigue including placebo.

Introduction to FGF-19 and C4:

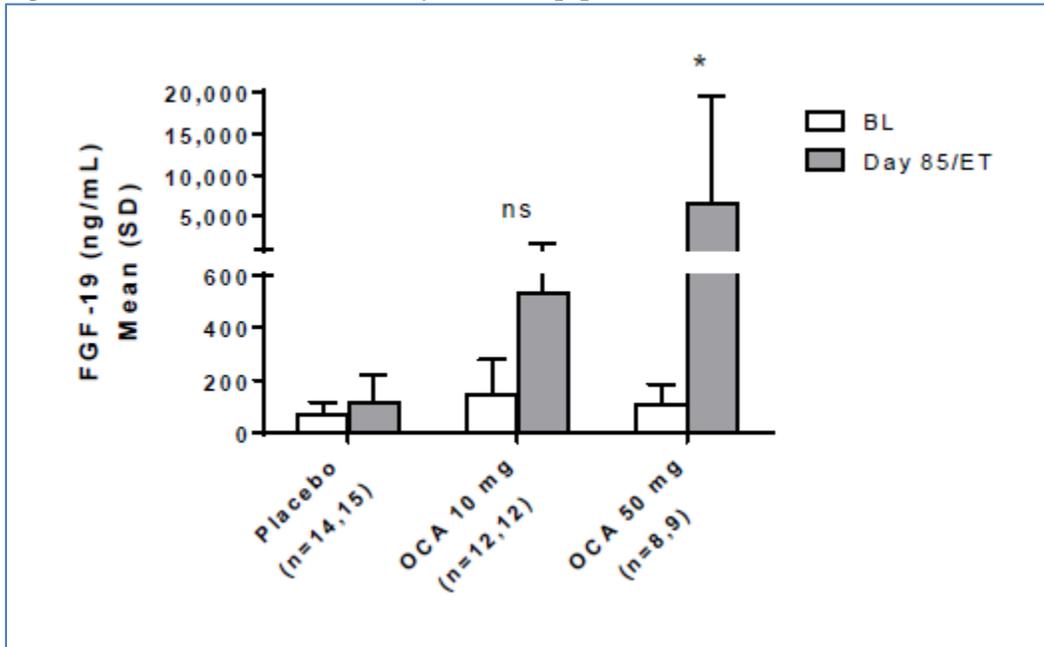
FXR activation by OCA induces a dose-related increase in serum levels of FGF-19, which is FXR-responsive gene product. FGF-19 is further known to down-regulate bile acids synthesis, leading to a reduction in bile acid synthesis and the intermediate thereof, C4.

C4 (serum 7α -hydroxy-4-cholesten-3-one), C4 is bile-acid intermediate, it estimates the rate of hepatic bile acid synthesis rate and strongly correlates with the activity of cholesterol 7-hydroxylase (CYP7A1), which is the rate-limiting enzyme of bile acid synthesis.

FGF19: The baseline values of mean FGF-19 levels were 72.3 (44.5) ng/L in placebo arm, 147.1 (130.9) ng/L in the OCA 10 mg arm, and 103.6 (81.4) ng/L in the OCA 50 mg arm. The baseline values were higher in OCA treatment arms compared to placebo. The mean (SD) levels at Day 85/ET were 532.0 (1120.2) ng/L in the OCA 10 mg arm, and 6412.3 (13 200.7) ng/L in the OCA 50 mg arm; whereas the levels only increased to 116.3 (104.8) ng/L in the placebo arm. The median values for the OCA treatment arms at Day 85/ET were 178.1 ng/L and 269.9 ng/L for the OCA 10 mg and OCA 50 mg arms, respectively, compared to 68.0 ng/L in the placebo arm.

FGF19 increase indicates the pharmco-dynamic effect of OCA. A dose dependent increase in FGF19 was noted in this trial.

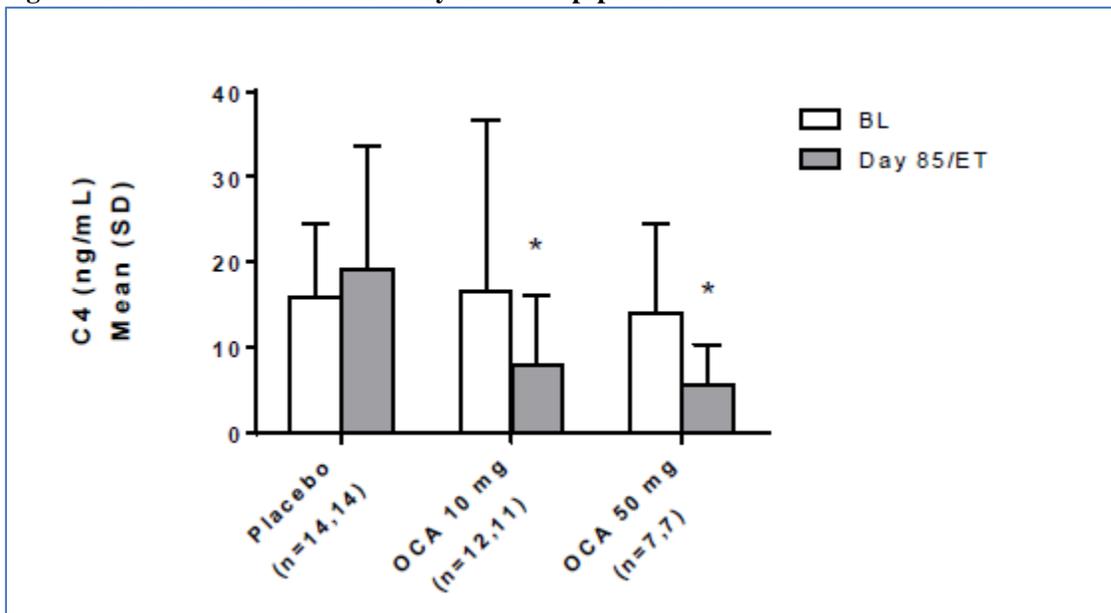
Figure 15: FGF19 at baseline and Day 85 in ITT population



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Serum levels of C4 were elevated at baseline with the mean (SD) levels ranging from 14.0 (10.5) ng/mL to 16.6 (20.1) ng/mL across the 3 treatment arms. The mean (SD) absolute change in baseline to Day 85/ET was statistically significant in OCA 10 mg (n=11) -11.1 (16.3) p=0.0508 and in OCA 50 mg arm (n=7) was -9.4 (11.7), p=0.0485 when compared with placebo (n=14). The percent change in serum levels of C4 expressed as mean (SD) from baseline by 40.1% (OCA 10 mg arm; p = 0.01) and 47.3% (OCA 50 mg arm; p = 0.03) at Day 85/ET.

Figure 16: C4 levels at baseline and day 85 in ITT population



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Reviewer Comment: C4 decrease in the OCA treated patient.

Efficacy Conclusions:

1. The ALP levels reduced from baseline to Day 85/ET. Both absolute and percent change reduction were statistically significant comparison to placebo arm. The ALP reduction of 10, 20%, 40% reduction were achieved numerically in higher number of patients treated with OCA relative to placebo. As assessed by different responder criteria numerically higher number of patients achieved endpoint in the OCA treated arm relative to placebo. A total of 5 patients achieved ALP normalization in OCA 10 mg treatment arm compared to zero patients in OCA 50 mg and placebo arm.
2. Post hoc analyses to assess the primary endpoint of the pivotal trial shows: Mayo II plus 15% ALP reduction criteria were achieved by 1 (5%) placebo patients compared 7 (44%) patients dosed with OCA 10 mg and by 7 (50%) patients dosed with OCA 50 mg treatment arm. Notably three out of seven who achieved Mayo II+ 15% ALP reduction, in OCA 10 mg treatment arm, also achieved the composite endpoint, i.e., reduction in both ALP and TB.
3. The TB and conjugated bilirubin were with in normal range for majority of patients; however, a downward trend of TB was seen in both the OCA treatment arms in comparison to placebo arm. Four patients who had elevated TB at baseline and 3 patient achieved reductions in TB in the OCA 10 mg treated group. One patient dosed with OCA 10 mg who had normal TB at baseline had increase in TB at day 85. However data are limited by small sample size and whether these effects can be replicated in PBC population is not clear. However, the trend towards reduction for TB seems favorable to OCA 10 mg treated group.
4. If the baseline albumin was low, and did not improve with OCA use.
5. Hepatic biochemical parameters of GGT and ALT reduced in the both OCA treated arm, supporting the primary efficacy endpoint.

6.1.1.3 Review of Safety

Extent of exposure: A total of 59 patients were exposed to investigational product: 23 patients received placebo, 20 patients received OCA 10 mg, and 16 patients received OCA 50 mg. Patients randomized to OCA received OCA as a monotherapy.

Drug Exposure: Dosing was modified during the study for 4 patients: 1 placebo, 1 OCA 10 mg, and 2 OCA 50 mg patients. The dosing modification included dose interruption in 1 patient each in placebo, OCA 10 mg and OCA 50 mg arms who completed the study, and change in dosing schedule in 1 OCA 50 mg patient who did not complete the study.

Table 18-Duration of Investigational Product Exposure: Safety Population (N = 59)

	Placebo	OCA 10 mg	OCA 50 mg
Number of Days on Investigational Product			
n	23	20	16
Mean (SD)	98.7 (2.6)	91.2 (15.6)	74.1 (32.3)
Median	98.0	98.0	95.5
Min, Max	92.0, 106.0	41.0, 100.0	13.0, 99.0

Source: Copied and electronically reproduced from Applicant's CSR 747-201 Study report submission

Reviewer Comments: It is not clear why some patients received investigational product for 106 days in placebo arm and 99-100 days in the OCA treated arm, since the duration trial was 85 days.

Death: No deaths were reported during the conduct of the trial.

Serious adverse event (SAE) Only a single SAE of rash was reported over the course of the study and occurred in a placebo treated patient (19-003-1057).

Summary of SAE: Patient had an AE of maculo-papular rash after receiving IV hydromorphone (patient was allergic to morphine but no known drug allergy to hydromorphone and had received the drug due to lumbar pain). The therapy was discontinued for 1 day while the patient was hospitalized, rash was biopsied and histology was consistent with drug reaction. The rash with acute symptoms (lumbar pain, fever) resolved and the patient resumed therapy with investigational agent (which was placebo) and completed the trial.

Drop outs and/or Discontinuations due to adverse events:

There was no mandatory discontinuation during the trial.

All placebo patients (n = 23) completed the study.

In the OCA 10 mg arm, 3 (15%) of 20 patients discontinued due to an AE of pruritus;

In the OCA 50 mg arm, of 6 (38%) out of patients 16 discontinued due to pruritus, and 1 patient (Patient 10-001-500) was discontinued due to a major protocol violation of failing to return to the clinic. Five of the 6 patients who discontinued did so within 6 days of dosing with OCA 50 mg.

Reviewer Comments: Patient 23-004-802 in the OCA 50mg treatment arm had a deviation on Day 57 (conjugated bilirubin level was 2x ULN), which should have resulted in a mandatory discontinuation; however, a waiver was granted for this deviation. An information request for obtaining more information (clinical and liver biochemical laboratory value) was sent to the Applicant. Reviewer agrees with the waiver, other than CB neither laboratory values showed any significant changes or increase.

Pruritus is a dose dependent adverse event. The OCA 10mg achieved similar magnitude of biochemical response; additionally patients in the 10mg arm had less pruritus events.

Table 19 -Incidence of TEAEs by Severity: Safety Population (N = 59)

Parameter	Treatment Group
-----------	-----------------

	Placebo (n = 23)	OCA 10 mg (n = 20)	OCA 50 mg (n = 16)
	Patients (%)	Patients (%)	Patients (%)
Total number of TEAEs	21 (91)	18 (90)	15 (94)
Mild	18 (78)	16 (80)	10 (63)
Moderate	8 (35)	9 (45)	10 (63)
Severe	5 (22)	7 (35)	6 (38)

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Significant Adverse events:

The incidence of severe TEAEs was similar in the OCA treatment arms (35% and 38% of patients in the OCA 10 mg and OCA 50 mg arms, respectively), and compared with placebo (22%). The higher incidence of severe TEAEs in the OCA treatment arms was primarily due to a higher incidence of severe pruritus.

Treatment Emergent Adverse Events and Adverse Reactions:

No dose-related patterns were noted among other commonly reported TEAEs; the small number of patients precludes further interpretation of this finding.

In all treatment arms, most of the TEAEs that were severe were the AE of pruritus (5 patients [22%], 7 patients [35%], and 6 patients [38%] in the placebo, OCA 10 mg, and OCA 50 mg arms. In the placebo arm: 3 patients had severe TEAEs and included 1 patient with a TEAE of cold sweat, 1 patient with a TEAE of pruritus, and 1 patient with a TEAE of rash. A severe TEAE of insomnia was experienced by 2 patients (13%) in OCA 50 mg arm.

Pruritus is the most common AE seen in patients with PBC and is an AE of special interest in PBC patients. The incidence of pruritus was greater in the OCA 10 mg (14 patients [70%]) and OCA 50 mg (15 patients, [94%]) arms compared with placebo (7 patients [30%]). The incidence of severe TEAEs of pruritus was higher in the OCA treatment arms (6 of 14 OCA 10 mg patients and 6 of 15 OCA 50 mg patients with at least 1 event of pruritus) compared to placebo (1 of 8 patients with at least 1 event of pruritus).

Table 20: Time to Onset of First Episode of Clinically Significant Pruritus: Safety Population (N = 59)

	Treatment Groups		
	Placebo (n = 23)	OCA 10 mg (n = 20)	OCA 50 mg (n = 16)
n (%) patients with at least 1 clinically significant pruritus	3 (13) ^a	9 (45) ^a	13 (81) ^a
Mean (SD) days	46.3 (33.1)	12.2 (9.3)	8.7 (9.6)
Median (days)	33.0	14.0	6.0
Range: minimum, maximum (days)	22, 84	3, 27	0, 29
Interquartile range (days)	22, 84	3, 18	2, 8

Source: Copied and electronically reproduced from the Applicant submission CSR 747-202- page 116-1264

Table 20 above shows the median time to onset for pruritus was 6 days in OCA 50 mg versus 14 days for OCA 10 mg compared to 33 days for placebo arm. The pruritus was seen as early as 2 days in patient treated with OCA 10 mg and 2 days in patient treated with OCA 50 mg group.

Table 21: The Outcome of Clinically Significant Intervention in Patients with Pruritus (N = 25)

	Treatment Group		
	Placebo	OCA 10 mg	OCA 50 mg
Patients (n) with at least 1 clinically significant pruritus and at least 1 event of clinically significant intervention for pruritus	n = 3	n = 9	n = 13
Intervention Success (n [%])^a			
Yes (i.e., continued on study)	3 (100%)	6 (67%)	7 (54%)
No (i.e., discontinued study)	0 (0%)	3 (33%)	6 (46%)

Source: Copied and electronically reproduced from the Applicant submission CSR 747-202- page 116-1264
a Intervention success was defined as the patient completing the study. These categorizations were done during blinded data review meeting.

Intervention for pruritus:

13% patients in placebo arm

45% patients in the OCA 10 mg arm

81% patients in OCA 50 mg arm required treatment intervention for pruritus.

Per the SAP, “significant pruritus” was defined by discontinuation of investigational product, or the use of one or more of the following interventions to reduce the severity of pruritus:

1. interruption of dosing; decrease in dosing frequency;
2. or administration [or an increase in dose] of other drugs, such as
 - a. Bile acid binding resins (cholestyramine, colestipol, colesevelam), or
 - b. Antihistamines and other antipruritic agents.

Treatment discontinuation was done in patients who did not respond to treatment intervention for pruritus.

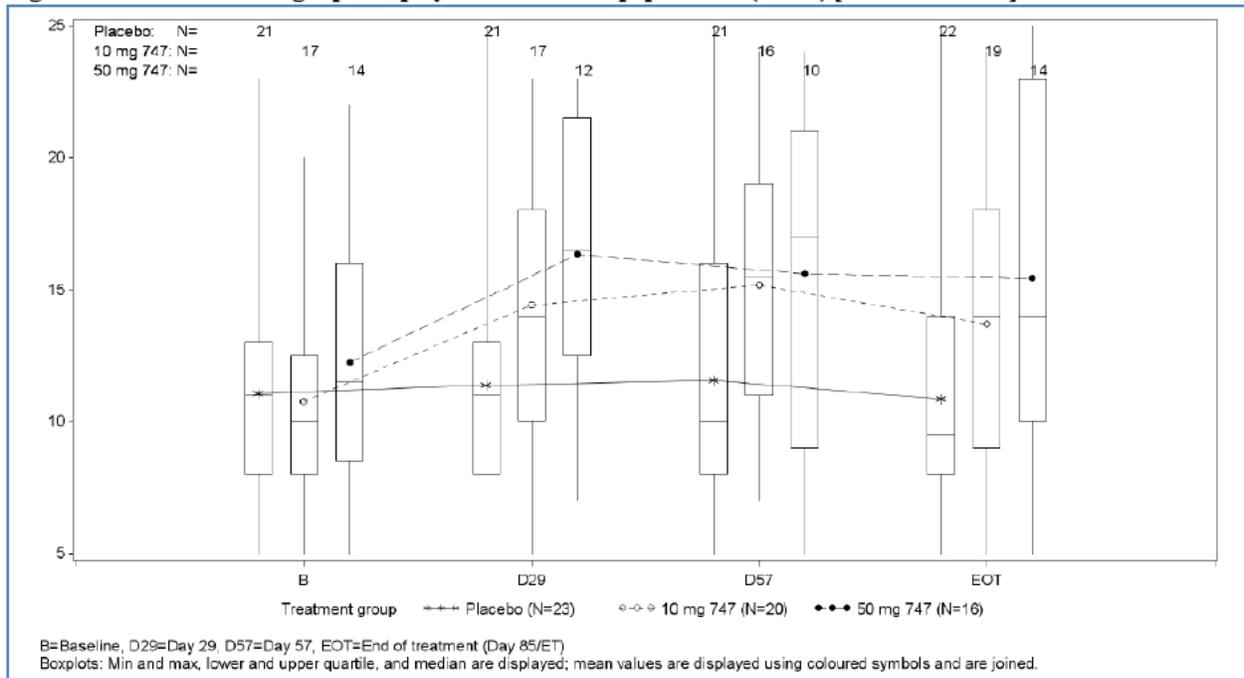
All placebo patients responded to clinical interventions for pruritus as per protocol, whereas only 67% patients in OCA 10 mg and 57% in OCA 50 mg responded to intervention.

None in the placebo arm required treatment discontinuations compared with 3 in OCA 10 mg and 6 in OCA 10 mg arm required treatment discontinuations. The patients dosed with OCA 50 mg responded less to therapeutic intervention.

For the patients who discontinued due to pruritus, the mean (SD) time to resolution following discontinuation was 24.0 (13.7) days in the OCA 10 mg group and 15.7 (9.4) days in the OCA 50 mg group. The median time to resolution of pruritus was 27.0 days in the OCA 10 mg group and 14.5 days in the OCA 50 mg group. The majority of these patients (n = 8 [89%]) had a resolution time >7 days.

MO Comment: The pruritus is reversible with OCA discontinuation.

Figure 17: 5D dimension graph display over time ITT population (N=59) [5 D total score]



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Reviewer Comment: 5 D pruritus scale assessment performed over trial duration (5 D scales assess pruritus in the domains of duration, degree, disability, and direction). Figure 17 above shows the increase AE of pruritus in patients who were dose with OCA (OCA 10 mg and OCA 50 mg) in comparison to almost a flat line for the placebo treatment arm patients. There were only 1-2 components of the instrument that drove this scale, and this was consistently seen across all the three trials.

Table 22-TEAEs by SOC and Preferred Term Reported ≥ 2 Patients in Any Treatment Arm: Safety Population (N = 59)

System Organ Class MedDRA Preferred Term	Treatment Group		
	Placebo (n = 23)	OCA 10 mg n = 20)	OCA 50 mg n = 16)
	Patients (%)	Patients (%)	Patients (%)
Patients with any TEAEs	21 (91)	18 (90)	15 (94)
Skin and subcutaneous tissue disorders			
Pruritus	7 (30)	14 (70)	15 (94)
Pruritus generalized	1 (4)	0 (0)	0 (0)
Nervous system disorders			
Headache	5 (22)	4 (20)	2 (13)
Dizziness	4 (17)	0 (0)	0 (0)
Infections and infestations			

Naso-pharyngitis	2 (9)	3 (15)	1 (6)
Urinary Tract Infection	0 (0)	3 (15)	1 (6)
Upper Respiratory Tract Infection	0 (0)	2 (10)	0 (0)
Psychiatric disorders			
Insomnia	1 (4)	1 (5)	2 (13)

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(Table Continued: IEAEs by SOC and Preferred Term Reported ≥2 Patients in Any Treatment Arm: Safety Population (N = 59))

System Organ Class MedDRA Preferred Term	Treatment Group		
	Placebo (n = 23)	OCA 10 mg (n = 20)	OCA 50 mg (n = 16)
Gastrointestinal disorders			
Abdominal Pain	1 (4)	1 (5)	2 (13)
Nausea	4 (17)	0 (0)	4 (25)
Abdominal Distension	0 (0)	0 (0)	2 (13)
Constipation	0 (0)	0 (0)	2 (13)
Diarrhea	1 (4)	0 (0)	2 (13)
Faeces pale	0 (0)	0 (0)	2 (13)
Hemorrhoids	0 (0)	0 (0)	2 (13)
Abdominal Pain Upper	2 (9)	0 (0)	0 (0)
Pyrexia	2 (9)	0 (0)	0 (0)
General disorders and administration site conditions			
Fatigue	3 (13)	0 (0)	1 (6)
Influenza Like Illness	2 (9)	0 (0)	1 (6)
Musculoskeletal and connective tissue disorders			
Arthralgia	2 (9)	0 (0)	0 (0)
Back Pain	4 (17)	0 (0)	0 (0)

Source: copied and electronically reproduced from Applicant submission 747-201 page 110 of 1264

Reviewer Comment: Adverse events related to gastrointestinal disorders were higher in patients who received OCA 50 mg compared with placebo, with the exception of nausea.

Fatigue is a common PBC symptom and 3 patients with fatigue in placebo arm versus one patient treated with OCA 50 mg experienced AE of fatigue.

This reviewer observes that despite enrolling ~ 50% (9 out of 20 patient) patients with moderately advanced stage disease patients in OCA 10 mg arm, patients did not experienced AE or SAE, with exception of abdominal pain. The safety finding in this trial is different than 747-202 and 747-301 in that there appeared to be less hepatic toxicity when OCA was used as monotherapy than when used in conjunction with UDCA.

6.1.1.3.1 Hepatic-Related Adverse Events

No serious hepatic adverse event in occurred in this study.

Patient 19-002-1056 (OCA 10 mg arm) had ongoing hepatic pain. An IR was sent, liver biochemical tests were not provided. Data in JMP dataset for “adlb” reviewed and the patient did not have any laboratory abnormality, specifically for TB/DB and ALP.

Patient 19-001-1055 and 23-005-1025 enrolled in OCA 50 mg arm had pale faces. The patient 23-005-1025 (OCA 50 mg) was discontinued from trial in 3 days after dosing with OCA 50 mg. Patient 19-001-1055 (OCA 50 mg) the AE was reported as resolved, and “adlb” dataset was queried for changes in liver related and serum creatinine laboratory data, and not significant changes were identified.

The reviewer considers these as non-serious AE and there was no clinical relevance associated with these AE.

Hepatic and Renal Biochemistry Markers:

No clinical relevant findings of concerned were noted.

Cardiovascular adverse events: None reported in trial 747-201.

No pregnancy was reported during the trial.

Laboratory findings:

Hematology: No clinically significant shifts from normal to abnormal were observed for any of the hematology parameters assessed (including hemoglobin, leukocytes, lymphocytes, monocytes, eosinophils, basophils, neutrophil granulocytes, platelets, and erythrocytes) across treatment arms.

Coagulation factors- Mean and median aPTT and INR values were stable over time, and were within central laboratory reference (normal) ranges.

Chemistry: All values were within normal ranges, and no differences in absolute mean changes from baseline to each assessed time point were observed across treatment arms, with exception of liver biochemistries which changed favorably in OCA treated patients. One patient in the placebo arm had hypokalemia, this hypokalemia resolved without sequelae.

6.1.1.3.2 Lipid related adverse event:

Table 23: Mean HDLc changes from Baseline to EOT-Trial 747-201

	OCA 10 mg (N = 38)	OCA 25 mg (N = 48)	OCA 50 mg (N = 41)	Placebo (N = 38)
<u>Mean HDLc (mg/dL)</u>				
Baseline	67.6	71.5	75.4	69.9
Day 85	58	61.4	58	73.7

Change from base line	-10	-10	-17	+4
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Source: Reviewer Generated

Reviewer Comment: HDLc reductions were seen in patients treated with OCA and not in the placebo treated patients. At this time the impact of HDLc lowering on cardiovascular outcomes in PBC patients when treated chronically with OCA are not known.

In the OCA 10 mg dosed patients 12 patients had some reduction in HDLc

In the OCA 50 mg dosed patients 11 patients had some reduction in HDLc

In the placebo arm 9 patients had some changes in HDLc

Table 24: HDLc Reduction distribution in Trial Patients at End of Treatment

	Number of patients with HDLc reduction >1 SD but <2 SD / Total number patients with changes in HDLc (22-44 mg/dL)	Number of patients with HDLc reduction >2 SD / total number patients with changes in HDLc (44 mg/dL)
OCA 10 mg (N=12)	3/12	2/12
OCA 50 mg (N=11)	2/11	2/11
Placebo (N=9)	0/9	0/9

Source: Reviewer Generated from the Applicant's data submitted to NDA

Reviewer Comment: The mean total cholesterol reduced, but the majority of this reduction was related to lowering of mean HDLc in the patients treated with OCA. Table 25 shows reduction > 1 SD (>22 mg/dL) change in 85 days. Patients who discontinued from trial also affected the interpretation of final HDLc reductions.

Vital Signs, Physical Findings and Other Observations Related to Safety

Vitals, body weight and physical examination: There were no noted in any of the treatment arms during the study, with exception of this patient:

One patient treated with OCA 50 mg lost weight (3.5 kilograms) during the trial and this was reversible, i.e., gained weight on discontinuing OCA, the reviewer thinks this was seen in one patient across all treatment trial, therefore it is not a likely adverse event related to OCA. However, this AE must be watched and if patients lose weight must be reported.

12-Lead Electrocardiogram:

The abnormal ECGs (QTcF changes) occurred across all treatment arms, was well balanced across treatment arms and coded as mild AE. Please see TQT consult summary in Section 8.3.9

6.1.1.3.3 Safety Conclusions:

- OCA treatment at doses of 10 mg and 50 mg once daily for 3 months was generally safe, and the 10 mg dose was better tolerated compared with the 50 mg dose in patients with PBC as assessed by extent of discontinuations due to the TEAE of pruritus.

2. The patients dosed with OCA 10 mg had no hepatic adverse events, despite the fact about 50% patients (n/N=9/20) had moderately advanced disease. It appears that the OCA 10 mg dose may be safe when used as monotherapy even in moderately advanced stages at least for 3 month duration (b) (4)
3. TEAEs were reported by 90%, 94%, and 91% of patients treated with OCA 10 mg, OCA 50 mg, and placebo, respectively. The majority of these TEAEs were mild or moderate in severity.
4. The most commonly reported TEAE across all treatment groups was pruritus.
 - a. The incidence of pruritus was dose-related and was higher in the OCA-treated patients compared with placebo treated patients.
 - b. The incidence of severe TEAEs of pruritus was higher in the OCA treatment groups compared with placebo.
 - c. The median time to the onset of first episode of clinically significant pruritus was shorter in the OCA treatment groups (14 days for the OCA 10 mg group and 6 days for the OCA 50 mg group) compared to 33 days for placebo.
 - d. Intervention for pruritus were successful in 3 placebo patients (100%), 6 OCA 10 mg patients (67%), and 7 OCA 50 mg patients (54%). Patients treated with OCA 50 mg have only 50% response to medical interventions for pruritus.
 - e. No patient in the placebo group discontinued due to pruritus. Study discontinuations in the OCA treatment groups were attributed to a TEAE of pruritus (9 discontinuations: 3 OCA 10 mg patients [15%], and 6 OCA 50 mg patients [38%]), though 1 patient in the OCA 50 mg group withdrew due to both a TEAE of pruritus and nausea.
5. There were no deaths in this study.
6. There was one SAE (rash) in the placebo group, and none in the OCA treatment groups.
7. There were no mandatory discontinuations in the study.
8. No liver related SAE occurred in this study. Two patients (13%) in the OCA 50 mg group and 1 patient each in the OCA 10 mg and placebo groups experienced relevant TEAEs as follows: hepatic pain, faeces discolored, and faeces pale. However as noted above in review these were not associated with changes in liver biochemical tests or function tests or hepatic decompensations.
9. The magnitude of HDLc reduction was greater in the OCA treatment groups, and seemed dose dependent.
10. In comparison to trial 747-202 and 747-201, the overall AEs and SAEs reported in this trial were low and there were no hepatic adverse events. Further investigation to see if OCA monotherapy has a better safety profile by conducting a dedicated OCA monotherapy trial.

6.2 Trial 747-202

Phase 2 trial: "A Study of INT-747 (6-ECDCA) in Combination with Ursodeoxycholic Acid in Patients with Primary Biliary Cirrhosis"

Study 747-202 was designed to investigate the efficacy and safety of OCA 10 mg, 25 mg, and 50 mg doses, compared with placebo in combination with UDCA (the current standard of care).

Of note, in this trial liver related adverse reactions and serious adverse reactions were higher in the treatment groups than in placebo. Three patients experienced one adverse event each: one experienced gastrointestinal hemorrhage, second patient experienced new onset jaundice, and primary biliary cirrhosis flare.

Ethical Conduct of the Study

This study was conducted according to globally accepted standards of good clinical practice (as defined in the International Conference on Harmonization E6 Guidance for Good Clinical Practice April 1996; 62 FR 25692, May 9, 1997), in agreement with the latest revision of the Declaration of Helsinki and the appropriate United States (US) Food and Drug Administration (FDA) Code of Federal Regulations (CFR) as well as other international regulatory agency requirements.

6.2.1 747-202- Study Design

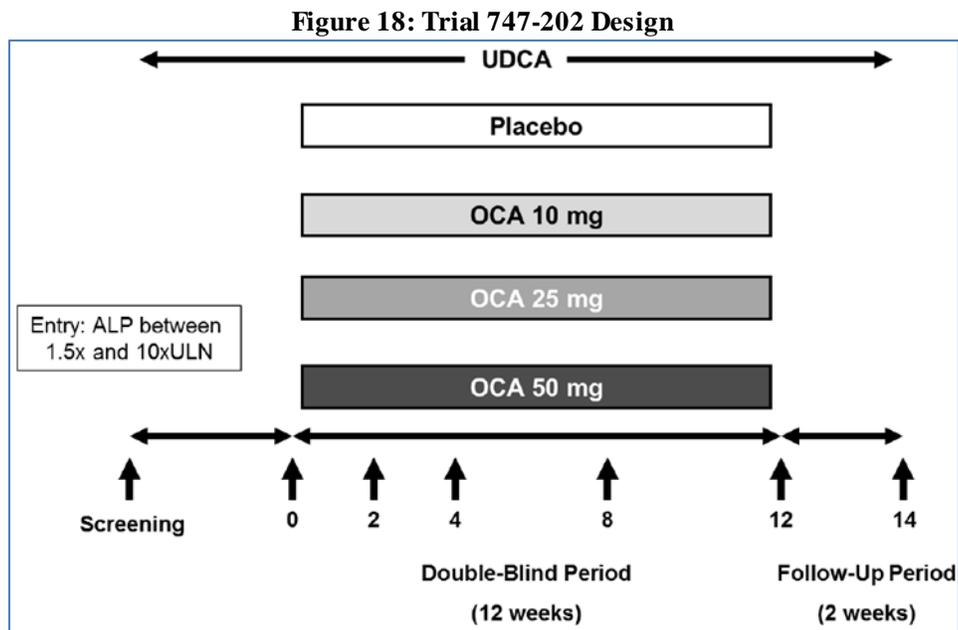
Overview and Objective This is a multi-center, randomized, double-blind, placebo-controlled, multi-dose, parallel arm trial to evaluate safety and efficacy of OCA in combination with UDCA (the current standard of care) in patients with proven or likely diagnosis of PBC. This trial was conducted in 8 countries at 30 investigational sites, with 30 investigators and comprised of 11 Investigators (11 sites) in the United States (US), 6 Investigators (6 sites) in Canada, 4 Investigators (4 sites) in Germany, 4 Investigators (4 sites) in the United Kingdom (UK), 2 Investigators (2 sites) in The Netherlands, 1 Investigator (1 site) in Austria, 1 Investigator (1 site) in France, and 1 Investigator (1 site) in Spain. This trial was started on 30th October 2007 and completed on 8th Sept 2009.

The primary objectives of the study were to assess the effects of OCA in PBC patient on the following:

1. Alkaline phosphatase (ALP) levels
2. Safety

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

1. Hepatocellular injury and liver function
2. Disease-specific and general health symptoms
3. Biomarkers of hepatic inflammation and fibrosis
4. Plasma trough concentrations of OCA and its major known conjugates (referred to as “metabolites” in the Study Protocol and Statistical Analysis Plan [SAP])



Source: Figure 19: Copied and electronically reproduced from the Applicant's submission of CSR 747-202. Page 23 of 1652

Figure description: The arrows represent study visit days as follows: Screening, Day 0, Week 2 (Day 15 visit), Week 4 (Day 29 visit), Week 8 (Day 57 visit), Week 12 (Day 85 visit), and Week 14 (Day 99 visit).

The double-blind, placebo-controlled phase of the study consisted of a screening period ≤ 4 weeks, a 3-month treatment phase, and 2-week follow-up period for a total duration of 18 weeks. Written informed consents were obtained before enrollment, patients were screened for eligibility. Patients who met the enrollment criteria were randomized in a 1:1:1:1 to placebo, OCA 10 mg, OCA 25 mg, or OCA 50 mg arms. Patients were instructed to self-

administer OCA tablet starting on Day 1 orally and once daily until Day 85 (last day of treatment period). The patients remained on their previous stable dose of UDCA throughout the study.

During the 3-month double-blind phase, patients returned to the study site for 4 visits (Day 15, Day 29, Day 57, and Day 85) for evaluations of efficacy, safety, tolerability, and compliance with investigational product. In addition, patients at the UK sites also had a Day 8 study visit for evaluation of safety endpoints. There was a 2-week follow-up period after Day 85 and patients returned for the follow-up visit on Day 99.

A total of 222 patients were screened, of which 165 patients met the study entry criteria and were randomized as follows: 38 patients to placebo arm; 38 patients to OCA 10 mg arm, 48 patients to OCA 25 mg arm, and 41 patients to OCA 50 mg. The doses were selected based on safety data from the healthy volunteer trial, and therefore doses lower than OCA 100 mg were chosen.

Key Inclusion Criteria:

1. Adult male or female and on a stable dose of UDCA for at least 6 months prior to screening
2. Female patients had to be either postmenopausal, or surgically sterile, or if premenopausal use contraception. Both males and females had to use 1 effective method of contraception with all sexual partners during the study and for 14 days after the end of dosing.
3. Screening ALP level between 1.5x upper limit of normal (ULN) and 10x ULN
4. Proven or likely PBC, as demonstrated by the patient presenting with at least 2 of the following 3 diagnostic factors:
 - a. History of increased ALP levels for at least 6 months prior to Day 0
 - b. Positive antimitochondrial antibody (AMA) titer
 - c. Liver biopsy consistent with PBC

Key Exclusion Criteria:

1. History or presence of other concomitant liver diseases, for example, hepatitis B or C, primary sclerosing cholangitis, alcoholic liver disease, definite autoimmune liver disease, or biopsy proven nonalcoholic steatohepatitis
2. History or presence of hepatic decompensation (e.g., variceal bleeds, encephalopathy, or poorly controlled ascites)
3. Screening conjugated (direct) bilirubin >2x ULN; ALT or AST >5 X ULN; serum creatinine >1.5 mg/dL (133 µmol/L)
4. History or presence of other concomitant liver diseases or human immunodeficiency virus (HIV) or other viral hepatitis infection
5. Clinically significant medical condition, and gastrointestinal conditions affecting drug ADME
6. Participation in another investigational drug, biologic, or medical device study within 30 days prior to Day 0
7. Blood or plasma donation within 30 days prior to dosing
8. If female: pregnant, lactating, or positive serum or urine pregnancy test
9. On concomitant medications including colchicine, methotrexate, azathioprine, or systemic corticosteroids (during the 3 months prior to enrollment)

Table 25: Schedule of Assessments

Study Time	Screen -4 to -1 Weeks ^a	Day 0 (Baseline)	Day 15	Day 29 ^b	Day 57 ^b	Day 85/ET ^b	Follow-Up/ Day 99
Study Procedures							
Informed Consent	X						
Medical History	X						
Inclusion/Exclusion Criteria	X	X					

Physical Examination	X ^c					X ^c	
Electrocardiogram	X					X	
PBC-40 QOL and 5-D Questionnaires	X	X	X ⁱ	X	X	X	
Study Time	Screen -4 to -1 Weeks^a	Day 0 (Baseline)	Day 15	Day 29^b	Day 57^b	Day 85/ET^b	Follow-Up/ Day 99
SF-36 QOL Questionnaire		X				X	
Pruritus VAS Questionnaire		X	X	X	X	X	
Transient Elastography ^h		X				X	
Prior and Concomitant Medications	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X
Dispense Investigational Product		X		X	X		
Investigational Product Accountability				X	X	X	
Investigational Product Administration		X ^d	X	X	X		
Clinical Laboratory Evaluations							
Serum Chemistry ^e	X	X	X	X	X	X	X
Hematology ^e	X	X	X	X	X	X	X
Serum bile acids ^e		X	X	X		X	
Liver Panel ^e		X				X	
Pharmacokinetics ^f		X	X	X	X	X ^f	
Urinalysis	X					X	
Urine Based β -hCG Pregnancy Test	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	

Source: Electronically copied and reproduced from the Applicant submission-747-202 CSR pages 23 and 24 of 1652

β -hCG = beta-human chorionic gonadotropin; QOL = quality of life; PBC-40 QOL questionnaire = QOL questionnaire for PBC, contains 40 questions; 5-D questionnaire = 5-dimensional questionnaire; SF-36 = short form (36) health survey; VAS = visual analog scale
 a Screening evaluations occurred between Day -28 and Day -7, relative to Day 0.

b Acceptable variation for actual study visits was ± 3 days from nominally scheduled day for Day 29, Day 57, and Day 85/Early Termination (ET) visits. However, every effort was made to maintain the nominal visit schedules of patients as predicated by the occurrence of the Day 0 visit.

c Physical examination at Screening included patient height and weight and on Day 85/ET included patient weight.

d Investigational product administration on Day 1 (the following morning), approximately 30 minutes before breakfast with water, or on Day 0 while at the study site, approximately 30 minutes before breakfast with water.

e 8-hour fasting requirement applied only to Day 0 and Day 85/ET clinical laboratory evaluations.

f A blood sample for pharmacokinetic analysis was to be drawn shortly before the next dose from every patient on Days 0, 29, 57, and 85, as well as from those who discontinued the study due to ALT/AST and/or bilirubin increases.

g Urine-based β -hCG pregnancy test was performed in females of childbearing potential. If positive, a confirmatory blood test must have been performed at the site. If the blood test is also positive, the patient was discontinued from the study.

h Transient Elastography (TE) was conducted at selected centers using the Fibroscan® TE device (Echosens, Paris, France).

i The 5-D questionnaire was completed at Day 15.

Mandatory discontinuation: See Trial 747-201 mandatory discontinuation criteria (Section 6.1.1).

Special considerations:

One site (Mayo Clinic, USA) instituted a titration schedule that allowed investigational product to be administered once every 3 days in the first week, followed by once every 2 days in the second week, and daily from the third week onwards. Fourteen patients were enrolled at the Mayo clinic study site, using this titration strategy.

Pruritus management:

Patients with severe pruritus at baseline were excluded from the trial. As clinically indicated, investigators could attempt to decrease the severity of a patient's pruritus by one or more of the following interventions:

- a. Discontinuing investigational product
- b. Interruption of dosing
- c. Decrease in dosing frequency
- d. Administration (or an increase in dose) of other drugs:
 - a. Bile acid binding resins: cholestyramine, colestipol, colestevlam
 - b. Anti-histamines and other anti-pruritic agents
- e. Decreasing the concomitant dose of UDCA

The patients with TEAE of pruritus, the "clinically significant interventions," and the success or failure of these interventions were identified during the data review. The success or failures of these interventions were defined as follows:

- Intervention failure: Patient discontinued investigational product
- Intervention success: Patient completed the study.

Pruritus was assessed by VAS* scores, and 5-D scores*.
PBC-40* questionnaire was performed to assess quality of life.
*Please see appendix for more information on these tests.

Determination of Sample Size

The study sample size was calculated in terms of effect size: 35 patients per arm provided 80% power to detect an effect size of 0.70 which translates to approximately a mean of 10% greater reduction in ALP levels between arms.

Statistical Analysis Plan 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. Analyses performed subsequent to breaking the blind were considered post-hoc and exploratory.

Analyses population:

The following analyses populations were used for efficacy, PK, and safety:

1. **The mITT Population** included all randomized patients who received at least 1 dose of investigational product and had at least 1 post-baseline ALP evaluation taken ≤ 7 days after their last dose of investigational product. Patients were analyzed according to the treatment arm to which they were randomized. The primary efficacy analysis was based on the mITT Population.
 - a. A sensitivity analysis of the primary efficacy endpoint was also performed based on patients who had at least 1 post-baseline ALP evaluation taken up to 15 days after their last dose of investigational product.
2. **The Intent-to-Treat (ITT) Population** included all randomized patients who received at least 1 dose of investigational product. Patients were analyzed according to the treatment arm to which they were randomly assigned (intent-to-treat principle). Secondary efficacy analyses were based on the ITT Population.
3. **The Completer Population** included all randomized patients who received at least 1 dose of investigational product based on the treatment arm assignment and participated until the end of the 3-month, double-blind treatment period (i.e., Day 85).

4. **The Safety Population** included all randomized patients who received at least 1 dose of investigational product. If the administration of any investigational product was not certain, the patient was included. Patients were analyzed according to the treatment they actually received.

Efficacy Analysis

All primary and secondary endpoints were analyzed using descriptive methods. For all tests, a 2-sided significance level of 5% was applied, unless otherwise noted. The analysis of the primary endpoint, using the mITT set was considered confirmatory. The analyses of the secondary endpoints were considered exploratory.

Primary Efficacy endpoint: Percent change (%) in serum ALP from Baseline to End of Study (EOS) [EOS=Day 85 or last observed ALP value on treatment].

The percent (%) change from baseline to EOS was described using summary statistics. The primary efficacy endpoint was analyzed using the 2-sided Wilcoxon-Mann-Whitney test at the 5% level of significance. A hierarchical testing strategy was proposed to account for multiple comparisons. The statistical significance was evaluated in order as follows: if statistical significance at $\alpha = 0.05$ was observed for the OCA 50 mg arm versus placebo, then the statistical significance at $\alpha = 0.05$ for the OCA 25 mg versus placebo was to be performed, thereafter the statistical significance at $\alpha = 0.05$ for the OCA 10 mg versus placebo was to be performed. If no statistical significance was observed at $\alpha = 0.05$ at the first step, then the subsequent comparisons were not considered statistically significant, regardless of the p value.

All other statistical testing, including that for the sensitivity analysis, secondary endpoints, and post-hoc analyses were descriptive and exploratory. No statistical testing was done on sub-group analyses.

Dose selection: The OCA doses (10 mg, 25 mg, and 50 mg once daily) were based on the safety results of two phase 1 studies (747-101 and 747-102) in healthy volunteers.

Secondary Efficacy Endpoints Analyses: All secondary analyses were performed using the ITT population. Pairwise comparisons of continuous variables for placebo versus OCA treatment arms specified for on-treatment visits were conducted using the 2-sided Wilcoxon-Mann-Whitney test at a 5% level of significance.

Again, the reviewer notes that the statistical testing for secondary endpoints was descriptive and exploratory.

Secondary Efficacy Endpoints

1. Absolute and percent changes in serum ALP levels from Baseline to Day 15, Day 29, Day 57, Day 85/ET and Follow-Up (Day 99)
2. Absolute and percent change in serum gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) values from Baseline to Day 15, Day 29, Day 57, Day 85/ET and Follow-Up (Day 99)
3. Absolute and percent changes in serum albumin and conjugated (direct) bilirubin values from Baseline to Day 15, Day 29, Day 57, Day 85/ET and Follow-Up (Day 99)
4. Enhanced liver fibrosis (ELF) score and change in levels of its components, hyaluronic acid, aminoterminal peptide of pro-collagen III, and tissue inhibitor of matrix metalloproteinase-1 from Baseline to Day 85/ET
5. Absolute and percent changes in levels of C-reactive protein, non-esterified fatty acid, tumor necrosis factor alpha, tumor necrosis factor beta, tumor growth factor beta, bile acids, glutathione, immunoglobulin M, and osteopontin from Baseline to Day 85/ET
6. Disease-specific and general health questionnaires:
 - a. SF-36 Quality of Life Questionnaire (QOL): Change from Baseline to Day 85/ET for scale scores and summary measures
 - b. PBC-40 QOL Questionnaire: Change from Baseline to Day 29, Day 57, and Day 85/ET for each of 5 domains
 - c. Bile acid analysis: Absolute and percent changes in the levels of total bile acids and OCA plasma concentrations, and their conjugates, from Baseline to Day 85/ET
7. Absolute and percent change in fibroblast growth factor-19 (FGF-19) levels from Baseline to Day 85/ET

Post-Hoc Efficacy Endpoints Reported in CSR:

1. Absolute and percent changes in the levels of 7 α -hydroxycholest-4-en-3-one (C4) from Baseline to Day 85/ET
2. Percentage of patients who met the disease prognostic risk criteria defined as ALP < 1.67x ULN and total bilirubin \leq ULN, and ALP decrease of \geq 15% from Baseline (i.e., Mayo II plus 15% ALP Reduction)

Safety Endpoints:

1. Treatment-emergent adverse events (TEAEs)
2. Vital sign measurements (body temperature, heart rate, and sitting blood pressure)
3. 12-lead electrocardiograms
4. Physical examination findings
5. Concomitant medications
6. Clinical laboratory assessments

Safety parameters of special interest for OCA were as follows:

- Pruritus-related assessments:
 - Pruritus TEAEs
 - Clinically significant interventions for pruritus
 - Day of onset of first episode of pruritus and resolution time
 - Discontinuations due to pruritus
- Hepatic-related TEAEs
- Cardiovascular-related TEAEs
- Pruritus-specific QOL questionnaires:
 - 5-Dimensional Pruritus Questionnaire: Change from Baseline to Day 15 (measured for a subset of patients), Day 29, Day 57, and Day 85/ET for each of 5 domains and total score
 - Pruritus VAS: Change from Baseline to Day 85/ET

Applicant made a note that pruritus specific assessments, 5-D questionnaire, and VAS were efficacy variables in the SAP. These variables were considered safety variables in the CSR.

Disease Prognostic Risk Criteria

Reviewer Comment: The Applicant utilized the Paris I criteria (Corpechot 2008), Rotterdam (Kuiper 2009), and Mayo II+15%ALP reduction and Mayo risk score for disease prognostic criteria in this protocol.

Protocol Amendments

The original Protocol 747-202, dated 08 Aug 2007 was amended 10 times and had 6 addenda. Most protocol amendments were to address safety monitoring, contraception use, plasma PK level (trough), and bile acid assessments. Few addendums were implemented for changes in LTSE trial: Addendum 4 (dated 13 Nov 2008) which implemented the LTSE phase of the study, Addendum 5 (dated 16 Jun 2009), and Addendum 6 (dated 12 Feb 2010) which amended the LTSE.

Reviewer Comment: The protocol amendments did not impair the performance of the trial or modify the analysis of the data. No significant changes were made to the protocol objectives or to data collection for safety and primary efficacy.

Data Quality and Integrity: Applicant's Assurance

Appropriately organized data sets were provided for efficacy and safety populations. The data quality assurance provided by the Applicant is acceptable to this reviewer.

6.2.2 747-202-Study Results

Compliance with Good Clinical Practices

The applicant stated that the clinical trial was conducted according to globally accepted standards of good clinical practice (as defined in the International Conference on Harmonization E6 Guidance for Good Clinical Practice April 1996; 62 FR 25692, May 9, 1997), in agreement with the latest revision of the Declaration of Helsinki, and the appropriate United States (US) Food and Drug Administration (FDA) Code of Federal Regulations (CFR) as well as other international regulatory agency requirements.

Financial Disclosure

Reviewer Comment: The applicant adequately disclosed financial arrangements involving the clinical investigators. These arrangements do not raise concerns over the integrity of the data.

Trial results:

Table 26: Analysis Population

Analysis Populations ^a	Placebo	OCA 10 mg	OCA 25 mg	OCA 50 mg	Total
Number of Patients, n (%)					
Enrolled (Randomized at Day 0)	38	38	48	41	165
mITT Population	37 (97)	38 (100)	47 (98)	39 (95)	161 (98)
mITT Population (for Sensitivity Analysis of Primary Endpoint) ^b	38 (100)	38 (100)	47 (98)	40 (98)	163 (99)
ITT Population	38 (100)	38 (100)	48 (100)	41 (100)	165 (100)
Completer Population	37 (97)	32 (84)	42 (88)	25 (61)	136 (82)
Safety Population	38 (100)	38 (100)	48 (100)	41 (100)	165 (100)

Source: Copied and electronically reproduced from Applicant submission CSR 747-202 page 56-1652

A total of 136 (82%) patients completed the study. Of the 29 (18%) patients who did not complete the study, the primary reason for study discontinuation was a clinical or laboratory TEAE. Of these 29 patients who discontinued the trial 12 patients were on OCA 50 mg treatment arm. Early discontinuations due to clinical or laboratory TEAEs were primarily due to pruritus. The second most common reason for not completing the study included protocol mandated discontinuation criteria of elevated conjugated (direct) bilirubin (2 patients in OCA 50 mg arm, and 1 patient in OCA 10 mg arm) or elevated AST/ALT levels (1 patient in OCA 50 mg arm). Finally, 2 other discontinuations included withdrawal of consent (1 patient) and lost to follow-up (1 patient).

There was higher discontinuations in the OCA 50 mg dose treatment arm. A total of 61% of patients completed the trial for the duration of 3 months compared with 97% completion in the placebo arm.

Table 27: Patient Disposition: ITT Population (N = 165)

	Placebo (N = 38)	OCA 10 mg (N = 38)	OCA 25 mg (N = 48)	OCA 50 mg (N = 41)	Total (N = 165)
	n (%)	n (%)	n (%)	n (%)	n (%)
Completed Study					
Yes	37 (97)	32 (84)	42 (88)	25 (61)	136 (82)
No	1 (3)	6 (16)	6 (13)	16 (39)	29 (18)
Primary Reason for Discontinuation					

Withdrew Consent	0	0	0	1 (2)	1 (1)
ALT or AST Elevation ^b	0	0	0	1 (2)	1 (1)
Conjugated (Direct) Bilirubin Elevation ^{b,c}	0	1 (3)	0	2 (5)	3 (2)
Discontinued due to Other Clinical or Laboratory TEAE ^d	1 (3)	5 (13)	5 (10)	12 (29)	23 (14)
Discontinuation due to TEAE of Pruritus ^e	0	3 (8)	4 (8)	10 (24) ^f	17 (10)
Lost to Follow-up	0	0	1 (2)	0	1 (1)

Source: Electronically copied and reproduced from Applicant's submission CSR 747-202 page 55-1652

a The percentages for the number of patients not completing the study

b Development of clinical laboratory values during the course of the study that mandated patient discontinuation from the study included the following: Increases in ALT (≥ 3 x average predose value and $>ULN$), AST (≥ 3 x average predose value and $>ULN$), or conjugated (direct) bilirubin (>2 x average predose value and >1.5 mg/dL [25.7 μ mol/L].)

c Includes Patient 32-001-920 (OCA 10 mg arm) who was discontinued due to a TEAE of elevated bilirubin

d Excluding patients who were discontinued due to elevated ALT or AST, or due to elevated conjugated bilirubin

e Included in clinical or laboratory AEs.

f Does not include Patient 3-016-667 who was discontinued due to an SAE of Jaundice and also due to a TEAE of Pruritus

Protocol Violations/Deviations

In total, there were 296 protocol deviations. Waivers were granted for 83 protocol deviations; most protocol deviations were minor and did not affect the safety and efficacy of trial.

The majority of patients (n = 58) had a protocol deviation of investigational product accountability. The more relevant deviations included 38 related to inclusion/exclusion criteria. There were 4 deviations related to UDCA dose changes: 1 patient had started UDCA in 1994 with the UDCA dose raised from 900 mg/d to 1200 mg/d in 2008; 1 patient had their dose increased from 500 mg to 750 mg approximately 2 weeks prior to screening; UDCA dose was not stable for 1 patient; and 1 patient started UDCA dose <6 months (i.e., 12 days) before the first dose of investigational drug. One patient had a deviation in the category of concomitant medications. The patient's primary care physician had started the patient on the medication Lipitor without the investigator's knowledge. There were 3 deviations related to mandatory discontinuation criteria of elevated ALT, AST or conjugated bilirubin.

Reviewer Comment: Overall, the protocol deviations were determined not to have interfered with efficacy or safety assessments. Three patients had AST/ALT elevations observed on day 57 (placebo arm), day 15 (OCA 10 mg arm) and day 15 (OCA 50 mg arm) which all returned to baseline on continued treatment. These patients were granted waivers and continued in the treatment trial. This reviewer read the associated patient narratives and these waivers are considered acceptable. Inclusion of these patients does not affect the overall trial efficacy and safety assessment, as these patients remained stable during and after the trial completion i.e., did not have any hepatic decompensation events. Furthermore these laboratory values were transient elevations and normalized spontaneously without changes in OCA treatment.

Demographics:

The demographic characteristics, including sex, ethnicity, and age variables were well balanced across treatment arms. The majority of patients were female (95%) and white (96%), as expected in PBC. The mean age was 55.1 years and the mean BMI was 27.2 kg/m².

Baseline Disease Characteristics:

Table 28: Disease Severity Criteria: ITT Population (N = 165)

Disease Severity Criteria	Placebo (n = 38)	OCA 10 mg (n = 38)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)	Total (N = 165)
Number of Patients					
Paris I Criteria^a	n (%)	n (%)	n (%)	n (%)	n (%)
ALP \leq 3x ULN or AST \leq 2x ULN or total bilirubin \leq 1 mg/dL	37 (97)	38 (100)	46 (96)	40 (98)	161 (98)
ALP $>$ 3x ULN or AST $>$ 2x ULN or total bilirubin $>$ 1 mg/dL	1 (3)	0 (0)	2 (4)	1 (2)	4 (2)

Source: Copied and electronically reproduced from the Applicant submission: CSR 747-202 page 59 of 1652

Reviewer Comment: According to the Paris I criteria only 4% patients in trial were above the specified threshold as noted in the Table 31. Across the three treatment arms, the vast majority of the patients enrolled in the trial were in the early stage of disease by the Rotterdam criteria. There are slightly less numbers of patients in placebo arm with moderately advanced stage disease in comparison to OCA treatment arms.

Table 29: Disease Severity Criteria

Rotterdam Criteria	Placebo (N=38)	OCA 10 mg (N=38)	OCA 25 mg (N=48)	OCA 50 mg (N=41)
Early Disease: Normal Albumin, Normal Total Bilirubin, Elevated ALP	35 (92%)	29 (76%)	39 (81%)	34 (83%)
Moderately Advanced Disease: Either Low Albumin or High Total Bilirubin	3 (8%)	8 (21%)	7 (15%)	7 (17%)
Patients with Low Albumin	0	2 (25%)	3 (43%)	0
Patients with High Total Bilirubin	3 (100%)	6 (75%)	4 (57%)	7 (100%)
Advanced Disease: Both Low Albumin and High Total Bilirubin	0	1 (3%)	2 (4%)	0

Source: Copied and electronically reproduced from the Applicant submission; eTCD Sequence 0057 (58) 3-21-2016

- Total Bilirubin (TB) ULN 19.32 μ mol/L (females), 25.48 μ mol/L (males)
- Albumin LLN 35 g/L (females and males).

Baseline Liver Parameters

Table 30: Baseline Liver Parameters in Patients Enrolled to Trial 747-202

	Placebo (N = 38)	OCA 10 mg (N = 38)	OCA 25 mg (N = 48)	OCA 50 mg (N = 41)	Analyte Normal Range (or ULN)
ALP (U/L)					\leq 117 UL (females), \leq 129 U/L (males)
N	38	38	48	41	
Mean (SD)	275.2 (102.7)	294.4 (149.4)	290.0 (123.6)	289.5 (106.2)	
Median	249.5	234.8	255.8	262.5	
Min, Max	166, 599	163.5, 916.5	169, 882.5	167, 590.5	

Conjugated (Direct) Bilirubin (µmol/L)					≤7 µmol/L
N	38	38	48	41	
Mean (SD)	3.6 (2.8)	4.2 (3.1)	3.9 (2.4)	4.7 (3.3)	
Median	2.6	3.4	3.4	4.3	
Min, Max	1.7, 15.4	0.9, 13.7	0.9, 10.8	1.7, 16.3	
GGT (U/L)					≤50 U/L (Female), ≤73 U/L (Male)
N	38	38	48	41	
Mean (SD)	189 (139)	228 (212)	273 (267)	231 (182)	
Median	142	154	177	178	
Min, Max	22, 542	35, 859	32, 1408	12, 889	

Source: Copied and electronically reproduced from Applicant's submission CSR 747-202 page 61 of 1652

Reviewer Comment: The mean baseline ALP values were 2.4x to 2.5x ULN. Baseline ALP values were similar across all treatment arms.

There were 3 patients with conjugated (direct) bilirubin levels >2x ULN who were included in the study: Patients 1-006-607 (placebo), 1-002-606 (OCA 50 mg arm), and 7-006-621 (OCA 50 mg arm) had screening conjugated (direct) bilirubin levels of 15.4 µmol/L, 16.25 µmol/L, and 14.55 µmol/L, respectively. The total bilirubin data is not shown here, however, TB was normal in the majority of patients, with abnormal baseline TB levels observed in 20 patients out of 165 enrolled patients. Mean baseline GGT levels were slightly higher in the OCA treatment arms compared to placebo. GGT levels ranged from 3.8 X to 5.5 ULN as noted in Table 3.2.

Mean serum transaminase (ALT and AST) levels were less than ULN across treatment arms. Mean albumin levels were within the normal range across all treatment arms, except for 3 patients who had albumin <35 g/L. In addition, the baseline international ratio (INR) and partial thromboplastin time parameters were within normal range in all patients. All these parameters were similar across all treatment arms.

PBC diagnosis parameters were also similar across all treatment arms:

1. Approximately 96% of the patients had a history of increased ALP,
2. 81% of the patients had positive AMA titer, and
3. Approximately 88% of the patients presented with liver biopsy results consistent with PBC disease.

Reviewer Comment: Overall, 65% of the study population had a proven diagnosis of PBC (met all 3 diagnostic criteria), and remaining 35% had likely diagnosis of PBC (met 2 of 3 diagnosis criteria). About 40% of patients had PBC diagnosis for ≥7.5 years, the remaining 60% had a diagnosis of PBC for >7.5 years. Although this information is useful, it truly does not reflect the actual duration of disease because the diagnosis is not only dependent on patient's presentation to medical system. Some patients may have disease for a long time prior to initial presentation to a physician or prior to an accurate diagnosis.

The past medical histories reflected the underlying disease and were generally similar across treatment arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Patient compliance was assessed at each visit and confirmed by drug accountability (i.e., counting of returned capsules). Compliance was similar across treatment arms and for each study visit. Mean investigational product compliance was 99.6%, 98.3%, and 96.9% for Day 29, Day 57, and 85/ET respectively.

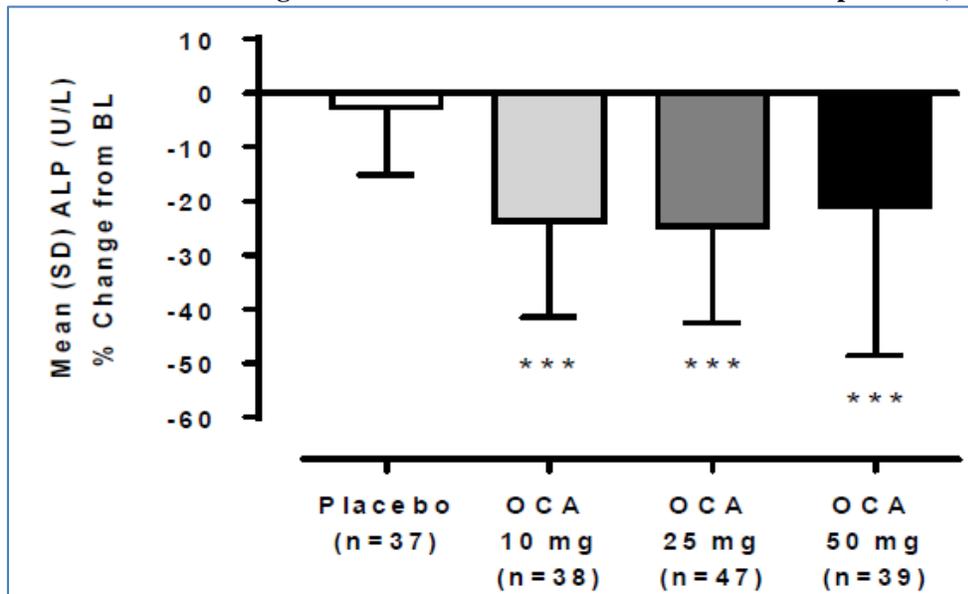
Concomitant medications included bile acid sequestrants (36%), calcium supplements (36%), multivitamins - plain (32%), vitamin D and analogues (30%), and proton pump inhibitors (25%). The number of patients taking these medications was similar between treatment arms.

At study entry, patients were on a stable dose of UDCA for at least 6 months entry as per the inclusion criteria except 4 patients in whom the UDCA dose was changed. Mean daily UDCA use at study entry was similar (approximately 15 to 16 mg/kg) across treatment arms.

6.2.2.1.1 Efficacy Results - Primary Endpoint

The primary efficacy endpoint was measured by the percent change (%) in serum ALP from baseline to EOS in the mITT population.

Table 31: Percent Change in ALP Levels from Baseline to EOS: mITT Population (N = 161)



Source: Copied and electronically reproduced from CSR 747-202 page 69-1652

p-value compares OCA treatment arms to placebo on the change from Baseline to Day 85/ET using Wilcoxon- Mann-Whitney test. p-value indicated in the figure is ***p < 0.0001.

Table 32: 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

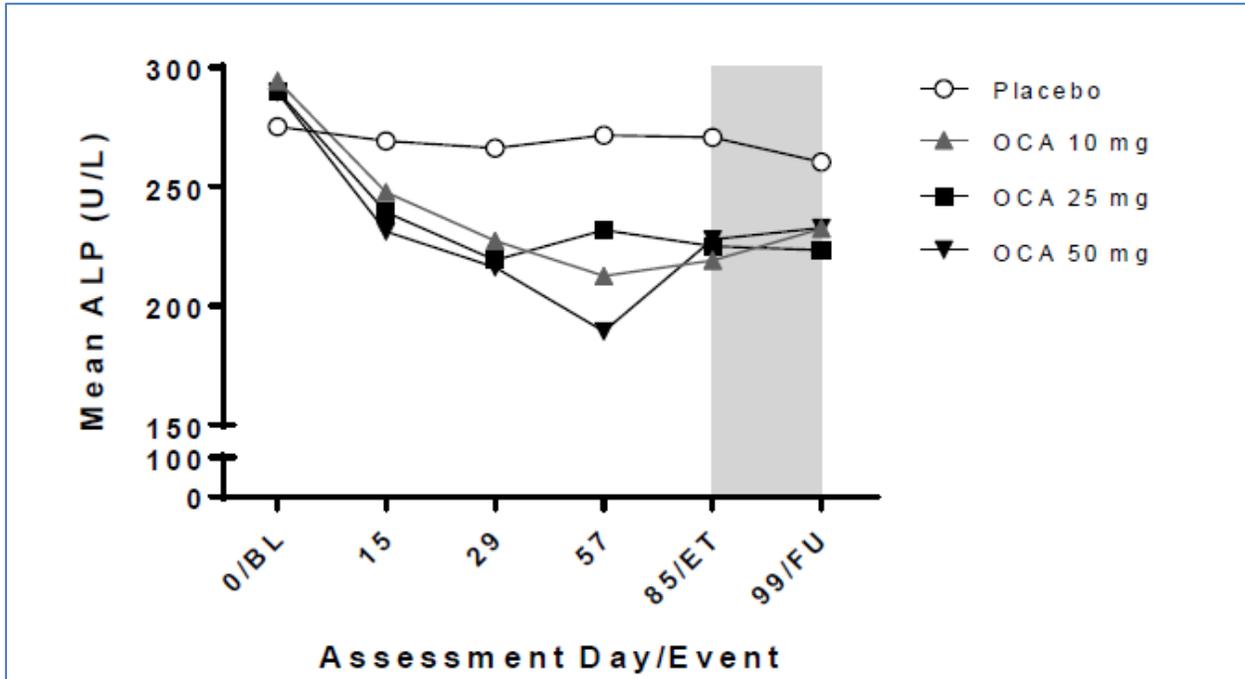
Source: CSR 747-202 page 69-1652

***p-value compares OCA treatment arms to placebo on the change from Baseline to Day 85/ET using Wilcoxon-Mann-Whitney test.

Reviewer Comment: The ALP mean percent reduction was seen at all OCA doses, relative to placebo and the mean percent reduction was generally similar across all OCA dose arms and was statistically significant compared to placebo. Doses higher than 10mg do not provide further ALP reduction. Therefore, the Applicant choose OCA 10 mg dose for the marketing approval trial, which seemed to be the lowest and most effective dose.

Secondary endpoint: *All statistical testing presented now on for this trial are descriptive and exploratory. The following analyses support the primary endpoint results.*

Table 33: ALP Levels from Baseline to Day 99/Follow-Up: ITT Population (N = 165)



Source: Copied and electronically reproduced from Applicant submission 747-202 CSR page 74-1652

The effect of OCA treatment on ALP serum levels was observed at week 2; the response was durable for the trial duration.

Responder and Sub group Analyses of ALP Response:

Patients who achieved normalization of ALP at month 3

- One (3%) patient in the OCA 10 mg arm
- Four (9%) patients in the OCA 25 mg arm,
- Two (5%) patients in the OCA 50 mg arm,
- Zero (0) in placebo arm.

Table 34: Percent ALP reduction from baseline to month 3

Criteria (% ALP Reduction from Baseline)	Patients Meeting Response Criteria			
	Placebo (n = 37)	OCA 10 mg (n = 38)	OCA 25 mg (n = 47)	OCA 50 mg (n = 39)
	n (%)	n (%)	n (%)	n (%)
10%	5 (14)	29 (76)	40 (85)	29 (74)
20%	3 (8)	23 (61)	30 (64)	22 (56)

40%	0 (0)	8 (21)	7 (15)	10 (26)
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Source: Adapted from the CSR 747-202 page 77-1652

Reviewer Comment: The percentage of patients at month 3 who achieved percent ALP reduction is shown in the table above. These analyses support the primary endpoint results. A 40% reduction in ALP is seen in 0%, 21%, 15% and 26% of patients in the placebo, OCA 10 mg, 25 mg and 50 mg arms respectively. These results highlight a plateau at 10 mg dose of the dose exposure response. Therefore, there is no benefit in increasing the OCA dose above 10 mg.

A post-hoc analysis was performed to determine the percentage of patients who achieved the criteria based on the ALP and bilirubin levels (ALP < 1.67x ULN and bilirubin ≤ ULN and ALP ≥ 15% reduction). Consistent with the primary endpoint of the phase 3 study 747-301, an ALP reduction of > 15% from baseline was added to exclude clinically insignificant ALP changes. This composite criterion is referred to as Mayo II prognostic risk criteria plus 15% ALP endpoint in this report.

Table 35: Percentage of Patients who achieved Mayo II plus ≥15% ALP Reduction

Criteria	Placebo (n = 38)	OCA 10 mg (n = 38)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)
	n (%) ^a	n (%) ^a	n (%) ^a	n (%) ^a
Patients meeting baseline criteria (N) ^a	32 (84)	30 (79)	39 (81)	35 (85)
Patients meeting responder criteria ^b	3 (9)	12 (40)	17 (44)	14 (40)

Source: Copied and electronically reproduced from Applicant Submission 747-201 page 78-1652

a The baseline criteria was defined as follows: ALP ≥ 1.67x ULN or total bilirubin > ULN.

b A responder is defined as follows: ALP < 1.67x ULN and ≥15% reduction in ALP and total bilirubin ≤ ULN. Patients with missing values are considered non-responders.

Reviewer Comment: In this post hoc analyses, similar number of patients (approximately 40%) treated with OCA achieved the composite endpoint at Day 85/EOS compared to 9% of the placebo-treated patients.

Sub-group Analysis of ALP Response

- Sex (male versus female) and Age: both male (n = 8) and female (n = 153) subpopulations ALP showed reductions in ALP levels with OCA compared to placebo.
However, the sample size is very small limiting interpretation of results. In patients >65 years the sample size was too small for reasonable interpretation.
- Years since PBC Diagnosis (<7.5 years versus ≥7.5 years):
The Applicant utilized a 7.5 year cutoff for PBC disease duration. This particular threshold appears to have been an arbitrary choice, as there are many factors that come into play for PBC duration such as the fact that some patients on presentation already have progressed to cirrhosis, therefore analysis of PBC duration was not considered as a major contributor of mortality for the purposes of this review.
- Pruritus (discontinuations versus completers): Sixteen out of 165 patients who withdrew due to pruritus provided ALP measurements at baseline and EOS. The number of patients who discontinued is as follows: patients in the OCA 10 mg (n = 3) and OCA 25 mg (n = 3) arms versus OCA 50 mg (n = 10) arm.
There is a dose dependent increase in the pruritus as well as severe pruritus resulting discontinuations.
- ALP >2.25 X ULN versus ≤2.25 X ULN:

The Applicant further divided ALP reduction in population on the basis of ALP > 2.25 X ULN versus ≤ 2.25 X ULN. This cutoff was derived based on the enrollment population. The Applicant concluded ALP reduction in the sub-arm with higher baseline ALP (> 2.25x ULN) was greater than those with baseline ALP ≤ 2.25x ULN. This is important and was also seen in the phase 3 trial (747-30)1, OCA performance appeared to be reduced as the ALP increased i.e., when ALP > 3 x ULN the number of patients who achieved primary endpoint decreased.

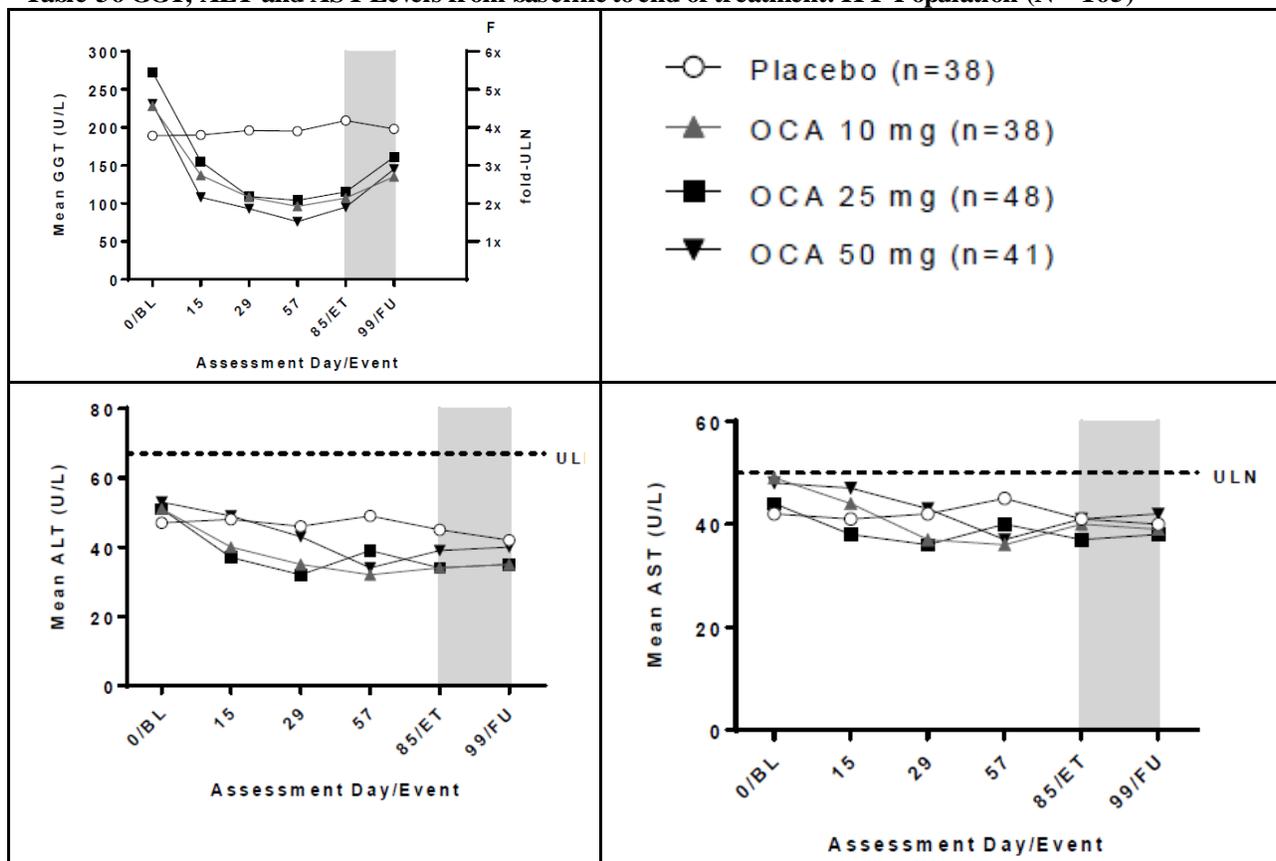
Liver Biochemical tests:

GGT, ALT and AST are liver biochemical tests that are elevated in PBC.

Reviewer Comment:

GGT The baseline GGT was approximately 2.6 X to 5.5 X ULN across all four treatment arms, and was slightly higher in OCA treatment arms. GGT levels decreased significantly in all OCA treated patients (nominal p < 0.0001) in comparison to placebo

Table 36 GGT, ALT and AST Levels from baseline to end of treatment: ITT Population (N = 165)



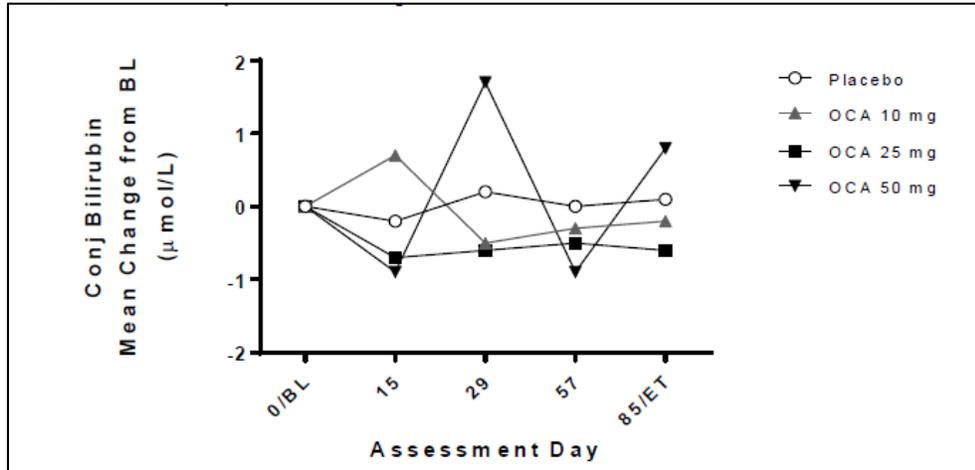
Source: Adapted and electronically reproduced from the Clinical Study Report 747-202 (page 82 and 83)

The ULN indicated in the figure are:
 GGT 73 U/L and 50 U/L (reference ranges for male and female populations)
 AST ≤ 50 U/L and ALT ≤ 67 U/L

Reviewer Comment: Reductions in ALT/AST: Given the ALT and AST were within normal reference ranges at baseline, the significance of reductions and potential related benefits are unknown. Although, the Applicant stated that ALT and AST changes from baseline and Day 85/ET were statistically significant, the absolute changes were very small and contributions to these changes came from reductions in a few patients. This reviewer also notes that natural variability in ALT and AST can be seen and it is currently unknown whether small reductions in ALT and AST are clinically meaningful. Dose related reductions were not seen in any of the treatment arms.

The conjugated bilirubin levels were within normal range ($\leq 7.0 \mu\text{mol/L}$) at baseline in the majority of patients at all post-dose time points for all treatment arms.

Table 37: Mean Change in Conjugated Bilirubin Levels from Baseline to Day 85/ET: ITT Population (N = 165)



Source: Copied and electronically reproduced from the Clinical Study Report 747-202 page 86 of 1652

Reviewer Comments: Patients who were dosed with OCA 50 mg had fluctuations in conjugated bilirubin (CB) with particularly an overall increase of CB. Patients dosed with OCA 50 mg appeared negatively impacted, in that their CB increased in just 3 months duration. Although, with OCA 10 mg use patients had reductions in CB of $1 \mu\text{mol/L}$ (0.06 mg/dL), the CB levels increased to pre-treatment baseline values at 2 months, therefore the reductions in CB were not sustained and do not appear durable.

Total Bilirubin: The total bilirubin data were not provided in the summary of the original clinical study report, but since most of the previously published data described TB and not CB, the reviewer requested additional analyses from the Applicant to better understand the effects of OCA treatment on TB.

Table 38: Mean total bilirubin ($\mu\text{mol/L}$) by treatment arm

Time point	Mean TB in ($\mu\text{mol/L}$) Trial 747-202			
	Placebo	10 mg	25 mg	50 mg
Baseline (a)	11.84	13.61	11.97	13.55
Day 85/EOS (b)	12.42	12.20	11.03	14.32
Change from Baseline at Day 85/EOS (b)	0.58	-1.41	-0.94	0.60

Source: Applicant's submission to NDA Serial 0056 (57)

^a Baseline is the average of all visit values prior to first dose in double-blind phase. If results from only one evaluation are available, the available data from this evaluation is used as the baseline value.

^b EOS = End of Study

Table 39: Change from Baseline in Total Bilirubin, Alkaline Phosphatase, and Albumin in Patients with Elevated Total Bilirubin at Baseline compared to End of Treatment

		Baseline (a)			Day 85/ET			Change from Baseline (a)		
Treatment Arm	Patient ID	TB (µmol/L)	ALP (U/L)	Alb (g/L)	TB (µmol/L)	ALP (U/L)	Alb (g/L)	TB (µmol/L)	ALP (U/L)	Alb (g/L)
Placebo	001006	27.37 H	398.5 H		35.90 H	386.0 H		8.53	-12.5	
	012012	22.20 H	506.0 H		23.90 H	523.0 H		1.70	17.0	
	019001	23.05 H	599.0 H		25.60 H	687.0 H		2.55	88.0	
10 mg OCA	003015	25.60 H	350.0 H		30.80 H	288.0 H		5.20	-62.0	
	003017	32.50 H	374.0 H		29.10 H	329.0 H		-3.40	-45.0	
	011002	23.90 H	224.5 H		20.50 H	219.0 H		-3.40	-5.5	
	015013	19.65 H	421.5 H		18.80	390.0 H		-0.85	-31.5	
	019007	34.20 H	207.0 H		34.20 H	165.0 H		0.00	-42.0	
	026003	22.20 H	916.5 H		9.10	748.0 H		-13.10	-168.5	
	032001	27.80 H	216.5 H	19.95 L	39.20 H	235.0 H	24.55 L	11.40	18.5	4.6
25 mg OCA	004012	23.05 H	232.5 H	34 L	20.50 H	224.0 H	32 L	-2.55	-8.5	-2
	004015	19.65 H	554.5 H		18.80	275.0 H		-0.85	-279.5	
	011007	21.35 H	466.0 H		37.60 H	335.0 H		16.25	-131.0	
	012007	23.95 H	210.5 H	34 L	15.40	231.0 H	33 L	-8.55	20.5	-1
	018012	21.35 H	882.5 H		23.90 H	1295.0 H		2.55	412.5	
	032002	19.35 H	305.5 H		18.00	265.0 H		-1.35	-40.5	
50 mg OCA	001002	35.05 H	447.0 H		23.90 H	576.0 H		-11.15	129.0	
	002003	23.05 H	317.0 H		15.40	116.0		-7.65	-201.0	
	003005	20.50 H	193.0 H		17.10	209.0 H		-3.40	16.0	
	003019	20.50 H	271.0 H		20.50 H	223.0 H		0.00	-48.0	
	004011	24.80 H	394.0 H		61.60 H	666.0 H		36.80	272.0	
	007006	26.50 H	428.0 H		23.90 H	303.0 H		-2.60	-125.0	
	040004	21.80 H	226.0 H		21.00 H	188.0 H		-0.80	-38.0	

Source: Applicant submission to NDA Serial 0056 (57)

^a Baseline is the average of all visit values prior to first dose in double-blind phase. If results from only one evaluation are available, the available data from this evaluation is used as the baseline value.

Reviewer Comment: If the TB was elevated, the majority of patients enrolled in OCA treatment arms had decreases in TB, even though decrements were small. As noted in Table 41 with baseline low albumin continued to have low albumin at the end of month 3. There was a slight change (increase or decrease) but no clear trends observed.

Table 40: Changes in Mean HDLc (mg/dL) from Baseline to End of Study

	OCA 10 mg (N = 38)	OCA 25 mg (N = 48)	OCA 50 mg (N = 41)	Placebo (N = 38)
Mean HDLc (mg/dL)				
Baseline	67.6	71.5	75.4	69.9
Day 85	58	61.4	58	73.7
Change at month 3	-10	-10	-17	+4

Source: Reviewer generated from the data submitted by Applicant; the lab values were converted to mg/dL from mmol/L, the lower limit of normal (LLN) was 40 mg/dl or ≥ 0.91 mmol/L

Reviewer Comment: One of the worrisome safety findings observed was HDLc reduction with the use of OCA. A 10 to 17 point reduction in mean HDLc was noted in the OCA 10 mg, 25 mg and 50 mg arms compared with a smaller but positive change in HDL within the placebo arm. The effect of HDLc lowering on the cardiac outcomes in PBC patients are unknown at this time.

Hepatobiliary Inflammation/Injury Biomarkers

IgM:

IgM levels are elevated in PBC. At baseline, mean IgM levels were approximately 1.3-fold to 1.9-fold higher than the normal range (0.4 g/L to 2.3 g/L) in the various treatment arms. There was a decline observed in IgM levels across all OCA treatment arms, although neither arm achieved normalization.

Table 41: IgM Levels from Baseline to Day 85/ET: IIT Population (N = 165)

	Placebo (n = 38)	OCA 10 mg (n = 38)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)
IgM (g/L)				
n at Baseline and Day 85/ET	32, 33	35, 29	41, 38	35, 31
Baseline (Mean [SD])	3.06 (1.73)	4.31 (2.12)	3.13 (1.95)	3.82 (3.35)
Baseline (Median)	2.56	3.89	2.62	3.20
Day 85/ET (Mean [SD])	2.97 (1.61)	3.73 (1.91)	2.62 (1.76)	3.02 (2.14)
Day 85/ET (Median)	2.58	3.49	2.25	2.66
Mean (SD) Change	0.02 (0.61)	-0.71 (0.94)	-0.58 (0.75)	-0.95 (1.57)
Median Change	0.01	-0.58	-0.39	-0.60

Source: Copied and electronically reproduced from the CSR 747-202 page 87-1652

Reviewer Comment: There was a trend toward reduction in IgM in OCA treated patients relative to placebo; however, none of the OCA treated patients achieved normalization of IgM. A downward trend in IgM levels supports the primary efficacy endpoint.

C - reactive protein (CRP)

CRP is a marker of acute inflammation, and is secreted by liver. Although there was a large degree of baseline variability in the CRP levels across treatment arms, there was not much change from baseline to day 85. The mean

CRP value was 7.9 at baseline which decreased to 6.4 mg/dL by day 85, the nominal p-value was not significant. The upper limit of normal for CRP is <3 mg/dL.

Reviewer Comment: CRP is nonspecific marker of inflammation and rises in any inflammatory condition. The change observed in CRP may support the primary endpoint.

Liver Fibrosis

ELF score is an exploratory marker for assessing fibrosis due to chronic liver disease and a composite derived from 3 serum markers: HA, P3NP, and TIMP-1. ELF scores for fibrosis range from 7.7 to ≥ 11.3 . A score of <7.7 suggests no or mild fibrosis, while a score of ≥ 7.0 to 9.8 suggests moderate fibrosis, and scores of >9.8 to <11.3 and ≥ 11.3 suggest high fibrosis and cirrhosis; respectively.

There was no change observed in the ELF scores from Baseline to Day 85 across treatment arms.

Disease Specific and General Health Questionnaires assessments were used during the trial. Using the SF-36, no consistent patterns for dose-response relationships were observed in the scores for any domain. The PBC-40 is a quality of life questionnaire, which consists of 5 domains: general symptoms, itch, fatigue, cognitive function, emotional/social. In general, all OCA treated patients experienced fatigue relative to placebo treated arm in whom the incidence of fatigue was lower. There were observed increases in itch score which were generally correlated with OCA dose and statistically significant higher in all OCA treatment arms at Day 85/ET compared to placebo.

Bile acids

Serum bile acids were measured as individual bile acids (sum of conjugated and unconjugated forms). (CA = cholic acid; CDCA = chenodeoxycholic acid; DCA = deoxycholic acid; LCA = lithocholic acid; UDCA = ursodeoxycholic acid).

The median level of total bile acids at baseline ranged from 12.415 $\mu\text{mol/L}$ to 27.102 $\mu\text{mol/L}$ in the four treatment arms. The median change in the levels of bile acids was seen across all treatment arms relative to placebo arm; there was a large variation in levels between patients. A mean total endogenous bile acids were decreased by 1.75 $\mu\text{mol/L}$ in OCA 10 mg treatment group and 4.07 $\mu\text{mol/L}$ in OCA 25 mg treatment groups however, increased by 7.89 $\mu\text{mol/L}$ in patients treated with OCA 50 mg and 2.44 $\mu\text{mol/L}$ in placebo group.

A median change (reduction) from baseline to Day 85/ET was observed for CDCA, DCA, and CA levels in the OCA treatment arms compared to placebo arm. Reductions of LCA level were not seen in placebo, OCA 10 mg, OCA 50 mg arms but a minimal reduction was observed in the OCA 25 mg treatment arm.

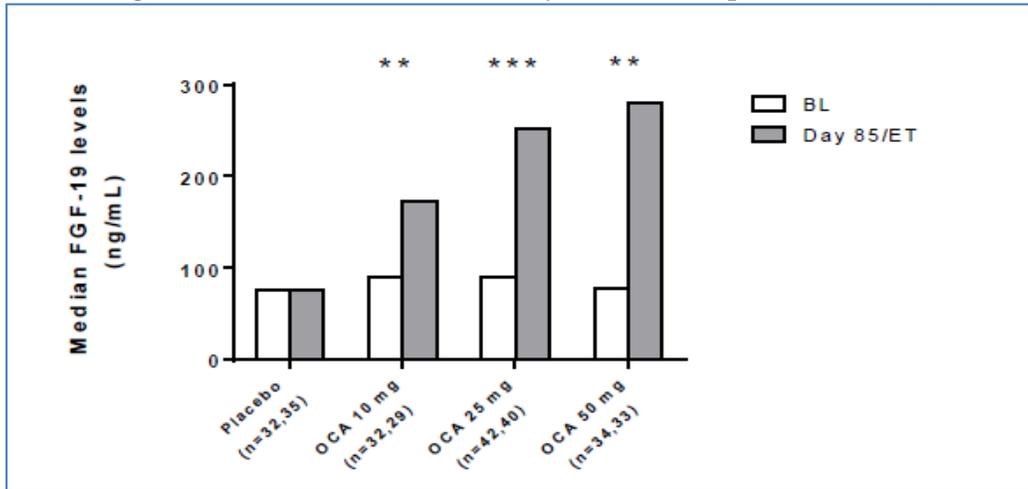
A dose-response relationship was observed from the median decrease in the total DCA levels, with greater decreases in the OCA 50 mg arm compared to the OCA 10 mg or OCA 25 mg arms. Total LCA did not decrease in the OCA 10 mg and OCA 50 mg arms, but decreased in the OCA 25 mg arms. The 6-ethyl-CDCA (OCA) was the only level that increased in the OCA treatment arms.

Reviewer Comment: In summary, there were decreases in total CDCA, CA and DCA levels with OCA treatment. LCA levels did not decrease, LCA remained stable and did not increase with OCA use and this is important to note because LCA is the toxic bile acid and its increase would have been concerning.

FGF-19 and C4 levels:

FGF-19: A dose related increase in serum FGF-19 levels was seen with FXR activation of OCA. Compared to baseline, median FGF-19 levels at Day 85/ET a dose-response reduction in FGF-19 was noted. There was no change in the median levels of FGF-19 in the placebo arm.

Figure 20: FGF-19 at Baseline and Day 85/ET: ITT Population (N = 165)

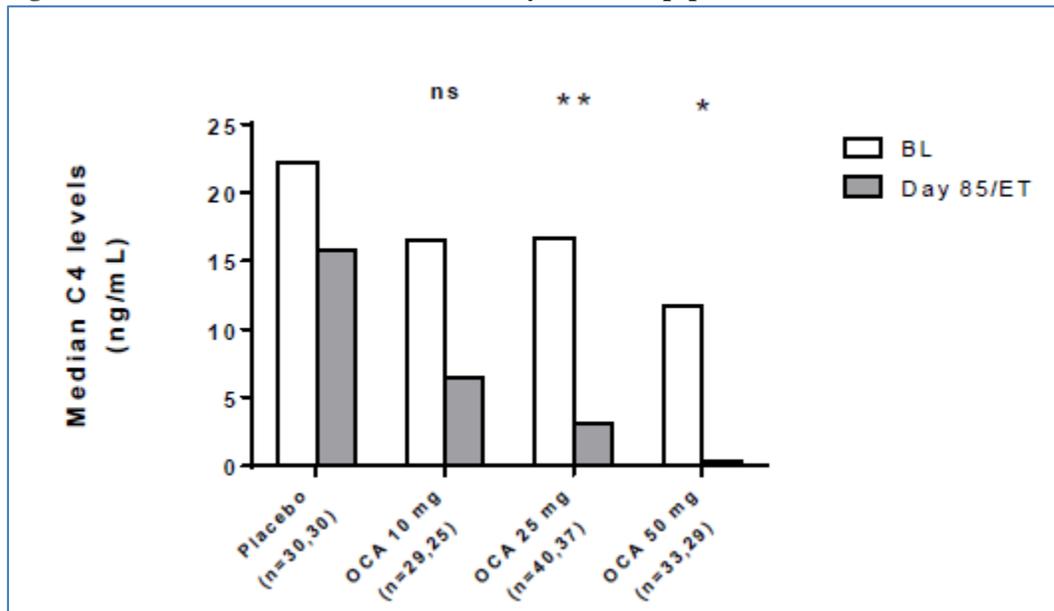


Source: Copied and electronically reproduced from the CSR 747-202 page 101/1652

The OCA treated patients had increase in FGF-19. This pharmaco-dynamic effect is dose dependent.

C4 (7 α -hydroxycholest 4-en-3-one) is a bile acid precursor. Serum levels of C4 were elevated at baseline with the median levels ranging from 11.7 ng/mL to 22.2 ng/mL across the 4 treatment arms.

Figure 21: Median C4 level at baseline and Day 85 in ITT population



Source: Copied and electronically reproduced CSR 747-202, page 101-1652

The number of patients (n) in X-axis labels represent the number of patients at baseline and at Day 85/ET, respectively. P-value compares OCA treatment arms to placebo on the change from Baseline to Day 85/ET using Wilcoxon-Mann-Whitney test. P-values are indicated in the figure as follows: ***p < 0.0001, **p < 0.01, *p < 0.05, ns = p \geq 0.05

Reviewer Comment: The C4 reductions seen in OCA 25 mg and OCA 50 mg treatment arms were statistically significant relative to placebo. Although the reduction in C4 was not statistically significant in OCA 10 mg arm, there was a trend towards reduction of C4.

Efficacy Conclusions

The effects of OCA (10 mg, 25 mg, or 50 mg dose) in PBC patients who had inadequate biochemical response to UDCA were assessed in this phase 2, placebo-controlled study.

1. The mean percent change in ALP levels with OCA, the primary efficacy endpoint of this study, was statistically significant for all three doses of OCA compared to placebo. The mean percent changes were as follows: -3.2% in placebo, -23.7 in OCA 10 mg arm, -24.9 in OCA 25 mg arm and -20.5 in the OCA 50 mg treatment arms. Doses greater than 10 mg were not more efficacious in reducing ALP.
2. Secondary/exploratory analyses: 40% ALP reduction was achieved by 8 out of 38 patients dosed with OCA 10 mg; 7 out of 47 patients dosed with OCA 25 mg; 10 out of 39 patients dosed with OCA 50 mg.
3. The OCA 10 mg dose was equally as efficacious as OCA 25 mg and 50 mg doses. A dose exposure higher than OCA 10 mg did not provide any further reduction in ALP. This is very important to note.
4. The secondary/exploratory efficacy endpoints, including GGT, significantly improved with OCA treatment. GGT is a marker of cholestasis and GGT reduction supports the primary efficacy endpoint. However, both the ALT and AST remained within normal range, and therefore the overall significance of changes is not clear.
5. Conjugated bilirubin were in normal reference range in the majority of patients, and very small mean CB changes were seen 0.2 µmol/L to 0.6 µmol/L (0.01 mg/dL to 0.03 mg/dL) at month 3 in OCA 10 mg and OCA 25 mg treatment arms. Meaningfulness of small changes oscillating within the normal reference range is unknown. Additionally, when CB was analyzed as a continuous variable, there were fluctuations and the response was not sustained in patients. Conversely, CB increased in the OCA 50 mg treatment arm.
6. Post hoc analyses: Since the overwhelming majority of patients had normal TB at the beginning of the trial, the main driving factor of the composite endpoint was ALP reduction. Treatment with OCA resulted in a significantly higher percentage of patients meeting the composite ALP and bilirubin criteria (as defined by Mayo II prognostic risk criteria plus 15% ALP reduction) compared to placebo. Overall, 41% of the OCA-treated patients achieved the composite endpoint at end of treatment compared to 9% of the placebo-treated patients; OCA 10 mg dose was maximally efficacious.
7. Reductions in IgM were also observed in OCA treated arms, and this finding is supportive of the primary efficacy endpoint.
8. No dose-response relationship was observed for the primary and majority of the secondary efficacy endpoints.
9. FXR activation by OCA was evident as shown by dose-dependent increases in FGF-19, in all the OCA treatment arms, and a statistically significant decreased in C4 was observed with OCA 25 mg and 50 mg dose, although not statistically significant reduction, a downward trend for C4 was observed for OCA 10 mg.

6.2.2.1.2 Review of the Safety Database for 747-202

Overall Exposure:

Table 42: Duration of Investigational Product Exposure: Safety Population (N = 165)

	Placebo (N = 38)	OCA 10 mg (N = 38)	OCA 25 mg (N = 48)	OCA 50 mg (N = 41)
Number of Days on Investigational Product				
N	38	38	48	41
Mean (SD)	82.7 (14.4)	74.9 (21.8)	76.8 (21.4)	58.5 (36.0)
Median	85.0	83.0	84.0	84.0
Min, Max	3.0, 93.0	13.0, 98.0	8.0, 92.0	3.0, 107.0

Source: Copied and electronically reproduced CSR 747-202, page 103-1652

Reviewer's Comment: It is not clear why some patients in this trial were on the investigational product (IP) for 92 days to 107 days of maximum duration of use. This is an 85 day trial; therefore all patients should either discontinue treatment at day 85 or at 2 weeks follow up post treatment discontinuation. One possible explanation is if treatment interruption or alternate day regimen led to increase in number of days on the IP, however, the Applicant did not clarify this in the CSR.

Relevant characteristics of the safety population: All patients had PBC and were on UDCA concomitantly.

ADVERSE EVENTS:

Applicant utilized MedDRA Version 12.1 was used to code verbatim AE terms recorded on the CRFs. Pretreatment AEs were collected as medical history. A TEAE was defined as any AE that was an unfavorable or unintended sign, symptoms, or disease temporally associated with the use of the study medication, whether or not considered related to the investigational product. For analyses by relationship, if the same TEAE (based on preferred term) was reported for the same patient more than once, the TEAE is counted only once for that preferred term and at the strongest relationship to investigational product. Related TEAEs were defined as those with a possible or probable relationship to investigational product based on the Investigator's assessment. For analyses by severity, the worse severity of any TEAE for each patient was used. A patient could be counted in more than 1 severity category. All TEAE summaries used the Safety Analysis Population.

Adequacy of the safety database: The review found the safety data base to adequate.

Table 43: Summary of TEAEs by Treatment Arm: Safety Population (N = 165)

	Treatment Group			
	Placebo (n = 38)	OCA 10 mg (n = 38)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)
	Patients (%)	Patients (%)	Patients (%)	Patients (%)
Patients reporting at least 1 TEAE	32 (84)	34 (89)	47 (98)	41 (100)

Source: Electronically copied and reproduced from CSR 747-202 page 105-1652

Table: Continued: Summary of TEAEs by Treatment Arm: Safety Population (N = 165)

	Treatment Group			
	Placebo (n = 38)	OCA 10 mg (n = 38)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)
Patients with related TEAE ^a	22 (58)	28 (74)	45 (94)	38 (93)
Related TEAEs of pruritus	17 (45)	18 (47)	39 (81)	33 (80)
Related TEAEs of pruritus generalized	0 (0)	0 (0)	1 (2)	0 (0)
Mild	31 (82)	25 (66)	35 (73)	27 (66)
Moderate	15 (39)	17 (45)	26 (54)	28 (68)
Severe	3 (8)	6 (16)	10 (21)	18 (44)
Patients with SAE	1 (3)	0 (0)	1 (2)	5 (12)
Patients who Discontinued Due to Other Clinical or Laboratory AE ^c	1 (3)	6 (16) ^d	5 (10)	15 (37) ^e

Subset of patients who Discontinued Due to Pruritus	0	3 (8)	4 (8)	10(24) ^f
Patients Meeting Mandatory Discontinuation Criteria ^g	1 (3) ^h	1 (3) ^h	0	3 (7)
Deaths	0	0	0	0

Source: Electronically copied and reproduced from CSR 747-202 page 105-1652

a Related AEs were considered to have a possible or probable relationship to treatment

b The worst severity of any TEAE for each patient was used. A patient could be counted in more than 1 severity category

c "Other Clinical or Laboratory AEs" as recorded on the CRF to differentiate from pruritus and/or mandatory discontinuations

d Includes Patient 32-001-920 who discontinued due to TEAE of increased bilirubin

e Includes 3 patients (OCA 50 mg arm) who also met protocol mandatory discontinuation criteria

f Does not include Patient 3-016-667 who was discontinued due to an SAE of Jaundice and also due to a TEAE of Pruritus

g Three (all in OCA 50 mg arm) of 5 patients who met the mandatory discontinuation criteria discontinued from the study

h Received waiver and completed the study

Note: A treatment-emergent adverse event (TEAE) is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. Patient 41-001-953 (10 mg arm) had an AE of dry tongue (classified as mild) and Patient 32-002-921 (25 mg arm) had an AE of insomnia (classified as moderate). Both of these AEs occurred 1 day before dosing began and are included in the summary Table as TEAEs

Safety Results:

Reviewer Comment: The most common related TEAEs occurring in ≥10% of patients were pruritus, fatigue, headache, and abdominal distention. There was a dose dependent increased incidence of AE of pruritus (OCA 10 mg < OCA 25 mg/50 mg).

Table 44: Incidence of TEAEs Occurring in ≥10% of Patients in any Treatment Group: Safety Population (N = 165)

System Organ Class/ MedDRA Preferred Term	Treatment Group			
	Placebo (n = 38)	OCA 10 mg n = 38	OCA 25 mg (n = 48)	OCA 50 mg n = 41
	Patients (%)	Patients (%)	Patients (%)	Patients (%)
Patients with any TEAEs	32 (84%)	34 (89)	47 (98)	41 (100)
Skin and Subcutaneous Tissue Disorders	21 (55)	19 (50)	43 (90)	36 (88)
Pruritus	19 (50)	18 (47)	41 (85)	33 (80)
Gastrointestinal Disorders	10 (26)	17 (45)	17 (35)	17 (41)
Abdominal Distension	1 (3)	2 (5)	0 (0)	4 (10)
Nausea	1 (3)	4 (11)	3 (6)	4 (10)
General Disorders and Administration Site Conditions	7 (18)	9 (24)	8 (17)	10 (24)
Fatigue	5 (13)	7 (18)	3 (6)	5 (12)
Nervous System Disorders	4 (11)	4 (11)	9 (19)	8 (20)
Headache	4 (11)	3 (8)	5 (10)	7 (17)
Respiratory, Thoracic and Mediastinal Disorders	6 (16)	3 (8)	4 (8)	11 (27)
Epistaxis	0 (0)	0 (0)	0 (0)	4 (10)
Musculoskeletal and Connective Tissue Disorders	5 (13)	5 (13)	3 (6)	6 (15)
Pain in Extremity	0 (0)	0 (0)	1 (2)	4 (10)

Source: Copied and electronically reproduced from CSR 747-202 page 106-1652

Reviewer Comment: A higher number of patients treated with OCA 50 mg experienced moderate and severe TEAEs compared with other treatment groups. The incidence of severe TEAEs were dose-related, and were reported by 16%, 21%, 44%, and 8% of the patients in the OCA 10 mg, OCA 25 mg, OCA 50 mg, and placebo groups, respectively.

Table 45: TEAEs by Severity: Safety Population (N = 165)

	Treatment Group			
	Placebo (n = 38)	OCA 10 mg (n = 38)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)
	Patients (%)	Patients (%)	Patients (%)	Patients (%)
Total Number of TEAEs	32 (84)	34 (89)	47 (98)	41 (100)
TEAEs by Severity^a				
Mild	31 (82)	25 (66) ^b	35 (73)	27 (66)
Moderate	15 (39)	17 (45)	26 (54) ^c	28 (68)
Severe	3 (8)	6 (16)	10 (21)	18 (44)

Source: Copied and electronically reproduced from CSR 747-202 page 106-1652

a Note: The worst severity of any TEAE for each patient with a patient's most severe rating (mild, moderate, or severe) only counted once regardless of the number of TEAEs reported. A patient could be counted in more than 1 severity category.

b Includes 1 AE that occurred 1 day before dosing began and was included in the summary Table as TEAE: Patient 41-001-953 (10 mg group) had an AE of dry tongue (classified as mild).

c Includes 1 AE that occurred one day before dosing began and was included in the summary Table as TEAE: 32-002-921 (25 mg group) had an AE of insomnia (classified as moderate).

Deaths : There were no deaths in the study.

Serious Adverse Events:

Overall, 7 patients (4%) experienced an SAE in the study. The incidences of SAEs reported in the study were as follows: 1 patient (3%) in the placebo arm had an SAE of dyspnea, 1 patient (2%) in the OCA 25 mg arm had an SAE of salivary gland neoplasm, 2 patients in the OCA 50 mg arm experienced angina pectoris and angioedema, and 3 patients in the 50 mg arm experienced GI hemorrhage, jaundice, and primary biliary cirrhosis (PBC flare).

Table 46: Incidence of SAEs by System Organ Class and MedDRA Preferred Term: Safety Population (N = 165)

System Organ Class/ MedDRA Preferred Term	Placebo (n = 38)	OCA 10 mg (n = 48)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)
	Patients (%)	Patients (%)	Patients (%)	Patients (%)
Number of Patients with SAE	1 (3)	0	1 (2)	5 (12)
Cardiac Disorders				
Angina pectoris	0	0	0	1 (2)
Gastrointestinal Disorders				
Gastrointestinal hemorrhage	0	0	0	1 (2)
General Disorders and Administration Site Conditions				
Chest pain	0	0	0	1 (2)
Hepatobiliary Disorders				
Primary biliary cirrhosis flare	0	0	0	1 (2)
Jaundice	0	0	0	1 (2)

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)				
Salivary gland neoplasm	0	0	1 (2)	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	1 (3)	0	0	0
Skin and Subcutaneous Tissue Disorders				
Angioedema	0	0	0	1 (2)

Source: Copied and electronically reproduced from CSR 747-202, page 109-1652

Patients (both in the OCA 50 mg arm) were discontinued from the study due to the SAE:

1. Patient 1-002-606, GI hemorrhage; and
2. Patient 3-016-667, jaundice.
3. Patient 4-011-676: PBC flare

One patient (19-005-1042) in the OCA 50 mg arm experienced 2 SAEs (angioedema and angina pectoris). Both of which were deemed unlikely related to the investigational product by the Applicant. The medical history of this patient included coronary artery disease, hypertension, hypercholesterolemia, emphysema, and aortic aneurysm. The patient presented to the emergency room with angioedema secondary to allergy caused by food. At the emergency room, the patient developed the SAE of angina pectoris which was secondary to epinephrine treatment for angioedema. The SAE of angina pectoris was resolved within approximately 20 minutes. The Investigator assessed the event of angina secondary to epinephrine (angina pectoris) as severe in severity and unlikely related to investigational product. *This reviewer agrees with the Applicant's assessment and believes angina pectoris is unlikely to be due to the OCA.*

Table 47: Summary of SAEs: Safety Population (N= 165)

Dose Group/ Patient ID	MedDRA Preferred Term	Severity	Time to Onset (Duration) Days	Relationship to Investigational Product	Action Taken	Outcome
Placebo						
3-014-665	Dyspnea	moderate	4 (5)	unlikely	Medication given/ Hospitalization	Resolved without sequelae
OCA 25 mg						
15-014-994	Salivary gland neoplasm	mild	63 (1)	unlikely	Medication given/ Hospitalization	Resolved with sequelae
OCA 50 mg						
1-002-606	Gastrointestinal hemorrhage	severe	15 (16)	possible	Patient discontinuation/ Hospitalization	Resolved without sequelae
3-016-667	Jaundice	severe	29 (26)	possible	Patient discontinuation/ Action Taken, Other	Resolved without sequelae
4-011-676	Primary biliary cirrhosis	severe	21 (5)	probable	Medication given/ Hospitalization	Resolved without sequelae

12-011-727	Chest pain	moderate	8 (4)	possible	Hospitalization	Resolved without sequelae
19-005-1042	Angioedema	severe	67 (2)	unlikely	Medication given/ Hospitalization	Resolved without sequelae
	Angina pectoris ^a	severe	67 (1)	unlikely	Hospitalization	Resolved without sequelae

Source: Copied and electronically reproduced from CSR 747-202 page 110-1652

6.2.2.1.3 Hepatic related adverse events:

Hepatic related adverse events:

Table 48: Hepatic-Related Treatment Emergent Adverse Events: Safety Population (N=165)

System Organ Class Preferred Term	Placebo (n = 38)	OCA 10 mg (n = 38)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)
	Patients (%)	Patients (%)	Patients (%)	Patients (%)
Patients with hepatic-related AEs	0 (0)	1 (3)	4 (8)	9 (22)
Hepatobiliary Disorders				
Primary Biliary Cirrhosis	0 (0)	0 (0)	0 (0)	1 (2)
Jaundice	0 (0)	0 (0)	0 (0)	1 (2)
Hepatomegaly	0 (0)	0 (0)	0 (0)	1 (2)
Portal hypertension	0 (0)	0 (0)	0 (0)	1 (2)
Gastrointestinal Disorders				
Faeces pale	0 (0)	0 (0)	0 (0)	1 (2)
Ascites	0 (0)	0 (0)	0 (0)	1 (2)
Gastrointestinal hemorrhage	0 (0)	0 (0)	0 (0)	1 (2)
Investigations				
Activated PT prolonged	0 (0)	0 (0)	1 (2)	0 (0)
INR increased	0 (0)	0 (0)	1 (2)	0 (0)
Alanine aminotransferase increased	0	0	1 (2)	1 (2)
Aspartate aminotransferase increased	0	0	0	1 (2)
Bilirubin conjugated increased	0	0	1 (2)	0
Blood bilirubin increased	0	1 (3)	0	0

Source: Copied and electronically reproduced from CSR 747-202, page 127-1652

Reviewer Comment: One patient (3%) in the OCA 10 mg arm experienced a hepatic-related TEAE compared to 4 patients (8%) in the OCA 25 mg and 9 patients (22%) in the OCA 50 mg arms who experienced a hepatic-related TEAE.

No patient in the placebo arm experienced a hepatic-related TEAE.

Reviewer Comment: Hepatic related SAEs were especially concerning in three patients who received OCA 50 mg dose. Patient 3-016-667 who had jaundice and ascites (had early disease), Patient 1-002-606 who had gastrointestinal hemorrhage, and patient 4-011-676 who had biliary cirrhosis flare (moderately advanced disease), as described earlier in the review. A fourth patient experienced and portal hypertension and ascites that presented on day 15 and AE lasted for 35 days and had moderately advanced disease. The reviewer recommends that in real time clinical practice, patients with advanced liver disease must be closely monitored for hepatic SAEs i.e., biochemical abnormality or advancement of liver disease. Dose adjustments must be considered in these patients.

The narratives of patients who experienced liver related serious adverse events are as follows:

Patient 1-002-606: Gastrointestinal hemorrhage

Preferred Term- Gastrointestinal hemorrhage

Intensity-Severe

Causality-Possible

Action Taken Patient discontinued from study, hospitalization

Outcome Resolved without Sequelae

AE Start Date/ Stop Date: (b) (6)

OCA 50 mg

Relevant medical history: PBC 24 years. No prior history of hepatic decompensations

White female, 54 y/o, diagnosed with PBC in (b) (6) was on stable dose of UDCA 600 mg. She had no episodes of GI decompensations in the past since her diagnosis, and had a stable course of PBC disease. The patient underwent upper endoscopy 22 days prior to trial entry, which showed mild esophageal varices and portal hypertensive gastropathy. Her baseline hemoglobin was 12 (b) (6) TB was 2.1 mg/dL and albumin was 4.8 g/dL (3.5-5.2). Investigational product (OCA 50 mg) started on (b) (6); one day after starting treatment patient started experiencing symptoms such as chills, insomnia, and pruritus. These symptoms persisted, and new symptoms of fatigue, malaise, diarrhea, painful defecation, severe pruritus and, headache appeared.

The investigational agent was stopped on Day 8 and on that day her TB was 2.1 mg/dL and albumin was 2.7 g/dL and hemoglobin was 9.7 g/dL. The patient presented anemia (hemoglobin 6.9 g/dL and hematocrit 19.2%) on Day 14; and key findings on CT scan were moderate amount of ascites and cirrhosis, with prominent spleen.

On (b) (6) (21 days after the IP was stopped) the patient was hospitalized again for black, tarry stools and weakness. She received a blood transfusion and underwent another EGD with banding esophageal varices, colonoscopy, and paracentesis.

Severity: Severe, and possibly related to IP as assessed by the Investigator as well as Applicant. Applicant noted that the patient's hemoglobin dropped from 12.2 g/dL to 6.8 g/dL, indicating that the blood loss was relatively rapid, which is typically associated with bleeding esophageal varices.

There were 2 GI bleeding events; the first one presented with a sudden drop in hemoglobin 12.2 → 9.7 → 6.8 mg/dL and the second event resulted in blood in stool (tarry stools). The patient had grade 1 esophageal varices, which are unlikely to bleed within the timeframe of the trial duration (drop in hemoglobin was seen <14 days after OCA dosing); as well as the patient developed moderate ascites which is a slow process in short duration. These decompensation events were unexpected in this patient. Of concern is the rapidity (appearance of symptoms within 14 days) and seriousness; this patient had a total of three hepatic decompensation events within 30 days. This reviewer agrees with the causality assessment of "possible" as provided by the Applicant. The reviewer has concerns using OCA 50 mg in patients with advanced stage of disease. Patients with advanced stage disease will have higher hepatic exposure (4-17 fold liver exposures) even at relevant OCA 10 mg dosing.

This reviewer's opinion is that the Applicant should conduct a trial in patients with advanced stage disease as per Rotterdam criteria i.e., both compensated and decompensation cirrhotic patients to assess if OCA is safe or harmful in this category of patients. This is now a post-marketing requirement under accelerated approval.

Patient 3-016-667; Event: Jaundice and worsening of ascites

Preferred Term: Jaundice

Intensity Causality: Severe; possibly related to IP;

Action Taken Patient discontinued from study

Event: Resolved

AE start date 13 Nov 2008 (Time to event: 28 day)

Duration of event: 8 months

OCA dose 50 mg

Date of First Dose/Last Dose of Investigational Product: 16 Oct 2008/ 09 Nov 2008

Pertinent medical history: PBC duration 5 years; Portal hypertension (2003 to present), Esophageal varices (2003), Ascites (2003 to present)

Patient 3-016-667, a 43-year-old white female with primary biliary cirrhosis (PBC) was randomized to the 50 mg OCA arm. Investigational product was taken orally (PO) and once daily (QD) in combination with ursodeoxycholic acid (UDCA) 1000 mg. Relevant medical history included PBC, mild pruritus, fatigue, ascites, esophageal varices, portal hypertension, osteopenia, hypothyroidism, , scattered moles, cherry angiomas, thrombocytopenia, light headedness, and menopausal.

The patient initiated investigational product on 16 Oct 2008 with OCA 50 mg, every other day. On the 10th day the regimen was changed to daily dosing the patient complained of increased pruritus. Diphenhydramine and cholestyramine was started. Patient was noted to have increase in TB (1.8 mg/dL) on Day 20. The patient experienced pruritus and the treatment was interrupted on Day 25, and was also the last IP dose given to patient (9th Nov, 2008).

On Day 28 (4 days after discontinuation of the IP, 13 Nov 2008) the patient reported jaundice and laboratory done on Day 33 the patient's TB was 8.3 mg/dL. On Day 34 after starting the IP, the patient reported moderate lower extremity edema and was started on spironolactone/hydrochlorothiazide.

On 24 Nov 2008, the patient reported improved jaundice and pruritus. On 08 Dec 2008, the concurrent event of lower extremity edema resolved with spironolactone/hydrochlorothiazide.

Table 49: Liver Biochemical Test in Patient with Jaundice

Test Reference Range	Screening - 9	Day 20	OCA stopped on Day 25	Day 33	Day 210
ALP <117 IU/L	390	521		498	425
AST <50 IU/L	128	125		109	123
ALT <67 IU/L	91	69		72	93
Total bilirubin <1.4 mg/dL	<u>1.1</u>	<u>1.8</u>		<u>8.3</u> → <u>8.7</u>	<u>1.2</u>
Direct bilirubin <0.4 mg/dL	<u>0.3</u>	<u>0.5</u>		4.5	NA

Albumin 3.1 to 5.2 g/dL	3.6	3.2		2.9	3.4
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Source: Reviewer Generated.

Reviewer Comment: The reviewer notes the event was considered by the investigator as “related” to the drug, symptoms appeared within 20 days of exposure to drug, de-challenge with OCA 50 mg reverted the liver biochemical parameters of the patient. The Applicant believes the causality as possibly related. Although the transaminases did not change much, the synthetic function of the liver was affected; the albumin and total bilirubin and direct bilirubin were all abnormal simultaneously. The adverse events also occurred in less than a month of exposure of the drug. We now know the OCA exposures are higher in patients who have hepatic impairment, and since this patient had evidence of advanced stage disease (signs of portal hypertension present). Therefore, dose adjustments are very important in hepatic impairment.

Patient 4-011-676

Preferred Term: Biliary cirrhosis primary

Intensity Causality: Severe; possibly related to IP;

Action Taken Patient discontinued from study

Event: Resolved

AE Start Date (b) (6)

AE stop date:

OCA dose 50 mg

Date of First Dose/Last Dose of Investigational Product: (b) (6)

Pertinent medical history: PBC duration 6 years, diabetes, cholelithiasis, fatigue, liver biopsy in (b) (6) showed bridging fibrosis suggestive of early cirrhotic changes.

This is a 48-year-old white female with primary biliary cirrhosis (PBC). The patient initiated investigational product (OCA 50 mg) on (b) (6). Five days after starting the investigational product, the patient experienced pruritus. Treatment included cyproheptadine, which decreased the pruritus.

On day 12 (b) (6), the patient presented to the emergency room with nausea, vomiting, dehydration, pruritus all over her body, and insomnia due to pruritus. Laboratory test results showed low albumin and high total bilirubin. IP was discontinued on the day 12.

On day 13 (1 day after discontinuing the IP), the patient experienced left eardrum perforation, labile diastolic blood pressure (DBP) levels, and continuing nausea and vomiting. Fourteen days after starting the IP and 3 days after its discontinuation, the patient experienced a diffuse rash on face/chest/arms, petechial rash on body.

Table 50: Changes in Laboratory parameters Overtime

	Day 0	OCA discontinued on day 12	Day 15	Day 21	Day 29	Day 41
ALP <117 IU/L	389		666		404	296
AST <50 IU/L	93		54		74	126
ALT <67 IU/L	90		39		53	97
Total bilirubin ≤20.5 μmol/L	27.4 μmol/L (1.6 mg/dL)		61.6 μmol/L (3.6 mg/dL)		118 μmol/L (7 mg/dL)	6.8 SI unit not available

PT/INR			16.4/ 1.4		
Platelet count			332	325	

Source: Reviewer Generated

On (b) (6) approximately 20 days after starting the IP and 9 days after discontinuation, the patient was hospitalized for a severe PBC flare, with symptoms of nausea, vomiting, diffuse rash and pruritus. Physical examination revealed icteric sclera. A computed tomography scan of the abdomen on (b) (6) showed hepatomegaly, absence of bile duct dilation, and mild diffuse fatty infiltration.

Reviewer Comment: The patient met the criteria for moderately advanced stage according to Rotterdam criteria at trial entry. The patient experienced AE within 12 days of starting the trial, and hepatic decompensation occurred. The hepatic exposures are higher in patients with hepatic impairment and can be a cause of liver injury as seen in this patient.

6.2.2.1.4 Dropouts and/or Discontinuations Due to Adverse Effects

Table 51: Summary of Patient Discontinuations by Treatment Arm: ITT Population (N = 165)

Adverse Event Resulting in Study Discontinuation	Treatment Group				Total (n = 165)
	Placebo (n = 38)	OCA 10 mg (n = 38)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)	
	Patients (%)	Patients (%)	Patients (%)	Patients (%)	n (%)
Total Number of Patients With Study Discontinuations due to TEAE					
Discontinuation due to Clinical or Laboratory AE	1 (3)	6 (16)	5 (10)	15 (37)	27 (16)
Discontinuation due to TEAE of Pruritus	0	3 (8)	4 (8)	10 (24)	17 (10)
Patients Who Met Mandatory Discontinuation Criteria and Were Discontinued From the Study	0	0	0	3 (7)	3 (2)

Source: Copied and electronically reproduced from Applicant submission CSR 747-202 page 111-1652

The incidence of TEAEs leading to discontinuation was higher in the OCA 50 mg arm (37%) compared with placebo, OCA 10 mg, and OCA 25 mg arms (3%, 16%, and 10%, respectively). The overall most common reason for study discontinuation was pruritus, which occurred most notably in the OCA 50 mg arm (10 patients).

Five patients (1 patient [3%] each in the placebo and OCA 10 mg arm, and 3 patients [7%] in 50 mg OCA arms) met the criteria of mandatory protocol discontinuation criteria (per elevated AST/ALT or conjugated bilirubin levels), of which 3 patients discontinued, remaining to received waiver and completed the study.

Reviewer Comment: The reviewer reviewed the narratives and considers the patient discontinuations were appropriate. The reviewer also notes that at the Mayo clinic site, where an alternate dosing regimen was utilized for fourteen patients enrolled at this site, the discontinuation rate in OCA treatment arms at the Mayo site was similar to the overall discontinuation rate, i.e., alternate day dosing does not tolerate the patients to pruritus outcome.

In the OCA 10 mg arm

1. Patient 3-015-666 experienced edema of extremities, abdominal distention, and polyuria. The event occurs 46 to 77 days after the initial IP (OCA 10 mg) dosing. The liver biochemical indices or imaging results were not provided with this narrative. Most likely the abdominal distention represented as cites and perhaps low albumin as it was associated with upper and lower extremity edema. Applicant noted the abdominal distention, polyuria, and peripheral edema causality relationship to be possibly due to the OCA, intensity moderate, and all three resolved without sequelae. *However the event of lower extremity swelling (which was moderate in intensity and causality assessment possibly related) was ongoing at the end of the study.*
2. Patient on OCA 10 mg arm 6-002-656 was initiated investigational product on 15 July 2008 with IP (OCA 10 mg). Seven days after initiation of IP the patient had events of maculopapular rash, nausea and, fatigue and the IP (OCA 10 mg) discontinued on Day 7. The events resolved in Aug 2008. *Again the reviewer is concerned as the liver biochemical indices and the imaging data at the time of, and after stopping OCA 10 mg were not available for the reviewer to assess. With the limited information in the narrative it is not possible to come to a conclusion; however, this reviewer's opinion is that these events are likely related to the drug because of the temporal association and resolution of symptoms upon de-challenge.*
3. Patient 32-001-920- the bilirubin increased on Day 14 after starting the IP (OCA 10 mg). At baseline patient's total bilirubin was 25.3 µmol/L (≤24.0) and direct bilirubin 10.40 µmol/L (≤7); on day 14 the total bilirubin increased to 32.5 µmol/L (≤24.0) → 39.2 µmol/L (≤24.0) on Day 20; and on day 14 direct bilirubin increased to 25.00 µmol/L (≤7) → 20.90 µmol/L (≤7) on Day 20. The follow up TB/DB was 36.6 µmol/L (≤24.0)/ 26.00 µmol/L (≤7). *This reviewer remains concerned about the rise in the TB/DB with use of OCA 10 mg. A rise in TB/DB, in absence of another cause for elevation may be considered criteria for discontinuation of OCA, since it is unclear how the patient would progress clinically if continued on OCA.*
4. There were 3 patients who discontinued due to severe pruritus in the OCA 10 mg arm; this reviewer agrees with the investigator's judgment for discontinuing these patients from the trial.

In the OCA 25 mg arm

1. Four patients discontinued due to severe pruritus. *All patients who experienced severe pruritus had the onset of AE in few days of starting the OCA 25 mg, and in 3 patients, pruritus resolved, except one, who had ongoing pruritus at follow up.*
2. *Patient 18-012-752 had elevations of alanine aminotransferase; was a 35 year old female with PBC who 56 days after initiation of IP (OCA 25 mg) had elevations of liver biochemical tests. The ALT the AST, and ALP increased. No further follow up of biochemical test is available after 28 July 2008. The liver indices did not return to baseline, until the last laboratory value follow up.*

Dose adjustment may be required, FDA has proposed an alternative dosing regimen, but further dose reductions or alternative regimens may be required in patients with different levels of hepatic functional capacity.

Table 52 Laboratory values during this event

Date	Test	Result (Range)
15 May 2009 (Day 0)	ALT	205 U/L (≤67)
15 May 2009 (Day 0)	AST	129 U/L (≤50)
15 May 2009 (Day 0)	ALP	915 U/L (≤117)
15 May 2009 (Day 0)	Total bilirubin	17.1 µmol/L (≤24.0)

10 Jul 2009 (Day 57)	ALT	471.0 U/L (≤67)
10 Jul 2009 (Day 57)	AST	311.0 U/L (≤50)
10 Jul 2009 (Day 57)	ALP	1270 U/L (≤117)
10 Jul 2009 (Day 57)	Total bilirubin	18.8 μmol/L (≤24.0)
28 Jul 2009 (Day 85/ET)	ALT	265.0 U/L (≤67)
28 Jul 2009 (Day 85/ET)	AST	173.0 U/L (≤50)
28 Jul 2009 (Day 85/ET)	ALP	1295 U/L (≤117)
28 Jul 2009 (Day 85/ET)	Total bilirubin	23.9 μmol/L (≤24.0)

Source: CSR747-202; page 1511 of 1652 Patient narrative 18-012-752

In the OCA 50 mg:

1. Six patients experienced moderate pruritus; and five patients experienced severe pruritus. A total of ten patients discontinued from trial due to AEs of pruritus. The timing of onset of both moderate and severe pruritus was similar as seen in trial 747-301. It ranged from presenting as early as day 5 and as late as day 148 (it is odd for a patient to report AE on day 148, when the duration of this trial was only 85 days). The majority of patients experienced AE of pruritus within 10 days and the pruritus was reversible in the majority of the cases.
2. Three patients met mandatory discontinuation criteria (elevation in liver biochemical tests). These include Patient 1-002-606, Patient 3-016-667 and, Patient 4-011-676.
3. Patient 4-011-676 had elevations of AST/ALT 19 days after the IP dosing (OCA 50 mg). The patient initiated IP (OCA 50 mg) on 04 Sep 2008, and 14 days after starting patient reported pruritus of mild severity; no treatment was given. On day 19 of IP dosing the patient was found to have elevated ALT, AST and ALP. The IP was discontinued on Oct 1, 2008 (on day 28). GGT did not change during this event.

Reviewer Comment: The AE reported in above patient is a drug related event, given a simultaneous rise in all the liver biochemical indices, and the temporal relationship to the administration of the drug. This young patient (44 y/o female) was diagnosed with PBC in 2005, and was on stable UDCA dose since 2006 and biochemically had an early disease. The patient did not have any other decompensation events in the past. Her disease was stable and was clinically doing well prior to initiating IP. She experienced hepatocellular injury and her laboratory parameters are as follow:

Table 53: Reviewer generated Table from Applicant submitted data

	Screening value	Day 19	Post-Discontinuation	Follow up
ALT (≤67 U/L)	21 U/L	247 U/L	67 U/L	29 U/L
AST (≤50 U/L)	20 U/L	162 U/L	46 U/L	29 U/L

ALP (≤117 U/L)	208 U/L	321 U/L	261 U/L	186 U/L
TB (≤24.0 U/L)	10.3 μmol/L	13.7 μmol/L	6.8 μmol/L	13.7 μmol/L
GGT ≤50.0 U/L	12	10	10	10

Reviewer generated Table.

Reviewer Comment: Higher OCA exposures are not tolerated well and are not be safe in PBC patients, irrespective of disease duration and stage of disease. Since OCA 10 mg can also give higher liver exposure the dose adjustments are very important as well as the label must clearly state the importance of close monitoring and conducting laboratory testing in symptomatic patients, within 4-6 weeks of initiating OCA.

4. Patient 2-006-740 (dosed with OCA 50 mg) experienced severe pruritus, swollen feet, pain in extremities, chills and, nausea. The IP dosing was given for 2 days, (started on 25 Nov 2008 and last dose received on 27 Nov 2008). Her symptoms of nausea and chills resolved on 29 Nov 2008, and pruritus resolved on 14 Dec 2008. The pruritus was reversible AEs as seen in this patient. Other symptoms swollen and painful feet, chills and nausea resolved in following 2-3 days.

Reviewer Comment: The reviewer opines that this event of pruritus, accompanied with chills and nausea may be associated with OCA use. Although the patients rash could be possibly related to UVB therapy.

Significant Adverse Events

1. Patients Meeting Mandatory Protocol Discontinuation Criteria

Five patients who met the protocol mandatory discontinuation criteria in the study which was based on ALT (≥3x average predose value and > ULN), AST (≥3x average predose value and > ULN), or conjugated (direct) bilirubin (> 2x average predose value and > 1.5 mg/dL [25.7 μmol/L]).

Table 54: Patients Meeting Mandatory Discontinuation Criteria

Group	Patient	Met AST/ALT Criteria ^a	Met Bilirubin Criteria ^a	Discontinuation/Waiver
Placebo	2-005-683	Yes	No	Received protocol waiver
OCA 10 mg	40-003-908	Yes	No	Received protocol waiver
OCA 50 mg	3-016-667	No	Yes	Yes
OCA 50 mg	4-010-639	Yes	No	Yes
OCA 50 mg	4-011-676	No	Yes	Yes

Source: Copied and electronically reproduced from the CSR 747-202 page 116-1652 Applicant submission.

Patient 4-010-639 was discontinued at Day 29, but the patient was later allowed to remain on the study after new tests were ordered and patient no longer met the discontinuation criteria.

2. Safety Parameters of Special Interest

- a. Pruritus is the most common symptom of PBC as well as dose-related AE associated with OCA and has been identified as an AE of special interest by the Applicant.
- b. Prior non-clinical studies and earlier phase clinical studies demonstrated adverse hepatic effects, including an acute rise in transaminase levels at higher OCA doses (at OCA >100mg repeat dosing). Therefore, the Applicant considers hepatic TEAEs and laboratory test results were also considered to be of potential special interest.
- c. Prior clinical study observations in patients with PBC have shown OCA-related decrease in high density lipoprotein cholesterol (HDLc) and increase in low-density lipoprotein cholesterol (LDLc). Conservatively, the Applicant considered these adverse cardiovascular safety signals to be of special interest.

6.2.2.1.5 Pruritus:

Table 55: Summary of Pruritus TEAEs: Safety Population (N = 165)

	Treatment Group			
	Placebo (n = 38)	OCA 10 mg (n = 38)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)
	Patients (%)	Patients (%)	Patients (%)	Patients (%)
Summary by MedDRA Preferred Term (Safety Population: N = 165)				
Patients with TEAE of Pruritus	19 (50)	18 (47)	41 (85)	33 (80)
Patients with TEAE of Pruritus generalized	0	0	1 (2)	0
Summary by Related TEAEs (Safety Population: N = 165)				
Patients with related TEAE of Pruritus	17 (45)	18 (47)	39 (81)	33 (80) ^a
Patients with related TEAE of Pruritus generalized	0	0	1 (2)	0
Summary by Severity^{b,c} (Safety Analysis Set: Patients with at least 1 Event of Pruritus [N = 112])				
MedDRA Preferred Term: Pruritus				
Mild	16 (84)	8 (44)	21 (50)	12 (36)
Moderate	5 (26)	8 (44)	19 (45)	21 (64)
Severe	0 (0)	6 (33)	9 (21)	15 (45)
MedDRA Preferred Term: Pruritus generalized				
Mild	0 (0)	0 (0)	1 (2)	0 (0)
Moderate	0 (0)	0 (0)	1 (2)	0 (0)
Severe	0 (0)	0 (0)	0 (0)	0 (0)

Source: Copied and electronically reproduced from CSR 747-202, page 117-1652

a Patient 3-016-667 was discontinued from the study due to an AE of pruritus but also had developed elevated levels of conjugated (direct) bilirubin. b Patients with episodes differing in severity (eg, mild and moderate) were counted in both categories of severity. c Percentages of patients in this subsection are based on the Safety analysis set comprising of patients with at least 1 event of pruritus (N = 112)

Reviewers Comment: The severity of pruritus is dose-related. Pruritus is the most common cause for discontinuation of treatment.

Mayo clinic study site evaluated whether a slow initial titration of OCA (i.e., every other day administration and gradually increase to daily administration of OCA) would result in a lower incidence of pruritus. All patients experienced pruritus, with exception of 2 patients in the placebo arm. However the reviewer notes due to small numbers of patients, interpretation of this particular titration strategy is not clear.

Table 56: Time to Onset of First Episode of Pruritus: Safety Population (N = 165)

	Placebo (n = 38)	OCA 10 mg (n = 38)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)
n (%) patients with at least 1 TEAE of pruritus (N = 112)	19 (50)	18 (47)	42 (88)	33 (80)
Mean (SD) days	37.5 (37.0)	11.5 (9.4)	10.5 (13.2)	3.3 (3.9)
Median (days)	25.0	6.5	5.0	2.0
Minimum, Maximum (days)	0, 98.0	0, 29.0	0, 68.0	0, 14.0

Source: Copied and electronically reproduced from 747-202 CSR, page 119-1652

This Table in the Applicant's submission only listed Safety Population, which included patients with at least 1 event of pruritus (i.e., N= 112).

Reviewer Comments: There is a dose-related median time to the onset of the first episode of pruritus as observed by the Applicant in Table 58. The median times to the first episode of pruritus were 6.5 days, 5 days, 2 days, and 25.0 days in the OCA 10 mg, OCA 25 mg, OCA 50 mg, and placebo arms, respectively.

The incidence of the TEAE of pruritus was higher in the OCA 25 mg and OCA 50 mg treatment arms compared with the OCA 10 mg and placebo arms (47%, 85%, 80%, and 50% of patients in the OCA 10 mg, OCA 25 mg, OCA 50 mg, and placebo arms, respectively). The incidence of the TEAE of pruritus in the OCA 10 mg arm was similar to that in the placebo arm.

Patients who experienced at least 1 TEAE of pruritus and received a clinically significant intervention, 67%, 71%, 94%, and 47% of patients in the OCA 10 mg, OCA 25 mg, OCA 50 mg, and placebo arms, respectively.

Management of pruritus: The Applicant reports, most common treatment medications used as an intervention for pruritus were bile acid sequestrants for e.g., cholestyramine, and antihistamines alone or in combination with bile acid sequestrants. Dosing interruption was required in 2 patients each on OCA 10 mg and OCA 50 mg. UDCA dose was decreased in 9 patients who experienced a TEAE of pruritus, including 2, 2, and 5 patients in these patients the OCA 10 mg, clinically OCA 25 mg, and OCA 50 mg treatment arms, respectively.

Table 57: Clinically Significant Intervention for Pruritus: Safety Population (N = 165)

	Placebo	OCA 10 mg	OCA 25 mg	OCA 50 mg
	Patients (%)	Patients (%)	Patients (%)	Patients (%)
Patients with at least 1 TEAE of pruritus (N= 112)	19 (50) ^a	18 (47) ^a	42 (88) ^{a, b}	33 (80) ^a

Patients with at least 1 TEAE of pruritus and any clinically significant intervention for pruritus (N = 82)	9 (47) ^c	12 (67) ^c	30 (71) ^c	31 (94) ^c
Outcome of Clinical Intervention for Pruritus^d				
Successful Intervention ^e ,	9 (100)	9 (75)	26 (87)	19 (61)
Not Successful Intervention	0	2 (17)	2 (7)	8 (26)
NA ^g	0	1 (8)	2 (7)	4 (13)

Source: Copied and electronically reproduced from 747-202 CSR, page 120-1652

a The percentage of patients with at least 1 TEAE of pruritus are reported in the context of Safety Population (N = 165).

b Includes 1 TEAE of pruritus generalized.

c The percentage of patients with at least 1 TEAE of pruritus and any clinically significant intervention for pruritus are reported in the context of those with at least 1 TEAE of pruritus (N = 121).

d The percentage of patients indicated are of those who received clinically significant intervention for pruritus.

e Clinically significant interventions were defined as interruption or frequency decrease of investigational product dosing, administration (or an increase in dose) of anti-pruritic agents, or decrease in dose of UDCA, as identified during the blinded data review meeting.

g NA refers to an intervention for pruritus but the outcome (success or not) as not available, in part, due to discontinuation of 5 of 7 patients.

Reviewer Comment: Although the overall incidence of pruritus was similar in placebo arm and OCA 10 mg treatment arm, there was a higher incidence of pruritus interventions required in patients dosed with OCA 10 mg (67%) in comparison to the placebo (47%) treatment arm. Additionally, 100% of patients in the placebo treatment arm responded to treatment interventions, with none requiring treatment interruption or discontinuations in comparison to patients on OCA treatment arms. Ten patients (24%) in the OCA 50 mg arm discontinued the study due to pruritus compared to 3 (8%) and 4 (8%) patients in OCA 10 mg and 25 mg arms, respectively. These patients who discontinued did not respond to treatment intervention, treatment interruption, and decrease in UDCA dose did not respond to interventions for pruritus. No patient in the placebo arm discontinued due to pruritus as can be seen in Table 60.

Table 58: Discontinuations due to Pruritus and those with a medical history of pruritus

	Placebo	OCA 10 mg	OCA 25 mg)	OCA 50 mg
Discontinued Due to any TEAE or a TEAE of Pruritus (Safety Population: N = 165)				
	N = 38	N = 38	N = 48	N = 41
Discontinuations due to a TEAE	1 (3)	5 (13)	5 (10)	14 (34)
Discontinuations due to a TEAE of Pruritus	0	3 (8)	4 (8)	10 (24)
Discontinuation Due to TEAE of Pruritus Among Patients With a Medical History of Pruritus (Safety Analysis Set: Patients with medical history of pruritus, N = 84)				
	N = 18	N = 21	N = 22	N = 23
Yes	0	3 (14)	1 (5)	6 (26)
No	18 (100%)	18 (86)	21 (95)	17 (74)

Source: Copied and electronically reproduced from CSR 747-202, page 122-1652

Discontinuation due to TEAE of pruritus in patients (N=84) with prior medical history of pruritus included 0%, 14%, 5% and 26% in placebo, OCA 10 mg, OCA 25 mg, and OCA 50 mg respectively.

Time to resolution of pruritus: No placebo patient was discontinued from trial due to pruritus. The mean (SD) time to resolution of pruritus in patients who were discontinued due to AE of pruritus was 11.5 days for OCA 10 mg, 8.3

days for the OCA 25 mg treated groups, 33.9 days for the OCA 50 mg treated group. 73% patients treated with OCA 50 mg who experienced pruritus had resolution of pruritus in >7 days (3 to 137 days) compared with OCA 10 mg and OCA 25 mg where the resolution of pruritus occurred between 6 to 16 days. *The pruritus is reversible. The resolution of pruritus was faster in OCA 10 mg arm in comparison to OCA 50 mg arm.*

Pruritus specific Quality of Life Questionnaires, the 5D score:

5D scores assess the magnitude of pruritus in PBC, 5-D findings showed similar results as noted above in the AE of pruritus. *Dose-dependent increases in the total 5-D score and scores in the domains of duration, degrees, disability, and distribution were observed in the all OCA dose arms in comparison with placebo, indicating worsening of pruritus in the patients treated with OCA.*

Reviewer Comment: A significant ($p < 0.01$) and dose-related increases in mean pruritus VAS scores were observed in comparison to the placebo group ($p < 0.01$) at Day 29, after which VAS score did not worsen. However, most patients drop out occurred within 30 days of starting therapy, therefore it was expected that the VAS scores would then stabilize thereafter.

6.2.2.1.6 **Lipid-Related Adverse Events:**

PBC patients have hypercholesterolemia, predominately contributed by elevated HDLc levels. A dose-related decrease in mean total cholesterol was observed in all OCA treatment arms compared to placebo.

Table 59: Changes in Mean HDL cholesterol

	OCA 10 mg (N = 38)	OCA 25 mg (N = 48)	OCA 50 mg (N = 41)	Placebo (N = 38)
Mean HDLc (mg/dL)				
Baseline	67.6	71.5	75.4	69.9
Day 85	58	61.4	58	73.7
Change at month 3	-10	-10	-17	+4

Source: Reviewer Generated. (HDLc LLN 40 mg/dL)

These data summarize the HDLc reduction and were analyzed by the reviewer from the data submitted by the Applicant.

In the OCA 10 mg treatment arm at least 23 patients had some decline in HDLc

1. 7 patients had HDLc reduction ≥ 22 mg/dL
2. 7 patients had HDLc reduction that were below 40 mg/dL (reduction as low as 17 mg/dL were noted).

In the OCA 25 mg arm, 33 patients had some decline in HDLc

1. At least 1 patients had HDLc reduction $> 2SD$ (i.e., decline ≥ 44 mg/dL) and 12 patients had reduction $> 1SD$ (22 mg/dL)
2. At least 5 patients had HDLc reductions < 40 mg/dL

In the OCA 50 mg arm at least 32 patients had some reduction in HDLc

1. At least 17 patients had reduction > 1 SD (≥ 22 mg/dL) and 3 patients had HDLc reduction > 2 SD (≥ 44 mg/dL)
2. At 6 patients had decline in HDLc less than 40 mg/dL. This group had more cornering finding, the HDLc decline was as low as 5 mg/dL, 8 mg/dL and 20 mg/dL.

Placebo arm:

A total of 4 patients had some decline in HDLc
No patient had decline > 1 SD (22 mg/dL)

There was slight reduction in LDLc at month 3 compared to baseline. There were no significant changes in the mean levels of triglyceride, or very low-density lipoprotein cholesterol (VLDLc) levels from baseline to Day 85/ET in any treatment arm.

Reviewer Comment: The cholestasis derived dyslipidemia may have different outcomes than nutritionally induced dyslipidemia as the Applicant notes in the CSR. However, PBC patients do not have cardiac adverse event related to dyslipidemia perhaps secondary to high HDLc which may be cardio-protective. The reviewer remains concerned about these HDLc reductions, although at this time it is unknown how these will impact cardiac disease.

The two patients developed hypercholesterolemia, however, narratives were not provided in 747-202 CSR for either patient. For one patient the increase in cholesterol values were noted in the abnormal chemistry the total cholesterol increased from 215 mg/dL to 427.02 mg/dL by day 85/ET, and the LDLc increased from 126.8 mg/dL to 246.3 mg/dL. However, the narrative and how the patient was treated were not provided.

Laboratory Findings:

Placebo: Increase in TSH was seen in 2 different patients and mild AEs of increases in WBC and RBC were seen in a third patient and causality was unlikely related.

OCA 10 mg: Increase in blood TSH was seen in one patient. An increase in TB was described earlier and is probably related.

OCA 25 mg: The rise in liver biochemical tests (increase in ALT, CB, and INR) are of concern and of relevance in PBC patients. However, the 25mg dose will not be utilized in clinical practice.

OCA 50 mg: Elevations of liver biochemical tests (ALT/AST increase) were observed at this dose as mentioned earlier in the review; this dose will also not be used in clinical settings.

PREGNANCY: *No pregnancies occurred during the conduct of the trial 747-202.*

Vital Signs: There were no meaningful exposures or dose-dependent changes in heart rate and systolic or diastolic blood pressure in any of the treatment arms. There were 3 patients who experienced 1 AE each related to vital signs; 2 patients in the placebo arm experienced an AE of palpitations and 1 patient in the OCA 50 mg arm experienced an AE of labile blood pressure. Three patients (8%) in the OCA 10 mg arm experienced a TEAE of pyrexia. One patient had a TEAE of labile blood pressure and was later discontinued from trial due to AE of biliary cirrhosis flare.

Electrocardiograms (ECGs): Applicant stated no clinically significant findings were noted in the absolute values or change from screening values for RR, PR, QRS, or QT.

QTcF:

Applicant states transient QTcF values > 450 ms were observed across all treatment arms. The number of patients in each treatment arm that had a baseline QTcF < 450 ms and a Day 85/ET ≥ 450 ms was similar across arms (n = 2, n = 3, n = 2, and n = 0, in placebo, OCA 10 mg, OCA 25 mg, and OCA 50 mg arms, respectively). *The reviewer agrees*

with the Applicant's assessment and since the QTcF prolongation was seen across all arms with equal frequency, it is difficult to determine a causal relationship with the use of OCA at this time.

Conclusions:

1. OCA 10 mg is safe. Higher AEs and SAEs were noted with OCA 25 mg and OCA 50 mg doses. Overall, 34 patients (89%) treated with OCA 10 mg, 47 patients (98%) treated with OCA 25 mg, 41 patients (100%) treated with OCA 50 mg, and 32 patients (84%) treated with placebo, experienced at least 1 TEAE during the study. Majority of TEAEs were mild or moderate, with few severe and few serious AEs observed during the trial.
2. There were no deaths in this study.
3. Three patients in the OCA 50 mg dose arm discontinued due to mandatory protocol criteria of elevated AST/ALT or elevated bilirubin.
4. SAEs were experienced by 7 (4%) patients, of which 3 patients in the 50 mg arm had GI/hepatic SAEs (GI hemorrhage, jaundice, ascites, primary biliary cirrhosis [PBC flare, hepatomegaly and portal hypertension]). These AEs are worrisome. There were high hepatic SAEs at OCA 50 mg dose both for hepatic decompensation events as well as for elevation of liver biochemical tests. However, it appears most biochemical enzyme elevations were seen in early stage disease, whereas decompensation events occurred in both early stage and moderately advanced stage disease patients. The OCA dose should be adjusted in patients who progress in stages of disease and this is a dynamic ongoing assessment, therefore a clinical and as well as laboratory follow up is very important.
5. Other than 5 patients (1, 1, and 3 patients in the placebo, OCA 10 mg, and OCA 50 mg arms) who met the mandatory discontinuation criteria (3 of whom actually discontinued due to TEAE or mandatory discontinuation), no other findings related to liver parameters (including ALP, total bilirubin, conjugated (direct) bilirubin, GGT, ALT, and AST) from a safety perspective were observed in this 85 day trial.
6. Pruritus was the most commonly reported AE across all treatment arms.
 - a. The incidence of pruritus is dose-related and incidence was greater in the higher OCA dose arms (25 mg and 50 mg) compared with the OCA 10 mg and placebo-treated patients. The incidence of moderate and severe pruritus was greater in patients who received OCA 50 mg compared with patients who received OCA 10 mg, OCA 25 mg, or placebo.
 - b. Although, the incidence of pruritus in OCA 10 mg arm was similar to that in the placebo arm, the majority of pruritus TEAEs in the OCA 10 mg arm was of moderate to severe intensity compared to mild in those who received placebo.
 - c. Overall, the higher incidence of severe pruritus, in the OCA 50 mg arm was responsible for the imbalance in the incidence of severe TEAEs in the OCA treatment arms.
 - d. The median time to the onset of pruritus was shorter in the OCA treatment arms (6.5 days for the OCA 10 mg arm; 3 days for OCA 25 mg; 2.0 days for OCA 50 mg) compared to 25 days for placebo.
 - e. Interventions for pruritus were successful in 63 (77%) of 82 patients who received pruritus intervention. The pruritus interventions were successful in 9 (100%) of 9 placebo, 9 (75%) of 12 OCA 10 mg, 26 (87%) of 30 OCA 25 mg, and 19 (61%) of 31 OCA 50 mg patients.
 - f. Discontinuations due to a TEAE of pruritus occurred only in the OCA treatment arms (3 OCA 10 mg patients [8%], 4 OCA 25 mg patients [8%], and 10 OCA 50 mg patients [24%]). No patient in the placebo arm discontinued due to pruritus.
7. The HDLc reductions were seen in majority of OCA treated patients (dose dependent effect), HDLc seems to be a cardio-protective factor in patients with cholestatic dyslipidemia.
 - a. Reductions in HDLc were seen with OCA treatment; these reductions occurred within weeks of initiation of OCA. Levels were as low as 5 mg/dL, 8 mg/dL and these are worrisome. .

Durability of Response

The response seen on primary endpoint biochemical markers (ALP) was durable for the trial duration.

6.3 Clinical Trial Protocol 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

Trial Acronym: PBC OCA International Study of Efficacy (POISE)

Rationale for dose selection in trial 747-301: OCA 10 mg once daily was better tolerated than 25 mg or 50 mg (as seen in Phase 2 trials). All OCA doses reduced ALP levels in patients with PBC, and doses higher than OCA 10 mg were not more effective. There was a dose related increase in the incidence and severity of pruritus observed across all evaluated doses. There were higher TEAEs at doses 25 and 50 mg as well as higher rates of discontinuation due to TEAEs. Three patients on OCA 50 mg experienced hepatotoxic adverse reactions.

Reviewer Comment: Based on findings from phase 2 studies, FDA recommended the Applicant also add a lower dose for the phase 3 trial. The Applicant added the OCA titration arm (OCA 5 mg → up-titrated to OCA 10 mg based on tolerability (i.e. pruritus) and/or if biochemical response not achieved).

Rationale for endpoint: The Applicant helped establish and has collaborated with the Global PBC study group to investigate if biochemical variables, particularly the phase 3 study 747-301 endpoints of ALP and bilirubin, could be used as acceptable surrogate endpoints “reasonably likely to predict clinical benefit.” The Global PBC study group concluded that higher levels of ALP and total bilirubin were associated with a higher risk of liver transplant or death.

Based on the Global PBC study group and other published biochemical treatment response criteria, the primary endpoint for study 747-301 was based on the percentage of patients achieving specific biochemical criteria for ALP $\leq 1.67 \times \text{ULN}$, **and** total bilirubin $\leq \text{ULN}$, was found to be optimal for evaluating therapeutic response. These criteria combined are commonly referred to as the Mayo II criteria (Momah 2012, Kumagi 2010b). In addition to the Mayo II criteria, a minimum ALP reduction of $\geq 15\%$ from baseline was also included as part of the composite endpoint to ensure that only patients with a change in ALP that was thought to be meaningful were judged to have a successful response. Thus, a patient with a pretreatment ALP value of $2.5 \times \text{ULN}$ needed to have an ALP $\leq 1.67 \times \text{ULN}$ (33% reduction) to be considered a treatment success; while a patient with a pretreatment ALP value of $1.75 \times \text{ULN}$ needed to attain an ALP value of $\leq 1.49 \times \text{ULN}$ to be considered a treatment success.

Reviewer Comment: It should be noted that the cutoff for the above responder criteria/biochemical marker were developed by studying a reasonably broad spectrum of PBC disease patients (i.e., early, moderate, or late stage disease). The enrollment population for trial 747-301 ended up primarily consisting of patients who met the inclusion criterion of ALP $\geq 1.67 \times \text{Upper Limit of Normal (ULN)}$. Patients having TB $\leq \text{ULN}$ signifies earlier stage disease patients.

The Rotterdam, which is the criteria most widely used in Europe for PBC disease staging, specifically defines early stage PBC disease as normal TB (i.e., TB $\leq \text{ULN}$) and normal albumin (i.e., albumin $\geq \text{LLN}$); moderately advanced stage PBC disease as having elevated ALP and either abnormal TB (i.e., TB $> \text{ULN}$) or abnormal albumin (i.e., albumin $< \text{LLN}$); and advanced stage PBC disease as having elevated ALP, abnormal TB, and abnormal albumin. Overwhelming majority of patients (i.e., 90.3%) enrolled in the pivotal 747-301 study were designated as early stage PBC patients using the Rotterdam criteria. (Please note that any reference to early stage PBC disease in this review document specifically refers to early stage PBC disease as defined by the Rotterdam criteria.)

6.3.1 Ethical Conduct of the Study

This study was conducted in accordance with the European Union (EU) Clinical Trials Directive (2001/20/EC and subsequent amendments), 21 CFR Part 312, Good Clinical Practice (CPMP/International Conference on Harmonisation [ICH]/135/95), and based on the ethical principles stated in the Declaration of Helsinki (amended Seoul, Republic of Korea, October 2008) as well as other applicable regulatory requirements.

Informed consent document: The Investigator explained the nature, purpose and risks of the investigation drug use in this study to the patient. A copy of ICD was provided to patient. The patient was informed that participation was voluntary and that her/his future medical treatment would not be compromised by participation in the study and that s/he could withdraw from the study at any time.

In this reviewer's opinion the conduct of trial and the ICD were acceptable. (ICD reviewed: in the Appendix 16.13., CSR 747-301)

6.3.2 Study Design

Overview and Objective

Some sections of this review were reproduced from the statistical reviewer (Dr. Benjamin Vali). Please refer to the statistical reviewer memo for further details.

The primary objective of this study in PBC patients was to demonstrate the efficacy of OCA relative to placebo, based on its effects on ALP and TB. Since 90% of patients had a normal TB, the efficacy was assessed solely on the basis of ALP.

The phase 3 study (Trial 747-301) included a screening period of up to 8 weeks, a 12-month double-blind placebo-controlled treatment period, and an open-label extension period of up to 5 years (for a total maximum participation duration of 74 months). All patients who completed or discontinued from the trial, for any reason, had a follow-up visit 4 weeks after their last dose of study medication. After the patient provided informed consent each patient underwent screening assessments to determine study eligibility. The two most significant inclusion criteria pertained to pre-treatment assessed ALP and TB values along with allowing concomitant usage of UDCA while participating in the study.

If all eligibility criteria were met, the patient was stratified into one of four groups, i.e., two factors each with two sub-categories (specified in parentheses):

1. Pre-treatment ALP > 3.0×ULN and/or aspartate aminotransferase (AST) > 2.0×ULN and/or TB > ULN; ('no' for all three conditions, 'yes' to at least one of the three conditions)
2. Intolerance to UDCA; ('no' hence UDCA usage for at least 12 months, with a stable dose for at least 3 months, prior to study start with the assumption of continued stable usage of UDCA throughout the study, 'yes' hence no UDCA usage for at least 3 months prior to study start with the assumption of continued non-usage of UDCA throughout the study).

The patients in each of the four possible strata were then randomized via Interactive Voice-Response System/Interactive Web-Response System (IVRS/IWRS) in a 1:1:1 ratio to receive 10 milligrams (mg) OCA, 5 mg OCA with the option to titrate up to 10 mg at Month 6 (i.e., the 'OCA Titration' treatment arm), or matching placebo. Study medication was administered orally, once daily as a single tablet, for 12 months. For all treatment arms (although specifically targeting the blinded OCA Titration treatment arm), the criteria to be eligible for up-titration at the 6 month time point/visit, assessed by the on-site investigator (and subsequently made via the IVRS/IWRS), was if the patient met any (i.e., "and/or") of the following conditions:

- ALP ≥ 1.67×ULN
- TB > ULN
- < 15% ALP reduction at Month 6 versus the mean double-blind pre-treatment ALP value(s)
- Provided adverse events (AEs) (e.g., severe pruritus) did not limit the administration of a higher dose.

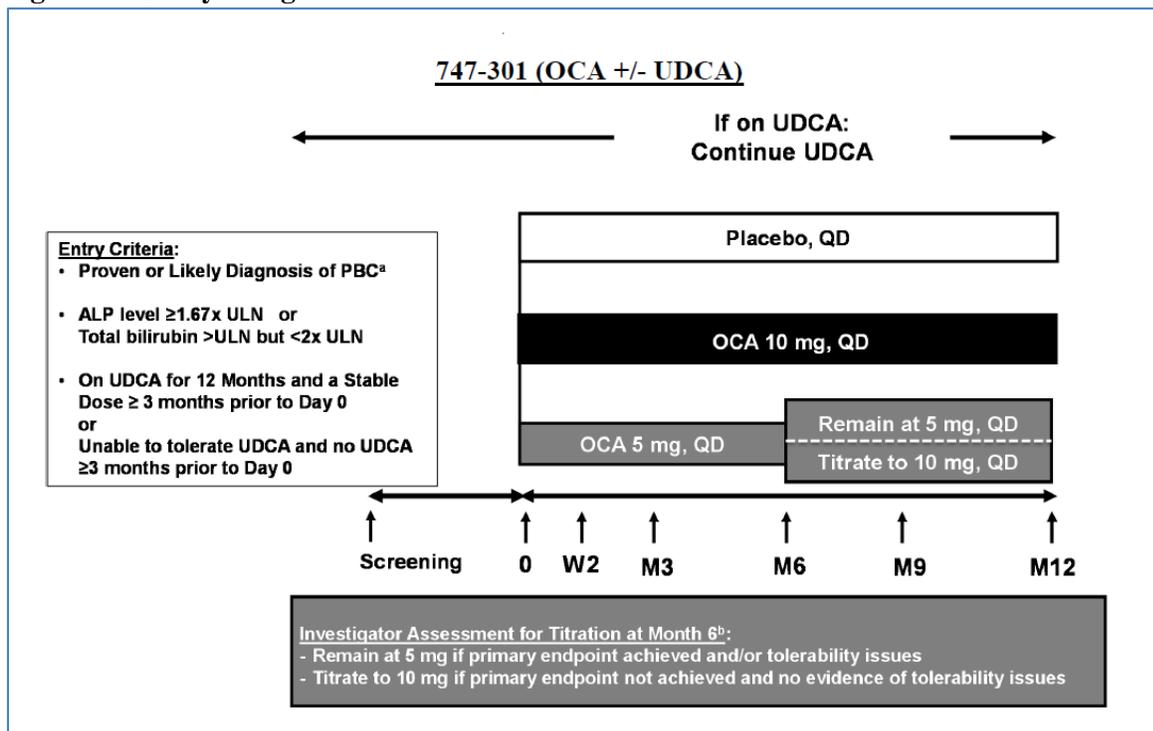
Note that the visit for assessing the potential for up-titration was the Month 6A visit while the actual, if eligible, up-titration occurred at the Month 6B visit in a blinded manner. The Month 6A and 6B visits were within seven days of each other.

Following randomization, patients had five in-clinic trial visits at Week 2 and Months 3, 6, 9 and 12 to evaluate efficacy, safety, tolerability and compliance with study medication. Three central laboratories were utilized, one for each geographic region (i.e., North America, Europe, and Australia), to aid in these assessments. Patients were contacted by the trial site staff on a monthly basis between clinic visits beginning with Month 1.

As previously stated, after completing the 12-month double-blind treatment period, each patient, regardless of their original randomized treatment assignment, was offered to continue on open-label OCA treatment during a long term safety extension (LTSE) period beginning at Month 12 and lasting up to 5 years. All patients participating in this LTSE period who were not being administered 10 mg OCA at the end of the double-blind treatment period would start on 5 mg OCA; patients being administered the 10 mg dose at the end of the double-blind treatment period would continue on their 10 mg dose. Clinic visits occurred every 3 months during the LTSE period and at each visit, patients would be assessed to see if they qualified for 5 to 10 mg incremented up-titrations (i.e., one eligible 5 to 10 mg up-titration per 3-month visit) up to a maximum trial dose of 25 mg. This maximum trial dose was later revised by an additional protocol amendment made on August 25, 2014 to not exceed 10 mg; patients who had titrated beyond a 10 mg dose prior to this amendment (i.e., on protocol versions on or before September 24, 2012) were allowed to remain on that higher dose if approved by the investigator. The criteria to be eligible for up-titrations at these visits were the same as previously presented for the Month 6 visit. All patients would continue their pre-study dose of UDCA throughout their participation in the double-blind and LTSE periods.

As previously stated above, all 747-301 trial data presented within this written review reflect a study data cutoff date of June 29, 2015. The overall study scheme for both the double-blind and LTSE periods are shown in **Figure 21** below. Note that the target sample size for the study was for 180 patients (i.e., 60 per treatment arm); a total of 217 patients were ultimately enrolled and randomized with 216 being administered at least one dose of study drug (see Section 3.2.3 below).

Figure 22: Study Design for Double-Blind Phase of 747-301



Source: Copied and electronically reproduced from the Applicant Submission, Summary of Clinical Efficacy page 27 of 190

^a Definite or probable PBC diagnosis (consistent with AASLD and EASL Practice Guidelines, 2009) as demonstrated by the presence of ≥ 2 of the following 3 diagnostic factors:

1. History of elevated ALP levels for at least 6 months
2. Positive AMA titer or if AMA negative or in low titer ($<1:80$) PBC specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
3. Liver biopsy consistent with PBC

Duration of Treatment: Screening period ≤ 8 weeks and a 12-month double blind treatment phase.

As noted in the statistical review by Benjamin Vail, MS:

Assuming from published literature and previous trial experience, that 40% of patients randomized to 10 mg OCA and 14% of patients randomized to placebo achieve a response based on the primary composite endpoint, a sample size of 180 randomized patients (i.e., 60 patients per treatment group) would provide 90% power to detect a statistically significant difference between OCA and placebo, using a two-sided test of equality of binomial proportions at a 5% level of significance (i.e., $\alpha=0.05$). A total of 217 patients were ultimately enrolled and randomized in this study, however, one patient discontinued prior to being dosed with the investigational agent.

Throughout the execution of this protocol, an IDMC operated according to a DMC Charter. It provided an ongoing, independent, and expert review of the safety data in order to provide risk management during the conduct of the study. Note that there were no formally planned interim analyses for this study. The investigator, the data safety monitoring committee (DSMC), or patients were not prematurely unblinded to treatment assignment. There were 2 inadvertent unblindings of investigational product to a clinical research associate (CRA) and the Applicant (please see section on protocol violation).

The reviewer notes these two un-blindings did not affect the assessment of safety and efficacy.

Multiplicity Adjustments:

The primary efficacy composite endpoint was the percentage of patients at month 12 with ALP $<1.67x$ ULN and total bilirubin \leq ULN and ALP decrease of $\geq 15\%$ from baseline. The primary efficacy analysis of the composite endpoint compared the OCA 10 mg group to placebo.

A hierarchical approach was used to control the overall significance level (type 1 error) for the key secondary efficacy analysis of the pairwise comparison of the OCA titration to placebo for the percentage of patients at month 12 with ALP $<1.67x$ ULN and total bilirubin \leq ULN and ALP decrease of $\geq 15\%$ from baseline. If the 10 mg OCA comparison to placebo was not statistically significant (i.e., p-value greater than or equal to 0.05), then the hypothesis test for the OCA titration comparison to placebo on the primary endpoint would be deemed as exploratory.

The key secondary efficacy endpoint was considered confirmatory only if the analysis of primary endpoint was statistically significant.

All other secondary endpoints were considered exploratory.

A subgroup analyses for gender, age ≥ 65 years, <65 years, ≥ 50 year and <50 years, race, baseline BMI <30 kg/m², ALP $> 3x$ ULN and $\leq 3x$ ULN, baseline UDCA use, baseline Bilirubin and geographic region was also conducted.

SITES: Fifty nine investigators from 13 countries participated in this study including 15 sites in the United States, 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.

Safety Assessment:

All adverse event (AE) summaries were restricted to TEAEs, defined as any AEs that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. If it could not be determined whether the AE was treatment emergent due to a partial onset date then it was counted as such. Verbatim terms on eCRFs were mapped to preferred terms and system organ classes using the MedDRA (version 15.0).

In the Table below is the description of AE severity as utilized by the Applicant to classify the AEs.

Table 60: Severity of Adverse Events

Grade	Clinical Description of Severity
1 = Mild	Causing no limitation of usual activities; the patient may experience slight discomfort.
2 = Moderate	Causing some limitation of usual activities; the patient may experience annoying discomfort.
3 = Severe	Causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain.

Source: Copied and electronically reproduced from CSR 747-301 page 53-3119

AE of pruritus was summarized reporting severity and frequency of the intervention required. Severity grading, mild, moderate and severe, used in this trial is shown in Table 5 below. Pruritus was assessed by VAS (visual analog scale), and 5-D questionnaire. The VAS ranges from 0 (no pruritus) to 100 (severe pruritus). 5-Dimensional questionnaire is used to assess itching in several different diseases utilizing 5 domains: degree, duration, direction, disability and distribution. Patient symptoms were also assessed using the PBC-40 question questionnaire. The PBC-40 scoring system assesses patient symptoms across several domains: fatigue, emotional and social, cognitive function, general symptoms, and itch.

Table 61: Severity of Pruritus

Pruritus Grade	Clinical Description of Severity for Pruritus	Titration Eligibility Guideline
1 = Mild	Generally localized; causing no limitation of usual activities or minimal sleep disturbance; the patient may have experienced slight discomfort. Medicinal intervention was not indicated.	Yes
2 = Moderate	Intense or widespread; causing some limitation of usual activities or sleep disturbance; the patient may have experienced annoying discomfort. Medicinal intervention may have been indicated.	Yes; use clinical judgment
3 = Severe	Intense or widespread and interfering with activities of daily living, i.e., causing inability to carry out usual activities, or severe sleep disturbance; the patient may have experienced intolerable discomfort. Medicinal intervention was typically indicated.	No

Source: Copied and electronically reproduced from CSR 747-301 page 53-3119

An adverse event or suspected adverse reaction was considered 'serious' if, in the view of either the investigator or Applicant, it results in any of the following outcomes:

1. Death
2. Is life threatening
3. Requires in-patient hospitalization or prolongs an existing hospitalization
4. Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect
6. An important medical event that may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Key Inclusion Criteria

1. Definite or probable PBC diagnosis as demonstrated by the presence of ≥ 2 of the following 3 diagnostic factors:
 - a. History of elevated ALP levels for at least 6 months

- b. Positive AMA titer or if AMA negative or in low titer (<1:80) PBC specific antibodies (anti-GP210 and/or anti-SP100 and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
 - c. Liver biopsy consistent with PBC
 2. At least 1 of the following qualifying biochemistry values:
 - a. ALP \geq 1.67x ULN
 - OR
 - b. Total bilirubin > ULN but < 2x ULN
 3. Age \geq 18 years
 4. Taking UDCA for at least 12 months (stable dose for \geq 3 months) prior to Day 0, or unable to tolerate UDCA (no UDCA for \geq 3 months) prior to Day 0.
 5. Contraception: Female patients had to be postmenopausal, surgically sterile, or if premenopausal, had to be prepared to use \geq 1 effective (\leq 1% failure rate) method of contraception during the study and for 30 days after the EOT Visit.

Key Exclusion Criteria

1. Any hepatic decompensation
 - a. portal hypertension, cirrhosis and complications of cirrhosis/portal hypertension
 - b. History of liver transplantation, current placement on a liver transplant list or current Model for End Stage Liver Disease (MELD) score \geq 15
 - c. Cirrhosis with complications, including history or presence of: spontaneous bacterial peritonitis, hepatocellular carcinoma, bilirubin > 2x ULN
 - d. Hepatorenal syndrome (type I or II) or Screening serum creatinine > 2mg/dL (178 μ mol/L)
2. Competing etiology for liver disease (example Hepatitis C, active Hepatitis B, nonalcoholic steatohepatitis (NASH), alcoholic liver disease (ALD), autoimmune hepatitis, primary sclerosing cholangitis, Gilbert's Syndrome)
3. Severe pruritus (Intense or widespread and interfering with activities of daily living) or pruritus requiring treatment with bile acid sequestrants, rifampicin within 2 months of day 0
4. On prohibited medications (such as fenofibrates, budesonide, corticosteroids, valproate, isoniazid etc.); please see the list of prohibited medications in protocol review.
5. Prolonged QT interval, pregnancy or lactation; previous participation in the OCA trial.
6. If female: known pregnancy, or had a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
7. Known history of human immunodeficiency virus infection
8. Presence of any other disease or condition that was interfering with the absorption, distribution, metabolism, or excretion of drugs including bile salt metabolism in the intestine. Patients with inflammatory bowel disease or who had undergone gastric bypass procedures were excluded (gastric lap band was acceptable).
9. Medical conditions that could cause nonhepatic 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 leukemia)
10. Other clinically significant medical conditions that were not well controlled or for which medication needs were anticipated to change during the study
11. History of alcohol abuse, or any other drug abuse.
12. Participation in another investigational drug, biologic, or medical device study within 30 days prior to Screening

Reviewer Comment: The enrollment population based on the inclusion and exclusion criteria, in addition to the AASLD/EASL criteria, has reasonably excluded all other etiologies with elevated or low ALP (bone disease or intestinal disease).

Patient Discontinuation

Female patients who became pregnant were required to stop taking investigational product and withdrawn from the study. The following additional events were considered appropriate reasons for a patient to discontinue from the study:

1. Patient had ≥ 28 days of drug holiday during the double-blind phase (days of drug holiday did not need to be consecutive).
2. Patient withdrew consent or requested to be withdrawn from the study.
3. Patient experienced an AE that in the opinion of the investigator or medical monitor was caused by or exacerbated by any of the study procedures or investigational product, and was of sufficient intensity to warrant discontinuation.
4. Patient refused to comply with the requirements for study participation.
5. Investigator's or Applicant's decision.
6. Patient initiated a new therapy for PBC.

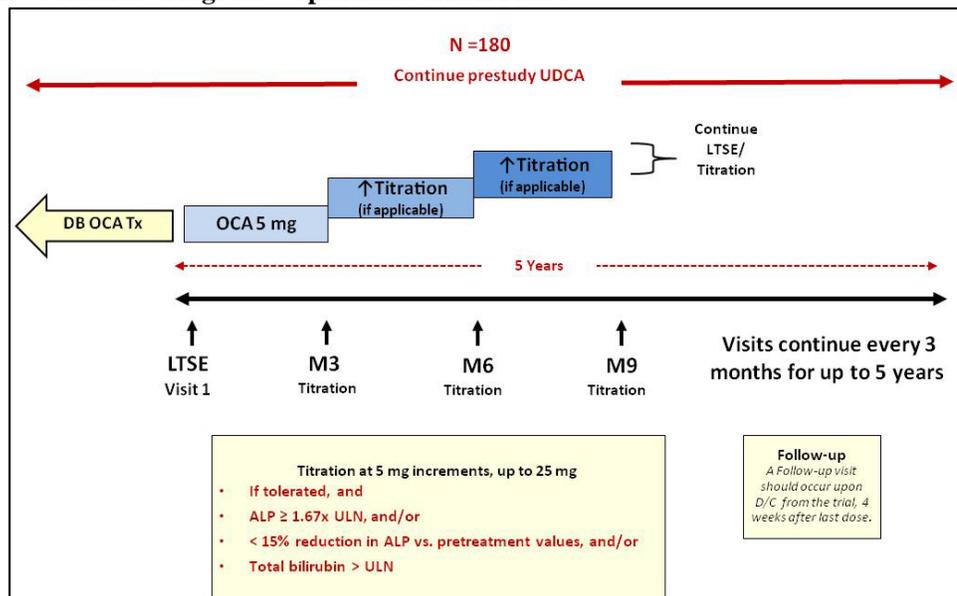
The date when the patient was withdrawn and the primary reasons for discontinuation was recorded in the electronic CRF (eCRF) and if possible, discussed with Applicant's medical monitor. Patients were considered "lost to follow-up" only after attempts to reach the patient proved unsuccessful. In all cases, a reasonable effort was made to determine the reason(s) that a patient failed to return for required study visits or discontinued from the study. If a patient was withdrawn from the study early (regardless of the cause), all of the EOT evaluations were performed at the time of withdrawal, to the extent possible. Additionally, the patient was requested to return for the follow-up visit, 4 weeks after his/her last dose of investigational product.

Reviewer Comment: In this reviewer's opinion, the follow up procedures for patients who discontinued from trial or were lost to follow-up were adequate.

Long term safety extension (LTSE) phase: Upon completion of the double-blind phase, all eligible patients will enter an open label LTSE phase during which they will start 5 mg OCA and may be titrated up to receive 10 mg of OCA for up to 5 years. As per the latest amended protocol, maximum allowed dose is OCA 10 mg and the up-titration in the LTSE was changed to 3 month instead of 6 months, similar to the labeling recommendation.

Patients taking UDCA before screening continued UDCA treatment during the LTSE phase, while patients who were unable to tolerate UDCA before screening received OCA monotherapy.

Figure 23: Schematic Diagram – Open Label LTSE Phase



Source: Copied and electronically reproduced from the Applicant Submission, August 25, 2014 Protocol Amendment, and page 33 of 391.

Table 62- Schedule of Trial Procedures – Double Blind Phase

DB Phase Visits	Screening		Day 0	W2	Safety Contact ⁶	M3	M6 (Visit A) ⁷	M6 (Visit B) ⁷	M9	M12/ LTSE D 1	EOT	Follow-up (4 weeks)
Visit Windows (+/-)	≤1 to -8 Wks.			±7 days	±7 days	±2 wks.	≤7 days vs. M6-VB	±2 wks.	±2 wks.	±2 wks.		±7 days
STUDY PROCEDURES												
Informed Consent	X											
Medical and Disease History	X											
Inclusion/Exclusion Criteria	X		X									
Physical Exam (Height at Screen only)	X							X		X	X	
Vital Signs	X		X	X		X		X	X	X	X	X
12-Lead Electrocardiogram	X							X		X	X ^B	
Patient Questionnaires ¹			X	X		X		X	X	X ^A	X ^A	X
Transient Elastography (TE) ²			X							X	X ^B	
Liver Biopsy ³	X											
DEXA Scan ¹⁰			X							X	X ^B	
Adverse Events			X	X	X	X		X	X	X	X	X
Prior and Concomitant Medications	X		X	X	X	X		X	X	X	X	X
Randomization/Treatment Assigned			X							X		
Dose Titration (if applicable)								X				
Dispense Study Medication (IP)			X	X		X		X	X	X		
IP Accountability/Compliance				X	X ⁶	X		X	X	X	X	
On-site IP Administration				X		X		X	X	X		
CLINICAL LABORATORY EVALUATIONS												
Serum Chemistry/Hematology	X ⁴	X ⁴	X	X		X	X		X	X	X	X
Serum Bile Acids			X				X			X	X	
Lipoprotein Analysis			X				X			X	X	
ELF/Other Analytes			X				X			X	X ^B	
Genetics Study			X							X		
Urinalysis (dipstick)	X		X				X			X	X	
Urine-based β-hCG Pregnancy Test ⁵	X		X	X		X	X		X	X	X	

Source: applicant's submission, NDA207999, Study 747-301 Protocol submitted on 24 September 2012, page 33/106

Table 1 Footnotes

1. Patient Questionnaires include PBC-40, 5-D Pruritus Scale, Pruritus VAS; also a Patient Research Questionnaire will be administered at DB M12, or DB EOT if early termination, only.
2. Transient elastography (TE) will be conducted at selected trial sites where the Fibroscan® TE device is available. If a TE was performed within 3 months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.
3. A pretreatment liver biopsy must be collected within 1 year of (prior to) the Day 0 visit.
4. Patients whose Screening ALP value is < 2x ULN OR whose Screening bilirubin is > 1x ULN, should return at least 2 weeks later for a second Screening ALP OR bilirubin assessment. For these patients, the mean of both Screening values (ALP and/or bilirubin) will be used to confirm eligibility.
5. Urine-based β-hCG pregnancy tests must be performed in females of childbearing potential. If positive, a confirmatory blood test must be performed at the site. If the blood test is also positive, the patient may not be enrolled or must be discontinued from the trial.
6. Patients should be contacted by telephone on a monthly basis (+/- 7 days) between at-clinic trial visits starting at Month 1 and continuing through the DB phase to assess for AEs and verify that s/he is dosing as directed.
7. The Month 6 trial assessment will occur across 2 separate at-clinic visits and a remote telephone Safety Contact for patients who meet the titration criteria (i.e., are presumably titrated).
8. If a patient has completed the following assessments within 3 months of terminating early, AND so long as safety issues do not warrant repeated tests, the 12-lead ECG, ELF/Other Analytes, and dual-emission X-ray absorptiometry (DEXA) scan may be omitted. Similarly, so long as a TE assessment has been done within 6 months, it may be omitted.
9. A genetics study will be conducted for patients and at trial sites willing to provide samples. Willing patients must specifically consent to participate in this evaluation.
10. The DEXA bone density scan will be done at selected trial sites only. Patients that have had a recent DEXA scan within 6 months prior to Day 0 and for which a report of the results is available for use in this trial, do not need to repeat the baseline DEXA scan. Otherwise, a window of ± 2 weeks for the scan is acceptable.

Table 63- Schedule of Trial Procedures – Long Term Safety Extension Open Label Phase

LTSE Visits	DB M12/ LTSE D1	W2/Post-titration Safety Contacts ¹ (Telephone)	LTSE Mo. 3	LTSE Mo. 6	LTSE Mo. 9	LTSE Mo. 12	EOT	Follow-up (4 weeks)
			(Annual Schedule) ²					
Visit Windows (+/-)	±2 wks.	±14 days	±2 wks.	±2 wks.	±2 wks.	±2 wks.		±7 days
STUDY PROCEDURES								
Physical Exam	X			X		X	X	
Vital Signs	X		X	X	X	X	X	X
12-Lead Electrocardiogram	X			X		X	X ⁴	
Patient Questionnaires	X		X	X	X	X	X	X
Transient Elastography (TE)	X					X	X ⁴	
Liver Biopsy						X ³		
DEXA Scan ⁵	X					X	X ⁴	
Adverse Events	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X
Randomization/Treatment Assigned	X							
Dose Titration (if applicable)			X	X	X	X		
Dispense Study Medication (IP)	X		X	X	X	X		
IP Accountability/Compliance	X	X ¹	X	X	X	X	X	
On-site IP Administration	X		X	X	X	X		
CLINICAL LABORATORY EVALUATIONS								
Serum Chemistry/Hematology	X		X	X	X	X	X	X
Serum Bile Acids	X			X		X	X	
Lipoprotein Analysis	X			X		X	X	
ELF/Other Analytes	X					X	X ⁴	
Urinalysis (dipstick)	X			X		X	X	
Urine-based β-hCG Pregnancy Test	X		X	X	X	X	X	

Source: applicant's submission, NDA207999, Study 747-301 Protocol: submitted on 24 September 2012, page 33/106

Table 2 Footnotes

1. All patients entering LTSE will be contacted by telephone for a Safety 2 weeks after starting the LTSE. Additionally, the investigator will contact the patient approximately 2 weeks following any dose titration to assess for AEs and verify that s/he is dosing as directed.
2. Patients who meet the titration criteria should be up-titrated during the LTSE. Titration will proceed incrementally by 5 mg to 10 mg at a frequency of no more than one up-titration every 3 months. Visits at which titration will occur will be scheduled across 2 separate at-clinic visits and a remote telephone Safety Contact (e.g., refer to Table 1 Section 3.2, Month 6 - Visit A and Month 6 - Visit B.)
3. Liver biopsy: A follow up biopsy will be done after 3 years (± 3 months) of dosing on OCA. For patients randomized to receive placebo during the DB phase, this will occur at LTSE Month 36 (± 3 months) in the trial.
4. If a patient has completed the following assessments within 3 months of terminating early, AND so long as safety issues do not warrant repeated tests, the 12-lead ECG, ELF/Other Analytes, and DEXA scan may be omitted. Similarly, so long as a TE assessment has been done within 6 months, it may be omitted.
5. The DEXA bone density scan will be done at selected trial sites only. A window of ± 2 weeks for the scan is acceptable

Prohibited Medications

Prohibited 6 months prior to Day 0 and throughout the study (i.e., to last dose and/or EOT)

1. azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline
2. fenofibrate or other fibrates
3. budesonide and other systemic corticosteroids
4. potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)

Prohibited 12 months prior to Day 0 and throughout the study (i.e., to last dose and/or EOT):

1. Antibodies or immunotherapy directed against interleukins or other cytokines or chemokines

Permitted Medications

1. Topical or inhaled corticosteroids
2. Patients taking herbal supplements or botanical preparations that were purported to affect the liver (eg, milk thistle) were permitted to take these during the study, provided that the dose and treatment regimen of these agents was kept constant during the double-blind phase.
3. UDCA treatment dose and regimen were captured in the eCRF. Patients who entered the study as OCA monotherapy patients (i.e., not taking UDCA) could not initiate treatment with UDCA at any time during the double-blind phase.
4. Patients 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).
5. Patients taking hormonal contraceptives continued to take them. Changes in formulation or dosage during the study were recorded in the source documents and eCRF.
6. Concomitant medications were to be stable prior to Day 0. Investigators endeavored to keep the doses of all concomitant medications the same during the course of the study, where medically appropriate. Patients with other concomitant conditions that were not well controlled or whose medication needs were anticipated to change during the study were not enrolled in the study.

Efficacy and Safety assessments: The schedule of assessments for the double-blind phase is provided in Table 66 and Table 67. Notably, all the laboratory samples were analyzed in a central laboratory.

Table 64: Primary Endpoints for Trial 747-301

Primary Efficacy endpoint	Variable
ALP < 1.67x ULN and total bilirubin within normal limits (WNL), <u>and</u> ALP decrease of ≥ 15%	Percentage of patients (OCA 10 mg Vs. Placebo) achieving the composite endpoint at month 12
Safety and tolerability:	Adverse events (AEs): 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. Other safety related clinical outcomes: <ul style="list-style-type: none"> ▪ Death (from hepatic and nonhepatic related causes) ▪ Liver transplantation or placement on liver transplant list, MELD score ≥ 15 ▪ Portal hypertension and complications including esophageal bleeds, interventions to manage variceal bleeds (e.g., insertion of variceal bands or TIPS) and diuretic resistant ascites ▪ Cirrhosis with complications: development of hepatic decompensation (hepatic decompensation, hepatorenal syndrome [type I or II]), spontaneous bacterial peritonitis), hepatocellular carcinoma and histological development of cirrhosis

Source: Reviewer Generated from the Applicant Protocol (25th April 2014)

Table 65: Secondary Endpoints for Trial 747-301

Secondary Objectives	Variable
Key Secondary efficacy endpoint	Percentage of patients (OCA titration vs placebo) achieving composite endpoint at Month 12 ALP < 1.67x ULN and total bilirubin within normal limits (WNL), <u>and</u> ALP decrease of ≥ 15%
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-time points

	Percentage of patients with a decrease in ALP response rates of $\geq 10\%$, $\geq 15\%$, $\geq 20\%$, $\geq 40\%$ from baseline or \leq ULN
Other secondary endpoints	Percentage of patients achieving the biochemical treatment response criteria associated with improved clinical outcomes in patients with PBC: <ul style="list-style-type: none"> • ALP $\leq 3x$ ULN and AST $\leq 2x$ ULN and bilirubin \leqULN ((Corpechot 2008); Paris I) • ALP $\leq 1.5x$ ULN and AST $\leq 1.5x$ ULN and bilirubin \leqULN ((Corpechot 2011), Paris II) • ALP $\leq 1.67x$ ULN and bilirubin \leqULN ((Momah 2012), Mayo II) • ALP $\leq 1.76x$ ULN ((Kumagi 2010b), Toronto II) • Normal bilirubin (values \leqULN) and/or normal albumin (values \geqlower limit of normal [LLN]; (Kuiper 2009) [Rotterdam criteria])
Disease specific symptoms	Absolute and percent change from Baseline at all-time points on PBC-40 domains Percentage of patients with each response on the Patient questionnaires (5-dimensional [5-D] pruritus, and pruritus visual analog scale [VAS])
Biomarkers and noninvasive assessments of liver fibrosis	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-time points on C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), tumor necrosis factor-beta (TGF- β), fibroblast growth factor-19 (FGF-19) levels, interleukin-6 (IL-6), and CK-18.
Bile acids for Pharmacokinetic and Pharmacodynamics 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
Other Exploratory Evaluations	Absolute and percent change from Baseline on PBC autoantibodies (IgA, IgG, IgM), cytokines, and interleukins (IL-12 [p40], IL-23).

Source: Reviewer Generated from the Applicant Protocol (25th April 2014) and Clinical Study report

Treatment Compliance

The Investigator assessed the patient's compliance with dosing of investigational product, at least at each visit, by conducting drug accountability (i.e., count of returned tablets). The Investigator followed up with the patient to retrieve any investigational product bottles that had not been returned, even if empty.

Patients who missed a dose of investigational product were instructed to take it later the same day, as soon as they remembered. "Missed" doses were not to be taken on a subsequent day (i.e., the patient was instructed not to take more than the prescribed daily dose of 1 tablet in the double-blind phase).

Interim Analyses and Data Monitoring

This reviewer notes that no interim efficacy analysis during the double-blind phase was planned or conducted.

After all patients had completed the double-blind phase of the study, the database was locked and analyses were performed. An independent DSMC reviewed safety data (for AEs and SAEs, and clinical laboratory data) at periodic intervals. The Applicant stated that the members of the DSMC were not allowed to participate as investigators in this study and were not otherwise consultants for the Applicant.

Statistical Analysis Plan

The primary composite endpoint was assessed for patients within the OCA and placebo treatment groups. For descriptive purposes, the responder rates at Months 6 and 12 were calculated for all treatment groups separately along with corresponding 95% Wald Confidence Intervals (CI).

The applicant's analysis, based on DGIEP advice, utilized a Cochran-Mantel-Haenszel (CMH) test, which adjusted for both randomization stratification variables (as previously described above). In tandem with the CMH test, a Breslow-Day test was also conducted in order to test for the homogeneity of the treatment effect across the different randomization strata.

Protocol Amendments

The protocol for Study 747-301 was originally dated 07 September 2011 and had 4 protocol amendments from 7 February 2012 to 24 April 2014. Protocol amendments were performed during the double blind phase of the clinical trial and the SAP was changed prior to unblinding of the data.

Summary of the key changes in the amendments:

Addendum #1 (7 February 2012): The screening for pregnancy before and at adequate intervals over the course of the double blind and long terms safety extension of clinical trials were added to address the legal requirements in Austria.

Amendment # 1 (18 January 2012):

- Most of the changes were administrative and spelling corrections
- End of Trial clarified: when last patient(s) completes their follow up visit at conclusion of LTSE. For DB phase: occurs when the last patient(s) completes their DB month 12 study visit.
- The staggering of the bile acid sequestrants and UDCA dosing was revised.

Amendment # 2 (April 4th, 2012): The protocol was submitted to the European Clinical Trials Facilitation Arm (CTFG) for review under Voluntary Harmonization Procedure (VHP) on 24 November 2011. The changes in this amendment were to address the comments provided by VHP, most changes did not affect the protocol in general except:

- Drug holiday revised for clarification: Patients with drug holidays of > 28 days (original protocol >14 days) total during the DB phase should be discontinued from the trial.
- Other therapies for pruritus can be utilized as deemed clinically appropriate.
- Clarification of inclusion and exclusion criteria; timing of the liver biopsy for patient in DB phase who will continue LTSE phase changed from 48 months to 36 months (± 3 months).
- Severe pruritus definition: "patients requiring treatment with BAS or rifampicin within 2 months of Day 0" for the exclusion criteria was clarified.
- Timing of laboratory data collection (baseline and follow up) revised for clarity.

Amendment # 3 (24 September 2012): Most changes editorial or clarifications.

- The requirement for use of contraception was extended to 30 days AFTER the End of Treatment (EOT) visit from the original text reading, "...UNTIL the EOT" visit.
- Hepatitis B patients who seroconvert may be included in the trial.
- DEXA if available from past 6 months from Day 0 of trial, a baseline DEXA will not be obtained.

Amendment # 4 (April 24, 2014):

- During the LTSE phase, effective with Protocol Version 4, patients should be titrated to a maximum of 10 mg daily. Patients who were titrated above 10 mg prior to Protocol Version 4 may remain on their current dose or the dose may be decreased as clinically indicated.

Reviewer Comments: These amendments did not affect the safety and efficacy evaluation of the trial.

Global trial: Diagnostic criteria and definitions used for enrolling the patients are consistent with the meeting discussions between the FDA and the Applicant that occurred during the drug development program since 2004. PBC is a rare disease, therefore enrolling patients from foreign sites allowed the Applicant to recruit more patients that allowed an adequately powered clinical trial. The pathophysiology, disease course and standard of care are similar globally; therefore, this reviewer agrees that including foreign data (both for safety and efficacy) is applicable to the US population. In addition, similar clinical protocols for phase 2 and 3 were used for both the US and the foreign study centers.

Data Quality and Integrity: Applicant's Assurance

The submission was of good quality. The electronic application was well organized and easily navigable.

6.3.3 Study Results

6.3.3.1 Compliance with Good Clinical Practices

According to the Applicant, this study was performed in accordance with the European Union (EU) Clinical Trials Directive (2001/20/EC and subsequent amendments), 21 CFR Part 312, Good Clinical Practice (CPMP/International Conference on Harmonization [ICH]/135/95), and with the ethical principles stated in the Declaration of Helsinki (amended Seoul, Republic of Korea, October 2008) and applicable regulatory requirements of the countries in which they were conducted.

The application also included a debarment certification that the applicant did not use the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

6.3.3.2 Financial Disclosure

The Applicant provided a single signed copy of FDA Form 3454 with an appended list of investigator names from each covered study. This certified that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

One FDA Form 3455s was provided, which was related to grant money received by an investigator for another trial of OCA. This trial was conducted to support the nonalcoholic steatohepatitis (NASH) trial with OCA.

However, no investigators reported financial arrangements for conducting the phase 3 trial in PBC. There were 59 investigators at 59 sites in 13 countries involved in the trial.

Reviewer Comment: None of the reported financial disclosures (as noted above) affect the approvability of the application.

6.3.4 Patient Disposition

For Clinical trial 747-301 a total of 316 patients were screened, 217 were randomized to investigational product and 216 randomized patients received at least 1 dose of investigational product. One patient in the OCA titration arm withdrew consent after randomization and prior to first dose of investigational product.

A total of 198 patients completed the double blind phase of the 747-301 trial. A total of 19 patients discontinued the double-blind phase prematurely:

- 1 (<1%) due to death,
- 8 (4%) due to pruritus,
- 6 (3%) due to AEs other than pruritus, and
- 4 (2%) due to withdrawn consent.

At the end of the 12-month, double-blind period, approximately 90% of patients enrolled into the open-label, LTSE phase of the study.

Table 66: Patient Disposition: Randomized Population (N = 217)

Number of Patients, n (%)	Placebo	OCA Titration	OCA 10 mg	Total
Enrolled / Randomized	73	71	73	217
Dosed	73	70	73	216
Completed Month 6 Titration Visit, n (%) ^a	70 (96)	69 (97)	64 (88)	203 (94)

Completed Double-Blind Phase, n (%) ^{ab}				
Yes	70 (96)	64 (90)	64 (88)	198 (91)
No	3 (4)	7 (10)	9 (12)	19 (9)
Primary Reason for Discontinuation from 12-month Double-Blind Phase, n (%) ^a				
Death	0	1 (1)	0	1 (<1)
Pruritus	0	1 (1)	7 (10)	8 (4)
Other AEs	2 (3)	3 (4)	1 (1)	6 (3)
Withdrew consent	1 (1)	2 (3)	1 (1)	4 (2)
Enrolled in the LTSE Phase, n (%) ^a				
Yes	66 (90)	63 (89)	64 (88)	193 (89)
No	7 (10)	8 (11)	9 (12)	24 (11)

Source: Copied and electronically reproduced from CSR 747-301 page 84-3119

^a Denominator is based off the N of each treatment arm based on patients randomized.

^b Patients completing assessments through the double-blind, 12-month treatment period are considered completers.

During the double blind phase of trial 747-301, there was one death in OCA titration arm (due to cardiac failure). This SAE occurred in an 82 year female with pre-existing congestive heart failure, atrial fibrillation, deep venous thrombosis, myocardial infarction (x2), hypertension, gout, chronic renal impairment and implantable cardioverter defibrillator at study entry. On day 219, (b) (6) after initiation of the investigational product (IP), the patient experienced a SAE of cardiac failure. The patient was admitted to the hospital where UDCA and IP were interrupted briefly and then restarted; the cardiac status stabilized and patient was discharged home. On day 257 the patient had a second event of cardiac failure and was hospitalized. The IP dose was discontinued on (b) (6) and the patient died on (b) (6). The primary cause of death was noted as congestive cardiac failure and ischemic heart disease, the secondary cause of death was listed as chronic kidney disease and PBC.

Reviewer Comment: This reviewer concurs with the Applicant's causality assessment that this death is unlikely to be related to OCA.

There were a high proportion of patients who discontinued prematurely from the trial in OCA 10 mg treatment arm due to adverse events of pruritus. Pruritus leading to discontinuation was not seen in the placebo arm but was observed in one patient in the OCA 5 mg (titration) arm.

The study population met appropriate inclusion criteria.

- 66% patients met all 3 diagnostic PBC diagnostic criteria
- 72% patients met 2 of the 3 diagnostic criteria
- <1% patients met 1 diagnostic criteria (elevated ALP)

Reviewer Comment: The population enrolled in Trial 747-301 was the appropriate population per inclusion criteria definition. The inclusion criteria were met in all, but 2 patients. The 2 protocol violations were clarified by the Applicant further. The reviewer considers this protocol violation will not impact the efficacy result, since the patient in OCA titration arm did have a liver biopsy consistent with PBC, which supports the diagnosis. The patient in the placebo arm indeed met two criteria.

Populations Analyzed:

Table 67: Analysis Populations

	Number of Patients, n (%)
--	---------------------------

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

Source: Copied and electronically reproduced from CSR 747-301 page 85-3119

a All randomized patients 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 patients from the ITT population.

c All randomized patients 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 patients 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 patients who received at least 1 dose of OCA who have at least 1 confirmed fasted sample at Month 6 or Month 12 visits (patient 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 patients who received at least one dose of study drug. Treatment assignment was based on the treatment actually received.

For each analysis population, the number of patients across treatment arms was similar, with the exception of the PK population wherein 66 (93%) patients comprised the OCA titration arm and 60 (82%) patients comprised the OCA 10 mg arm.

As per protocol, the OCA titration arm could be titrated from 5 mg to 10 mg at Month 6 assessment, if they had not met the following criteria:

- ALP $\geq 1.67 \times$ ULN, and/or total bilirubin >ULN, or <15% ALP reduction at Month 6 versus the mean double-blind, pretreatment value(s), and no evidence of tolerability issues that limit administration of a higher dose (10 mg).
- Of the 36 patients who did not require titration, 21 (58%) achieved the primary endpoint at Month 6; and the remaining 33 patients were up-titrated to OCA 10 mg dose during the latter 6 months.

6.3.5 Protocol Violations/Deviations

Protocol violations in 747-301 are summarized in Table 71: Minor Protocol Deviations. Most protocol violations did not result in patients being excluded from the primary efficacy and safety analyses.

Table 68: Minor Protocol Deviations

Protocol Deviation ^a	Number of Patients (Number of Deviations)		
	Placebo (N = 73)	OCA Titration (N = 71)	OCA 10 mg (N = 73)
Concomitant Medication	1 (1)	1 (1)	5 (5)
Investigational Product Administration	14 (18)	13 (20)	20 (28)
Inclusion / Exclusion Deviations	19 (23)	12 (12)	9 (10)
Informed Consent	14 (16)	9 (10)	17 (19)
Laboratory	15 (22)	7 (10)	9 (13)
Missed Assessment	24 (55)	25 (53)	21 (43)
Missed Visit	22 (32)	11 (12)	12 (26)

Non-Compliance (i.e., trends, missed measurements)	24 (33)	20 (27)	20 (30)
Other	8 (9)	9 (10)	2 (2)
Out of Visit Window	46 (106)	47 (105)	43 (81)

Source: Copied and electronically reproduced from the Clinical Study report page 95 of 3119

^a Additional deviations that only occurred in 1 patient included: Patient 171001 (OCA titration), drug storage preparation; Patient 182002 (OCA titration), visit schedule; and Patient 171001 (OCA titration), SAE reporting.

Major protocol deviations occurred in five patients:

1. One patient (patient ID 182002, OCA titration) did not use any contraception and became pregnant while on the study drug (she notified the site 59 days after starting the investigational product). She had a spontaneous abortion. She resumed participation in the trial post spontaneous abortion.
2. Two patients in the placebo arm [ID 175003 and ID 142009], received therapy for pruritus with bile acid sequestrants (BAS) two months prior to randomization; and thus were excluded from both the EE and PK populations.
3. Patient ID # 145005 (OCA 10 mg) also received BAS within 2 months prior to randomization (Day 0). The patient also received cyproheptadine for pruritus at baseline. This patient was excluded from the PK population.
4. Patient #105002 (placebo) was non-compliant with investigational product for > 1 month due to shattered tibia and was directed by her physician to stop taking the IP.

Reviewer Comment: The protocol violations of entry criteria for the ITT population were reviewed and this reviewer agrees that the violations for inclusion criterion # 4 (composite endpoints) were comparable across treatment arms and unlikely to impact the efficacy evaluation. The Applicant performed post-hoc sensitivity analyses by removing the patients who deviated from inclusion criterion #4 and this did not affect the efficacy outcomes.

The majority of the violations of informed consent involved updating signatures and did not impact the safety and efficacy of the trial.

Out of visit window deviations were comparable (~60% in each arm) across treatment arms and unlikely to have impacted the efficacy evaluation.

6.3.6 Table of Demographic Characteristics

Table 69: Demographic and Baseline Characteristics: ITT Population (N = 216)

Number of Patients	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)
Number of Patients				
	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)	Total (N = 216)
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)

Source: Copied and electronically reproduced from the clinical study report page 87 of 3119

Reviewer Comments: There were 19% patients who were ≥65 years of age. As expected 91% patients enrolled were females, and 94% were white. PBC is a female predominant disease; therefore, the enrollment population is a representative distribution of the general population and this is acceptable in interpretation of the analyses. European sites enrolled 67% of the trial patients versus 29% of patients enrolled at the North American sites. After reviewing the data, the distribution of site locations has not affected the safety and efficacy of trial.

For the overall population, the mean age was 55.8 years with a range of 29-86 years. The overwhelming majority of patients were in the 40-60 year age range. The distribution of the different age groups is as follows (as calculated by the "adsl" dataset):

3 patient's ≤30 years of age
 12 patients were ≥31 years but ≤40 years of age
 47 patients were >41 years but ≤50 years
 114 patients were >51 years but ≤64 years
 22 patients were >65 years but ≤70 years of age
 18 patients were between age >71 and ≤86 years of age.

The mean body weight and BMI were 69.8 kg and 26.0 kg/m² (range 16.4-49.2 kg/m²) respectively; 82% patients had a BMI <30 kg/m². At baseline, 93% of the population was on UDCA, with balanced representation across each study arm.

A total of 29 patients (13%) had “in-study” pre-treatment liver biopsy performed). In-study biopsy represented a biopsy obtained 6 months prior to enrollment.

Table 70: Fibrosis Staging in Patients with Pretreatment “In-study” Biopsy

Number of Patients	Placebo (N = 7)	OCA Titration (N = 13)	OCA 10 mg (N = 9)	Total (N = 29)
Fibrosis				
No Fibrosis	0	0	0	0
Portal/Periportal Fibrosis Without Septa	0	2 (15%)	2 (22%)	4 (14%)
Portal/Periportal Fibrosis With Few Septa	3 (43%)	5 (38%)	1 (11%)	9 (31%)
Septal Fibrosis	2 (29%)	1 (8%)	5 (56%)	8 (28%)
Incomplete Cirrhosis	2 (29%)	2 (15%)	1 (11%)	5 (17%)
Cirrhosis	2 (29%)	3 (23%)	0	3 (10%)

Source: Applicant submission to NDA; Sequence 0035 (36)

Table 71: Summary of PBC Stage using Historical Biopsy in ITT Population

Category Stage	Placebo (n=56)	Titration OCA (n=52)	10 mg OCA (n=57)	Overall (n=165)
PBC Stage From Initial Diagnostic Liver Biopsy	56	49	55	160
Stage One: Portal Inflammation With Or Without Florid Bile Duct Lesions	18 (32%)	19 (39%)	23 (42%)	60 (38%)
Stage Two: Gradual Increase Of Periportal Lesions Extending Into The Hepatic Parenchyma	15 (27%)	18 (37%)	16 (29%)	49 (31%)
Stage Three: Distortion Of The Hepatic Architecture With Numerous Fibrous Septa	17 (30%)	11 (22%)	15 (27%)	43 (27%)
Stage Four: Cirrhosis With The Existence Of Regenerative Nodules	6 (11%)	1 (2%)	1 (2%)	8 (5%)
PBC Stage Of Most Recent Diagnostic Liver Biopsy	23	16	28	67
Stage One: Portal Inflammation With Or Without Florid Bile Duct Lesions	4 (17%)	2 (13%)	7 (25%)	13 (19%)

Stage Two: Gradual Increase Of Periportal Lesions Extending Into The Hepatic Parenchyma	10 (43%)	8 (50%)	12 (43%)	30 (45%)
Stage Three: Distortion Of The Hepatic Architecture With Numerous Fibrous Septa	6 (26%)	4 (25%)	7 (25%)	17 (25%)
Stage Four: Cirrhosis With The Existence Of Regenerative Nodules	3 (13%)	2 (13%)	2 (7%)	7 (10%)

Source: Applicant submission to NDA; Sequence 0035 (36)

Reviewer Comment: A pretreatment liver biopsy (performed within 6 month prior to enrollment in trial) was performed in only 13% of patients (87% patients had no pretreatment liver biopsy). However, majority of patients had liver biopsies performed which were not “in-study” pre-treatment liver biopsy performed.

Cirrhosis was classified by an initial or baseline “in study” biopsy result or with an Ishak score 6 (cirrhosis) or Ludwig/Scheuer PBC Stage 4:

Of the 216 patients in the pivotal trial, a total of 20 patients had Stage IV fibrosis (cirrhosis) present

- 9 patients in the placebo treatment arm
- 7 patients in OCA titration treatment arm
- 4 patients enrolled to OCA 10mg treatment arm.

6.3.7 Other Baseline Characteristics

Table 72: 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)
Pruritus at Baseline , n (%)^a				
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
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

Source: Electronically copied and reproduced from CSR 747-301 page 88 and 89 of 3119

^a Based on "Is the patient currently experiencing pruritus?" and the severity of pruritus collected Day 0 VAS eCRF.

Table 75 About 63% patients had history of pruritus, and 59% had pruritus at baseline. At baseline, 128 (59%) of patients had 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 patients in the placebo treatment arm (64%) and OCA 10 mg

arm (60%), compared with the OCA titration arm(53%). There were only 5 patients who were diagnosed with PBC <30 years of age, of which only 3 patients were <30 year of age at initiation of the trial. The mean duration of PBC at the time of study entry was 8.6 years (0.0 to 32.3 years), the duration of PBC of ≤ 7.5 years in 49% of patients and > 7.5 years in about 51% patients. A total of 59% patients reported a history of fatigue. The overall incidence of fatigue was slightly higher in patients in the placebo arm(67%) compared to the OCA titration and OCA 10 mg arm (54% to 56% respectively).

Baseline liver laboratory: The relevant demographics and baseline characteristics for all ITT patients are presented in Table 76.

Table 73: Demographics for Trial 747-301 For ITT population

	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)	Total (N = 216)
UDCA Usage – n (%)				
Yes	67 (91.8%)	65 (92.9%)	68 (93.2%)	200 (92.6%)
No	6 (8.2%)	5 (7.1%)	5 (6.9%)	16 (7.4%)
Total Daily UDCA Dose (mg)				
n	67	65	68	200
Mean (SD)	1110.5 (328.40)	1116.2 (289.41)	1061.8 (322.43)	1095.8 (313.55)
Median	1000.0	1000.0	1000.0	1000.0
Min, Max	300, 2000	600, 1800	500, 2700	300, 2700
Randomization Strata – n (%)				
1. ALP $\leq 3 \times$ ULN and AST $\leq 2 \times$ ULN and TB \leq ULN; UDCA Usage	45 (61.6%)	43 (61.4%)	45 (61.6%)	133 (61.6%)
2. ALP $\leq 3 \times$ ULN and AST $\leq 2 \times$ ULN and TB \leq ULN; No UDCA Usage	2 (2.7%)	2 (2.9%)	2 (2.7%)	6 (2.8%)
3. ALP $> 3 \times$ ULN and/or AST $> 2 \times$ ULN and/or TB $>$ ULN; UDCA Usage	23 (31.5%)	22 (31.4%)	23 (31.5%)	68 (31.5%)
4. ALP $> 3 \times$ ULN and/or AST $> 2 \times$ ULN and/or TB $>$ ULN; No UDCA Usage	3 (4.1%)	3 (4.3%)	3 (4.1%)	9 (4.2%)
ALP Concentration (U/L)				
n	73	70	73	216
Mean (SD)	316.3 (103.88)	325.9 (116.24)	327.5 (115.01)	323.2 (111.37)
Median	271.3	281.3	311.9	286.6
Min, Max	207, 620	187, 811	144, 746	144, 811
ALP Concentration (\times ULN)				
n	73	70	73	216
Mean (SD)	2.658 (0.878)	2.747 (0.9851)	2.760 (0.9732)	2.721 (0.9431)
Median	2.293	2.378	2.607	2.423
Min, Max	1.68, 5.23	1.58, 6.86	1.22, 6.31	1.22, 6.86
TB Concentration (μ mol/L)				
n	73	70	73	216
Mean (SD)	11.3 (6.69)	10.3 (5.51)	11.8 (7.38)	11.1 (6.59)
Median	9.2	9.1	9.2	9.1
Min, Max	2, 34	2, 36	2, 39	2, 39
TB Concentration (\times ULN)				
n	73	70	73	216
Mean (SD)	0.558 (0.3162)	0.514 (0.2490)	0.598 (0.3733)	0.557 (0.3181)
Median	0.473	0.456	0.478	0.469

Min, Max	0.08, 1.78	0.11, 1.43	0.12, 2.03	0.08, 2.03
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Source: Reviewer's Table generated from the 747-301 ADSL and ADLIVER datasets.

Note: Denominators for percentages are N.

Table continued: **Demographic and Baseline Characteristics (ITT Population)**

	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)	Total (N = 216)
PBC Disease Stage using Rotterdam Criteria				
Early	65 (89.0%)	64 (91.4%)	66 (90.4%)	195 (90.3%)
Moderately Advanced	8 (11.0%)	6 (8.6%)	7 (9.6%)	21 (9.7%)
Albumin \leq LLN	1 (1.4%)	2 (2.9%)	0	3 (1.4%)
TB > 1.0xULN	7 (9.6%)	4 (5.7%)	7 (9.6%)	18 (8.3%)
Advanced	0	0	0	0
ALP Baseline Categories – n (%)				
1. 1.0xULN < ALP < 1.67xULN	0	1 (1.4%)	1 (1.4%)	2 (0.9%)
2. 1.67xULN \leq ALP < 2.0xULN	20 (27.4%)	13 (18.6%)	16 (21.9%)	49 (22.7%)
3. 2.0xULN \leq ALP < 3.0xULN	33 (45.2%)	37 (52.9%)	33 (45.2%)	103 (47.7%)
4. 3.0xULN \leq ALP < 4.0xULN	12 (16.4%)	10 (14.3%)	15 (20.5%)	37 (17.1%)
5. 4.0xULN \leq ALP < 5.0xULN	6 (8.2%)	8 (11.4%)	5 (6.8%)	19 (8.8%)
6. ALP \geq 5.0xULN	2 (2.7%)	1 (1.4%)	3 (4.1%)	6 (2.8%)
TB Baseline Categories – n (%)				
1. TB \leq 1.0xULN	66 (90.4%)	66 (94.3%)	66 (90.4%)	198 (91.7%)
2. 1.0xULN < TB < 2.0xULN	7 (9.6%)	4 (5.7%)	6 (8.2%)	17 (7.8%)
3. TB \geq 2.0xULN	0	0	1 (1.4%)	1 (0.5%)
Relevant Combination Baseline Categories – n (%)				
1. ALP \geq 1.67xULN and Early Stage PBC Disease; UDCA Usage	60 (82.2%)	60 (85.7%)	61 (83.6%)	181 (83.8%)
2. 1.67xULN < ALP < 2.0xULN and Early Stage PBC Disease; UDCA Usage	18 (24.7%)	13 (18.6%)	15 (20.5%)	46 (21.3%)
3. ALP \geq 2.0xULN and Early Stage PBC Disease; UDCA Usage	42 (57.5%)	47 (67.1%)	46 (63.0%)	135 (62.5%)

Source: Statistical reviewer generated Table generated from the 747-301 ADSL and ADLIVER dataset

*Denominators for percentages are N

Normal reference ranges utilized in the trial 747-301:

ALP ULN = 118.3 U/L (Females) and 124.2 U/L (Males)

Total Bilirubin ULN: 19.32 μ mol/L (Female) and 25.48 μ mol/L (Male)

Conjugated (Direct) Bilirubin ULN: 3.42 μ mol/L (Female and Male)

GGT ULN: 23.6 U/L (Female) and 35.2 U/L (Male)

ALT ULN: 22.9 U/L (Female) and 33.4 U/L (Male)

AST ULN: 25.7 U/L (Female) and 33.0 U/L (Male)

Albumin LLN: 40.2 g/L (Female) and 40.3 (Male)

INR normal range: 0.9 to 1.1

Reviewer Comment: The Applicant changed the ULN reference range for this particular trial. For Phase 2 trials, the ULN for CB was 7 μ mol/L and for trial 747-301, the ULN was 3.42 μ mol/L. The number of patients with elevated CB would have changed significantly if the ULN of CB was similar to that used for the phase 2 trials. Mean conjugated bilirubin (CB) was within the normal reference range in ~50% of patients and was similar across at the treatment arms.

Serum transaminases (ALT and AST) were elevated across all treatment arms approximately 2x ULN and was similar across all treatment arms. GGT was elevated across all 3 treatment arms (approximately 9x ULN to 12x ULN). Mean baseline GGT levels were slightly higher in the placebo arm consistent with intrahepatic cholestasis (309.6 U/L), compared with OCA titration (252.8 U/L) and OCA 10 mg (261.1 U/L) arms. The placebo arm had a

greater degree of variability in GGT compared to the OCA arms, and notably also had higher mean GGT at baseline. Baseline INR was ≤ 1.3 in 95% (treatment arms) to 99% (placebo) of patients; INR was > 1.3 in 5 patients in the OCA arms.

Reviewer Comment: According to Rotterdam criteria of classification, the patients in trial 747-301 were mostly in early stages of disease as shown in Table 79 and the threshold utilized for classification includes:

Table 74: 747-301 Baseline Disease Stage Based on Rotterdam Criteria

Rotterdam Criteria	Placebo (N=73)	OCA Titration (N=70)	OCA 10 mg (N=73)
Early Disease: Normal Albumin, Normal Total Bilirubin, Elevated ALP	65 (89%)	64 (91%)	66 (90%)
Moderately Advanced Disease: Either Low Albumin or High Total Bilirubin	8 (11%)	6 (9%)	7 (10%)
Patients with Low Albumin	1 (13%)	2 (33%)	0
Patients with High Total Bilirubin	7 (88%)	4 (67%)	7 (100%)
Advanced Disease: Both Low Albumin and High Total Bilirubin	0	0	0

Source: Copied and electronically reproduced from the data submitted to NDA sequence 0057 (58)

Note: Baseline is determined from individual study data and is the average of all visit values prior to first dose in double-blind phase. If results from only one evaluation were available, then available data from the single evaluation is used as the baseline value.

Table 75: ALP and TB at Baseline

Study ID	N	ALP $\geq 1.0xULN$ and $< 1.67xULN$ and TB $< ULN$ n (%)	ALP $\geq 1.0xULN$ and $< 1.67xULN$ and TB $\geq 1.0xULN$ and $< 2.0xULN$ n (%)	ALP $\geq 1.67xULN$ and TB $< ULN$ n (%)	ALP $\geq 1.67xULN$ and TB $\geq 1.0xULN$ and $< 2.0xULN$ n (%)	ALP $\geq 1.67xULN$ and TB $\geq 2.0xULN$ n (%)
747-301	216	1 (<1%)	1 (<1%)	197 (91%)	16 (7%)	1 (<1%)
Placebo	73	0	1 (1%)	66 (90%)	5 (7%)	1 (1%)
Titration	70	1 (1%)	0	65 (93%)	4 (6%)	0
10 mg	73	0	0	66 (90%)	7 (10%)	0

Source: Copied and electronically reproduced from the data submitted to NDA sequence 0057 (58)

Note: Baseline is determined from individual study data and is the average of all visit values prior to first dose in double-blind phase. If results from only one evaluation were available, then available data from the single evaluation is used as the baseline value.

Alkaline Phosphatase (ALP) ULN: 118.3 U/L (females), 124.2 U/L (males); Total Bilirubin (TB) ULN: 19.32 $\mu\text{mol/L}$ (females), 25.48 $\mu\text{mol/L}$ (males).

To further understand the enrollment on the basis of ALP and TB see Table 78, and note that the majority of the patients had ALP $\geq 1.67xULN$ and TB $< ULN$. There were differences in the mean baseline ALP in three trials (747-201, 747-202, and 747-301). In trial 747-201 the mean baseline ALP was (range of 408.5 to 462 U/L) and was 3.5x ULN compared to trial 747-301 where the mean baseline ALP was (range 316.34 U/L to 327.5 U/L) and was 2.72x ULN.

Mean baseline ALP values for Study 747-202 (range 275.3 U/L to 294.4 U/L) were slightly lower than Study 747-301 (range 316.34 U/L to 327.5 U/L), which is most likely attributable to the difference in lower end of the minimum baseline ALP entry criterion for Study 747-202 (> 1x ULN) compared with Study 747-301 (>1.67x ULN).

Reviewer Comment: Mean total bilirubin was within normal limits for all 3 studies, given the early stage of the disease in most enrolled patients. Total bilirubin is normal until later stages of disease, and is indicative of advance stage of disease.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

As per protocol, patients were to receive investigational product daily during the entire 12-month duration of the double-blind phase. Applicant has used the following two terms to describe alternative dosing regimens:

1. Investigator-prescribed drug holidays and
2. Less frequent dosing regimens or alternative drug regimen: Alternative Dosing Schedule is defined as Every Other Day, Every 3rd Day, or Every 7th Day.

Both were permissible at any point in the study for patients who experienced adverse event of pruritus.

There was >99% compliance with investigational product across treatment groups. In placebo arm, 81% of patients remained at once a day dosing whereas in the OCA titration arm, 75% and 67% of patients in the OCA 10 mg arm remained on once a day dosing. A similar percentage of patients across treatment groups had investigator-prescribed holidays (14% to 15% for OCA-treated patients and 11% for placebo-treated patients). Patient non-compliance was higher for the OCA titration treatment group (16%) relative to the OCA 10 mg (8%) and placebo (7%) treatment groups.

Table 76: Investigational Product Compliance for IIT population

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
Investigational Product Compliance^a			
N	73	70	73
Mean (SD)	99.9 (0.4)	99.5 (1.8)	99.9 (0.5)
Min, Max	97, 100	87, 100	97, 100
Compliance With Protocol-Specified Dosing Regimen: n (%)			
Received QD With No Days Off	59 (81)	52 (74)	49 (67)
Did not Receive QD Dosing the Entire Study	14 (19)	18 (16)	24 (23)
Reason ^b			
Alternative Dosing ^c	4 (5)	7 (10)	14 (19)
Investigator Prescribed Drug Holiday	8 (11)	10 (14)	11 (15)
Non-Compliance ^d	5 (7)	11 (16)	6 (8)

Source: Copied and electronically reproduced from the Applicant submission “Clinical Study report” page 92/3119

^a Investigational product compliance was calculated as 100 x [number of days on study drug/(number of days on study drug + number of days on drug interruptions)].

^b Patients may be counted in more than one category

^c Alternative Dosing Schedule is defined as Every Other Day, Every 3rd Day, or Every 7th Day.

^d Non-compliance was defined as investigational product interruptions by a patient but does not include alternative dosing or investigator prescribed drug holidays.

The mean number of days off of the once a day regimen wherein patients used alternative dosing regimens was highest in the OCA 10 mg group (11.5 days), followed by the OCA titration (5.7 days) and placebo groups (3.0 days). Of the patients who were placed on alternative dosing regimens at some point in the study, the majority of patients across treatment groups received an “Every Other Day” regimen. Across treatment groups, the majority of investigator-prescribed holidays were ≤ 14 days. For more details on alternative dosing, days off investigational agent reader is refer to page 94 of 3119 of the Clinical Study report.

Reviewer Comment: More patients required alternative drug dosing regimens in the OCA 10 mg arm compared to OCA titration arm and least in the placebo arm secondary to pruritus. Pruritus was worse in the OCA 10 mg arm. Investigator-prescribed drug holidays were similar across all treatment arms. The majority of patients had drug interruptions that were <14 days in duration, with the exception of one patient who did not take OCA for >28 days.

Concomitant Medications:

A total of 97% of patients received at least 1 concomitant medication during the 12-month double-blind period. New concomitant medications that were most commonly taken overall (>10% of patients) included: anilides (e.g., acetaminophen, paracetamol; 29%), bile acid sequestrants (BAS) (19%), propionic acid derivatives (e.g., ibuprofen, naproxen; 19%), proton pump inhibitors (18%), and penicillin’s with extended spectrum (11%). A higher incidence of propionic acid derivatives and BAS was observed in both OCA treatment arms, compared with the placebo arm.

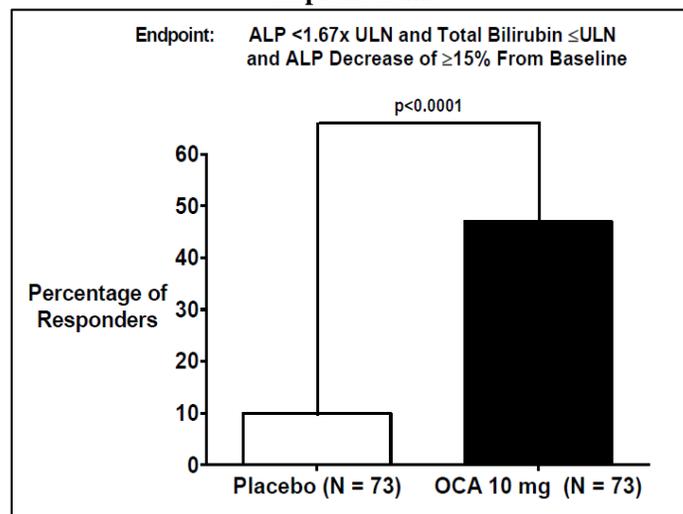
Reviewer Comment:

Pruritus is a dose dependent AE of OCA which required medications for symptom relief.

6.3.8 Efficacy Results

Primary Efficacy Endpoint: At Month 12, a total of 34 (47%) patients from the OCA 10 mg sub-group achieved the composite endpoint, compared with 7 (10%) patients from the placebo group.

Figure 24- Percentage of Patients Achieving Primary Efficacy Composite Endpoint at Month 12 Using Imputed Data



Source: Copied and electronically reproduced from the Applicant submission “Clinical Study report” page 100/3119; Figure 6 ITT Population (Placebo and OCA 10 mg, N = 146)

Table 77: Primary Efficacy Endpoint at Month 12 Using Imputed Data

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

Source: Copied and electronically reproduced from the Applicant’s submission “Clinical Study report” page 101/3119

Completer (Placebo and OCA 10 mg, N = 134) and EE (placebo and OCA 10 mg, N = 129) populations

Missing values were considered a non-response

^a- p-values obtained using CMH test stratified by randomization strata factor

Reviewer Comment:

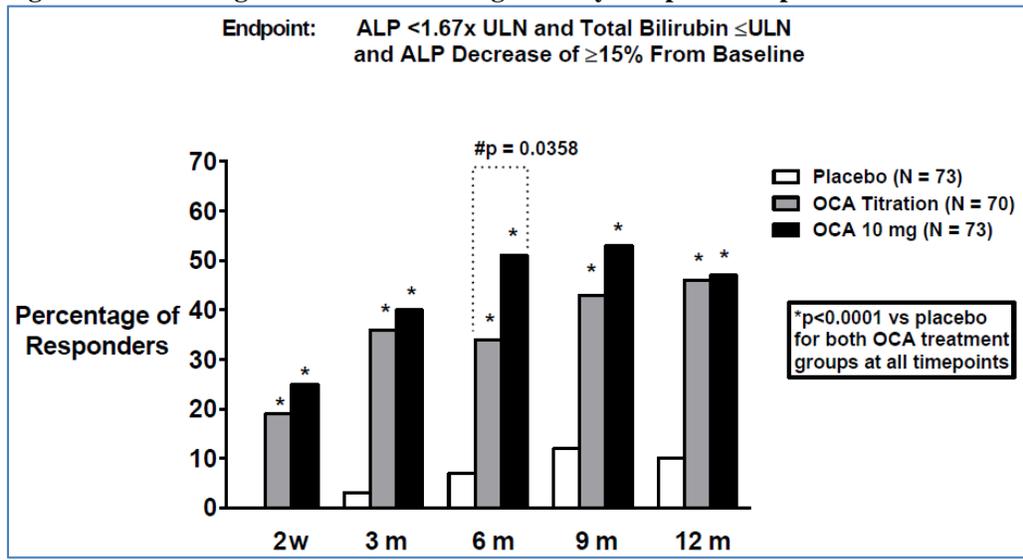
The primary efficacy is driven by the reduction of ALP and not by change in TB. Given 92% of patients in the trial did not have elevated TB, these results do not support “achieving the primary composite endpoint” but instead show “reduction in ALP”. The biochemical response of reduction in ALP was seen as early as 2 weeks and was sustained during the trial. This reviewer notes there was no worsening of TB during the trial in the majority of patients in either treatment arm i.e. placebo arm and drug arms (OCA titration and OCA 10 mg arm). Patients enrolled in the pivotal trial were in early stage of PBC and worsening of TB is not expected in 12 months. The majority of patients did not achieve normalization of ALP.

Secondary Analyses of the Primary Endpoint:

The key secondary analysis of the primary endpoint was the percentage of patients in the OCA titration arm achieving the composite endpoint at month 12.

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

Figure 25: Percentage of Patients Achieving Primary Composite Endpoint over Time Using Imputed Data



Source: Copied and electronically reproduced from the Applicant’s submission “Clinical Study report” page 102/3119

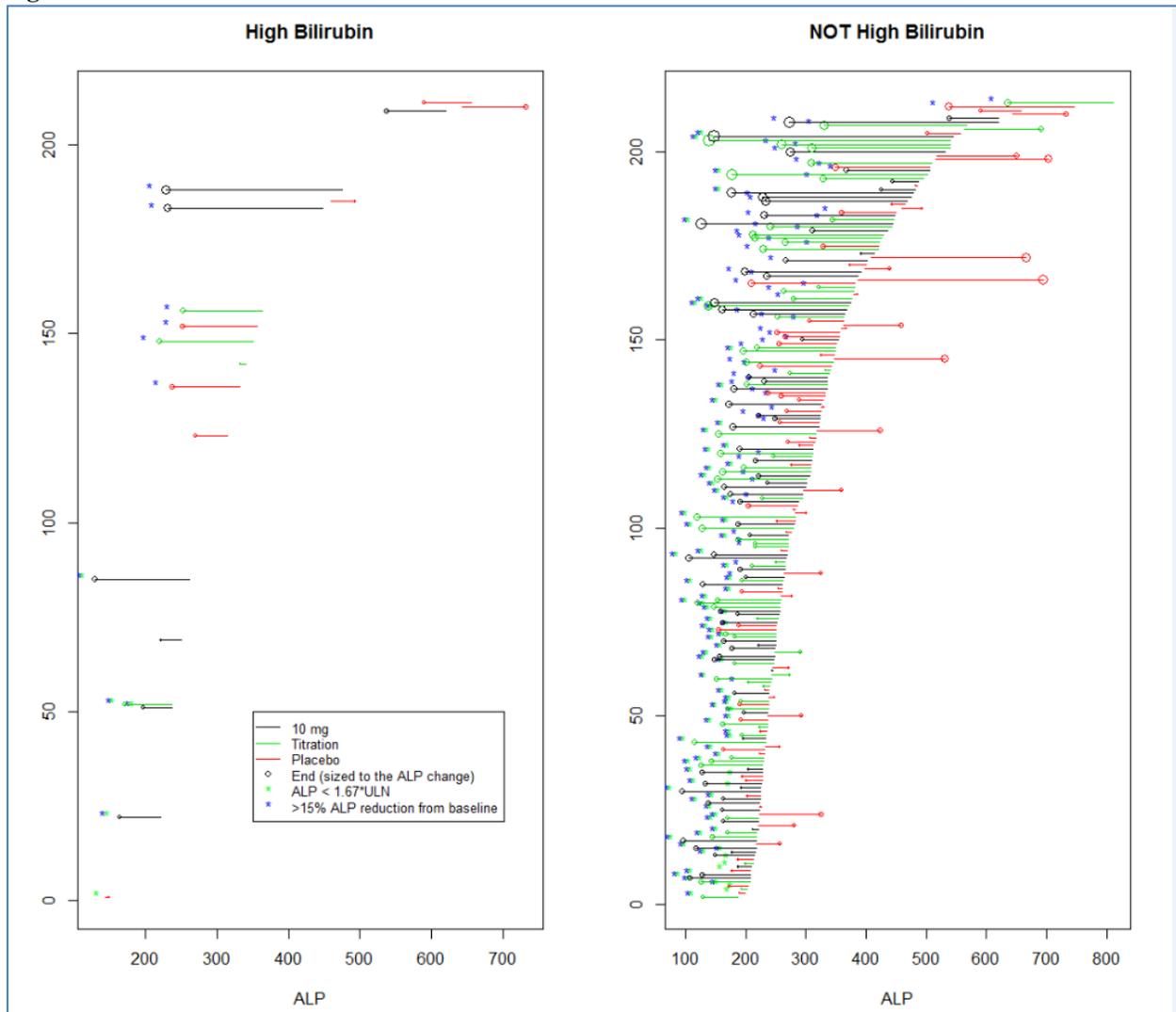
ITT Population (N = 216)

Missing values were considered a non-response.

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

Reviewer Comment: The response at Month 12 for both OCA titration and OCA 10mg arm showed durable reduction of ALP throughout the trial which was statistically significant when compared to placebo.

Figure 26: Reduction in ALP in Patients with Elevated Bilirubin and Non-elevated Bilirubin



Source: Generated by FDA Statistical Reviewer Andrejus Parfionovas from the Applicants “adsl” and Adliver” datasets

“x” axis: ALP in U/L; “y” axis represents: number of patients (N=216)

The circle at the end of each line represents the magnitude of response in either direction; Movement to left means reduction in ALP and movement to right represent increase in ALP

On the left side of **Figure 26** above, are 747-301 trial patients who had elevated TB at baseline, with movements to the left still representing reductions in ALP at Month 12. The right side of the figure represents patients with normal TB and the changes in ALP seen at Month 12. The patients treated with OCA, had a greater reduction in ALP relative to placebo, even when the TB was elevated.

Table 78: Proportion of Patients who Achieved Response and Components of Composite Endpoints

Statistics	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)
Response at Month 6 – n (%) [1] [2]	37 (50.7%)	24 (34.3%)	5 (6.9%)
Corresponding 95% Wald CI	39.2%, 62.2%	23.2%, 45.4%	1.1%, 12.6%
Response at Month 12 – n (%) [1] [2]	34 (46.6%)	32 (45.7%)	7 (9.6%)

Statistics	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)
Corresponding 95% Wald CI	36.5%, 59.4%	34.0%, 57.4%	2.8%, 16.3%
CMH Test p-value [3]	<0.0001	<0.0001	
Corresponding Breslow-Day Test p-value	0.9072	0.5045	
(1) ALP < 1.67×ULN at Month 12 – n (%) [2]	40 (54.8%)	33 (47.1%)	12 (16.4%)
(2) TB ≤ 1.0×ULN at Month 12 – n (%) [2]	60 (82.2%)	62 (88.6%)	57 (78.1%)
(3) Decrease in ALP ≥ 15% at Month 12 – n (%) [2]	57 (78.1%)	54 (77.1%)	21 (28.8%)

Source: Reviewer Generated from ADLIVER dataset.

Note: Denominators for percentages are N.

[1]: A patient was designated as a responder if all three of the following conditions were met: (1) 12-Month value of ALP < 1.67×ULN; (2) 12-Month value of TB ≤ ULN; (3) ALP reduction from baseline at Month 12 ≥ 15%.

[2]: Patients with missing data at these timepoints were designated as non-responders.

[3]: Month 12 Pair-wise comparison made between given OCA treatment group and Placebo adjusted for both randomization stratification variables

Reviewer Comment: Table 81 was adopted from Statistical Reviewer Benjamin Vali's review: "Both OCA treatment groups showed a superior difference in the proportion/percentage of patients achieving response at Month 12 when individually compared to placebo using the CMH test. It is important to note that no single site influenced the overall study results. In regards to ALP or TB values at Month 12, there were no patients who were designated as outliers (i.e., by having studentized residual values greater than three), and there was no impact on study conclusions between corrected laboratory values (as presented) and original (i.e., uncorrected) laboratory values. All of the previously presented analyses were re-conducted utilizing a baseline value that was the median of all pre-first dose measurements, and, separately, a traditional baseline definition; there was no impact on study conclusions with either approach. Considering the applicant's pre-specified step-down/closed sequential testing procedure, formal hypothesis testing is stopped at this point. Any subsequent inferential statistic reported should be considered exploratory".

Data Quality and Integrity – Reviewers' Assessment

Quality Assurance Plan as described by Intercept is acceptable for the clinical studies 747-201, 747-202 and 747-301. The Quality Assurance as described in multiple sections of the 747-301 protocol:

1. Section 11.6, Data Quality Assurance and Quality Control
2. 11.7.1, Trial Monitoring
3. 11.7.2, Trial Auditing

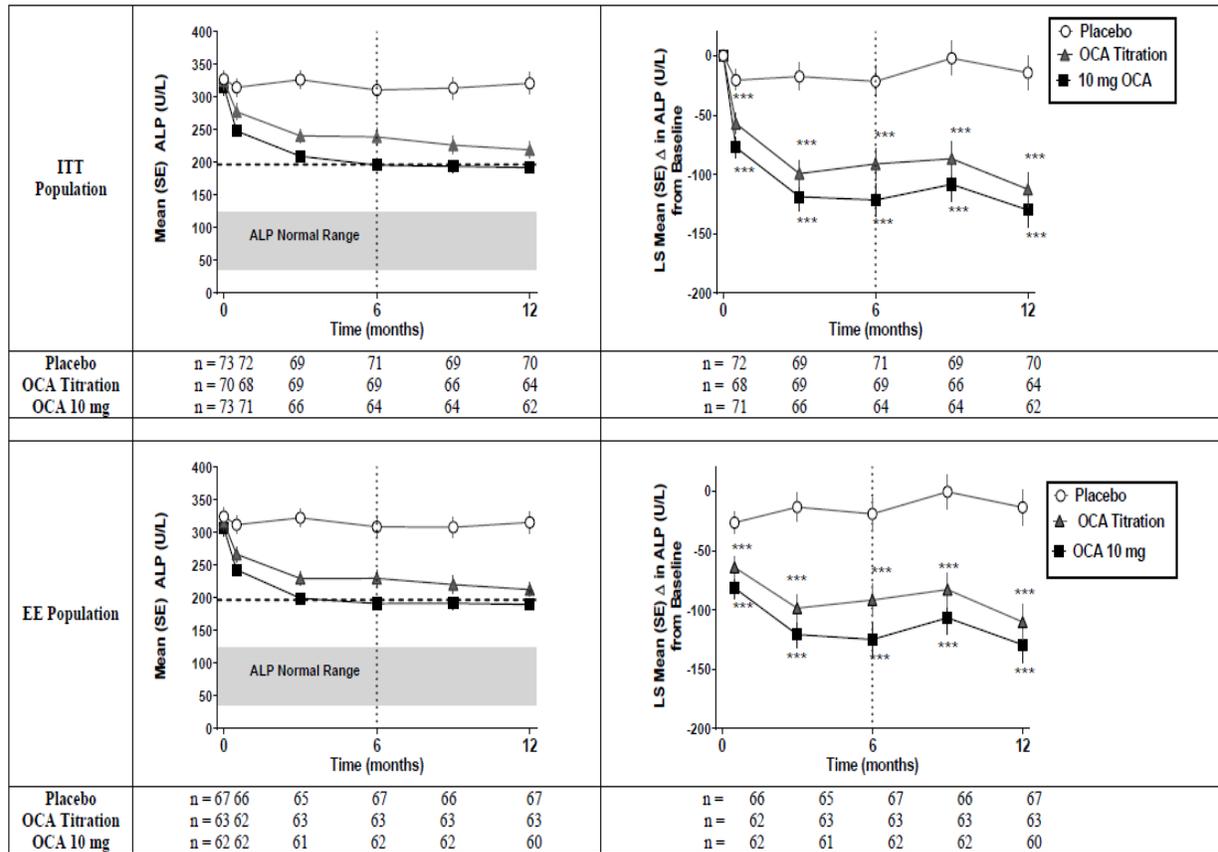
All the sections were reviewed.

The Office of Scientific Investigations (OSI) performed site investigations of 6 clinical sites. The results are present above in section 6.1.1

6.3.9 Secondary Efficacy Results

Secondary Analyses: For ALP and Bilirubin

Figure 27: ALP Values and Absolute Change from Baseline over Time: ITT (N = 216) top panel; and EE (N = 192) (lower panel) Populations



Source: Copied and electronically reproduced from Applicant submission: Clinical Study report page 107-3119; Figure 10

Footnote: *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).

Reviewer Comment: Similar graphical findings of percent change in ALP from baseline to month 12 were presented by the Applicant and have not been shown here. These graphs show that the response is durable.

This reviewer notes across the 3 treatment arms, mean ALP values at baseline were well balanced, and approximately one-third of patients had an ALP > 3x ULN. The reduction in ALP is significant, 46% in OCA 10 mg arm and 47% in the OCA titration arm achieved primary endpoint compared with 10% response seen in the placebo arm.

Total Bilirubin and Conjugated Bilirubin

The total bilirubin levels at baseline were normal in 92% patients at enrollment. The table below shows the distribution of TB in the trial patients:

Table 79: Total Bilirubin and Conjugated Bilirubin

	OCA10 mg (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)
Baseline TB Concentration			

TB ≤ 1.0 XULN	66 (90.4%)	66 (94.3%)	66 (90.4%)
1.0xULN < TB < 2.0xULN	7 (9.6%)	4 (5.7%)	6 (8.2%)
TB ≥ 2.0xULN	0	0	1 (1.4%)
Baseline TB Concentration (XULN)			
Mean (standard deviation)	0.55 (0.31)	0.51 (0.24)	0.60 (0.37)
Median	0.47	0.45	0.48
Min, Max	0.08, 1.78	0.11, 1.43	0.12, 2.03

Of the 18 patients with elevated TB only one patient enrolled to placebo arm had TB > 2 x ULN. Also the mean baseline TB was higher in placebo arm (~0.6 x ULN) compared to both OCA treatment arms (0.55 and 0.51 x ULN).

Figure 28: Total bilirubin at baseline and month 12 in patients with elevated baseline total bilirubin

Time point	OCA 10 mg	OCA titration	Placebo
Baseline TB ≤ 1.0xULN	66 (90.4%)	66 (94.3%)	66 (90.4%)
Baseline TB ≥ 1.0xULN	7 (9.6%)	4 (5.4%)	7 (9.6%)
Baseline TB ≤ 1.0xULN	n=66	n=66	N=66
Month 12 TB ≤ 1.0xULN [1]	55 (88.3%)	60 (90.1%)	56 (84.4%)
Month 12 TB ≥ 1.0xULN [1]	3 (4.5%)	0	7 (10.6%)
Month 12 TB missing	8 (12.1%)	6 (9.1%)	3 (4.5%)
Baseline TB > 1.0 x ULN [2]	n=7	n=4	n=7
Month 12 TB ≤ 1.0xULN [2]	5 (71.4%)	2 (50%)	1 (14.2%)
Month 12 TB ≥ 1.0xULN [2]	0	2 (50%)	6 (85.7%)
Month 12 TB missing	2 (28.6%)	0	0

Source: Statistical Reviewer's Table (Courtesy Benjamin Vali)

[1]: The denominator for this calculation is number of patients with TB ≤ 1.0xULN at Baseline

[2]: The denominator for this calculation is number of patients with TB > 1.0xULN at Baseline

Figure 28 shows 7 patients in placebo arm had elevated TB at baseline, and at month 12 the 7 patients continued to have elevated TB. In the OCA titration arm 2 out of 4 patients had improvement in TB and in OCA 10mg arm 5 out of 7 patients had normalization of TB.

Table 80: Patients with elevated Total Bilirubin at baseline for 747-301 safety population and changes at month 12 in Total Bilirubin and Alkaline Phosphatase

	Baseline ^a	DB Month 12	Change from Baseline ^a

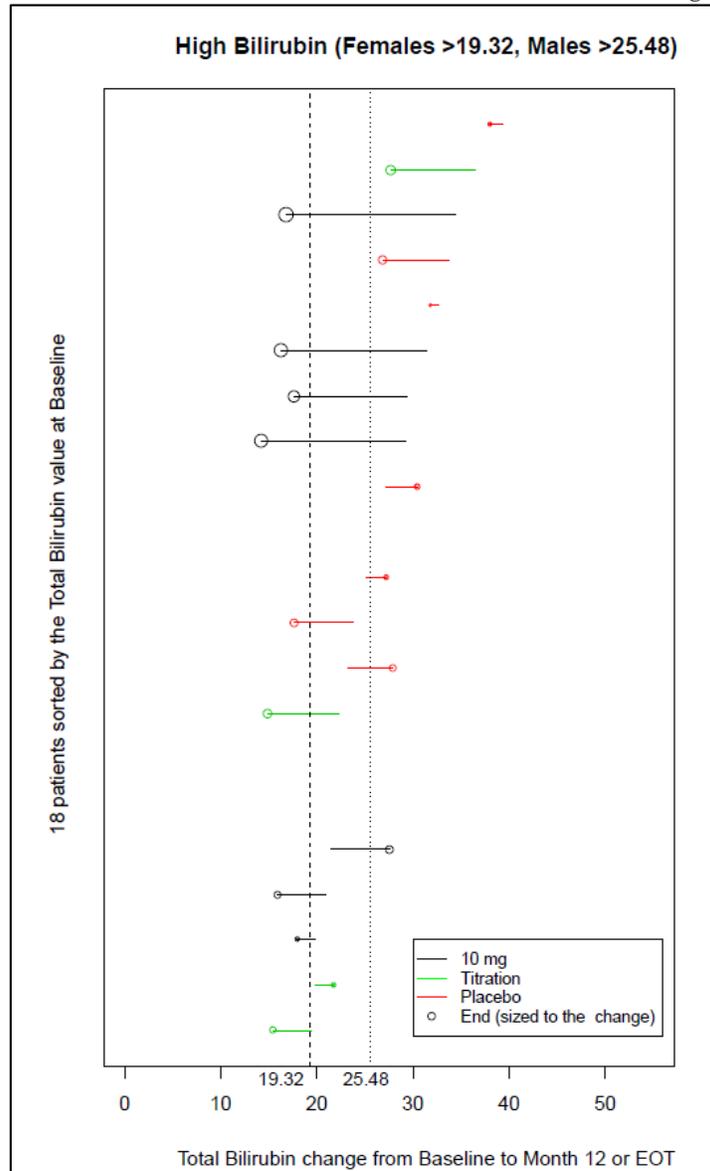
Treatment Group	Patient ID	Total Bilirubin (µmol/L)	Alkaline Phosphatase (U/L)	Total Bilirubin (µmol/L)	Alkaline Phosphatase (U/L)	Total Bilirubin (µmol/L)	Alkaline Phosphatase (U/L)
Placebo	105006	25.08 H	143.8 H	27.19 H	148.5 H	2.11	4.7
	138004	33.69 H	459.6 H	26.85 H	491.7 H	-6.84	32.1
	139005	23.83 H	314.9 H	17.61	269.9 H	-6.21	-45.0
	142009	27.13 H	355.7 H	30.44 H	251.0 H	3.31	-104.7
	148002	39.27 H	656.4 H	37.96 H	590.0 H	-1.31	-66.4
	162005	23.26 H	331.1 H	27.87 H	237.2 H	4.62	-93.9
	175003	32.60 H	642.7 H	31.81 H	732.6 H	-0.80	89.9
Titration OCA	109004	36.42 H	363.2 H	27.70 H	253.0 H	-8.72	-110.2
	130002	19.84 H	339.6 H	21.72 H	332.7 H	1.88	-6.9
	156001	19.44 H	237.4 H	15.39	170.2 H	-4.05	-67.2
	179004	22.23 H	349.7 H	14.88	219.0 H	-7.35	-130.7
10 mg OCA	102005	34.37 H	447.0 H	16.76	230.8 H	-17.61	-216.2
	136002	20.86 H	619.5 H				
	138005	29.36 H	221.3 H	17.61	162.8 H	-11.74	-58.5
	142001	31.41 H	475.4 H	16.25	228.2 H	-15.16	-247.2
	174012	21.43 H	237.2 H				
	180005	29.24 H	260.9 H	14.19	129.0 H	-15.05	-131.9
	183003	19.84 H	249.7 H	17.95	220.7 H	-1.88	-29.0

Source: Applicant submission to NDA sequence 0056 (57) submitted 3-17-2016

^a Baseline is the average of all visit values prior to first dose in double-blind phase. If results from only one evaluation are available, the available data from this evaluation is used as the baseline value. Baseline is from individual Trial data.

Reviewer Comment: In patients with elevated TB at baseline, numerically higher number of patients treated with OCA showed reduction in TB relative to placebo.

Figure 29: 747-301 Trial Patients with Elevated Total Bilirubin at Baseline and Changes Observed at Month 12



Source: Generated by Andrejus Parfionovas (Statistical Reviewer) from the Applicants “adsl” and Adliver” datasets

This graph above depicts that patients treated with OCA 10 mg and OCA titration had reduction in TB. The “x” axis represents bilirubin in $\mu\text{mol/L}$ and “y” axis represents number of patients. The circle at the end represents the magnitude of response. A shift to left indicates reduction in TB and a shift to right indicate increase in TB.

It appears OCA has an effect on improvement in patient with elevated TB, however, since the sample size is small, the result is not statistically significant.

The applicant presented the following graph for the overall trial to show changes in the TB from baseline to end of month 12 in overall trial patients.

Figure 30: Total bilirubin changes over time from baseline to month 12

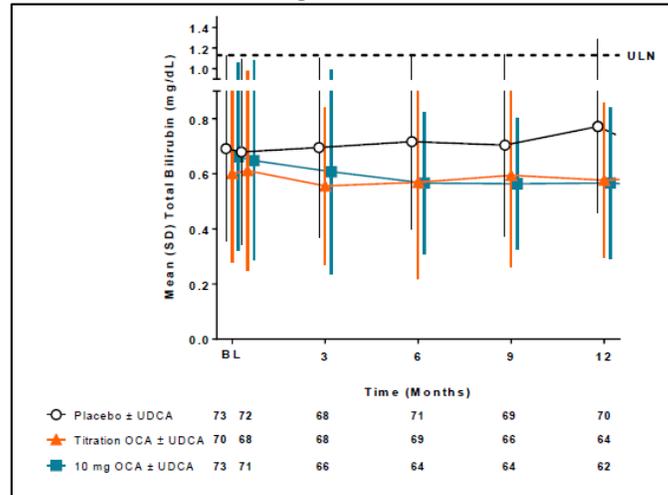


Figure source: Applicant's submission to the NDA Sequence 0058 (59)

Reviewer Comment: This reviewer notes when TB is within normal reference range, then minor decrements within the normal reference range may not indicate any clinical significance. Extent of variability in TB over time in PBC is not known; changes in TB during treatment trials must be considered in the context of the natural variability of TB. As exemplified in trial 747-301:

22 patients had high TB at screening,
 15 patients had high TB on repeat measure within 8 weeks (i.e. Day 0)
 Average of the two values (Screening + Day 0) led to a total of 18 patients with high TB.

Figure 31: Total Bilirubin Mean (SE) Values and Change from Baseline over Time by Randomized Dose: Safety Population (N = 172), OCA Weighted Average Daily Dose ≤10 mg

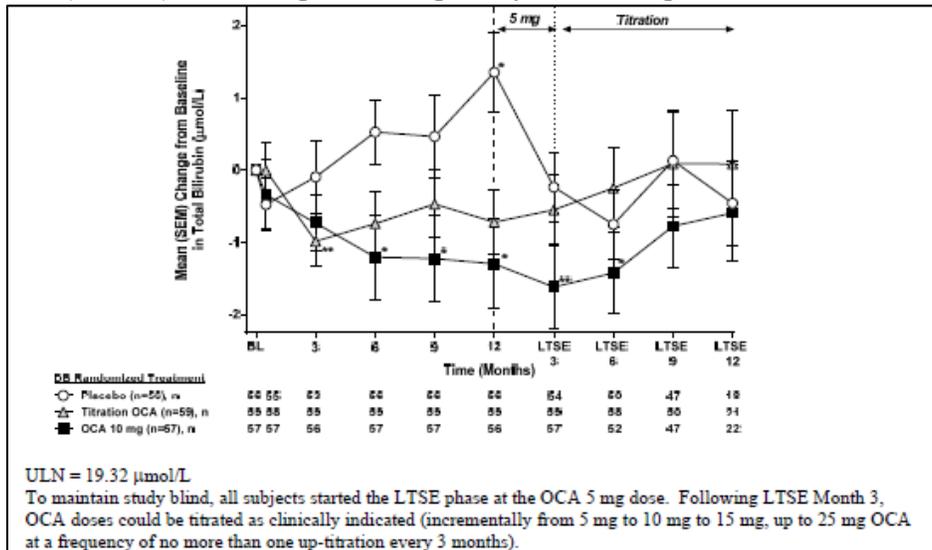
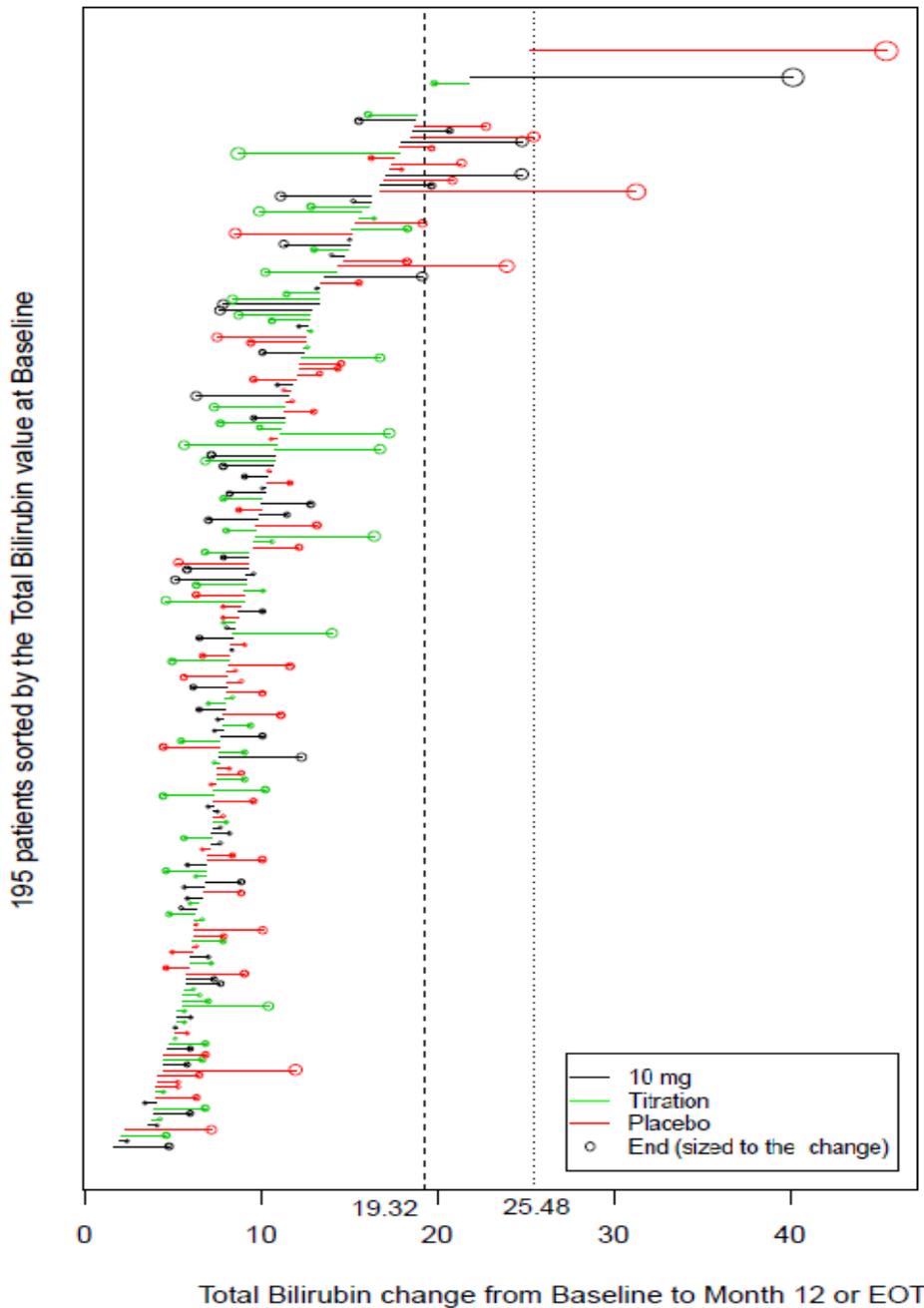


Figure Source: Copied and electronically reproduced from the Summary of Clinical efficacy page 161 of 190

In the trial, the overall majority of patients had normal TB. Trial 301 was not designed to show efficacy with respect to a reduction of TB that is already within the normal reference range. The significance of small decremental changes in TB that remain within the normal reference range over a 12 month duration is unknown. As shown in the Figure 30 and Figure 31 above, TB fluctuated in all treatment arms including the OCA treated patients. The

confidence intervals are overlapping for all three treatment arms. TB is within the normal reference range for majority of patients.

Figure 32: 747-301 Trial Patients with Total Bilirubin <1.0 x ULN at Baseline and Changes at Month 12

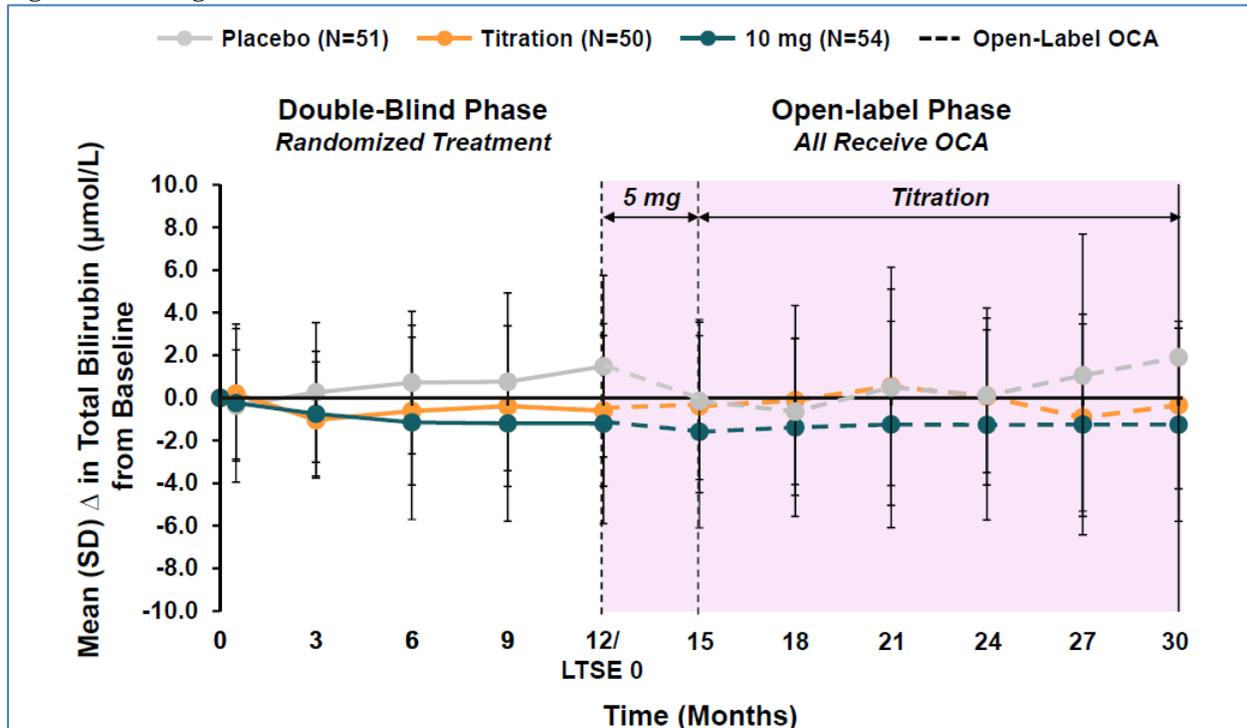


Source: Generated by Andrejus Parfonovas (Statistical Reviewer) from the Applicants “adsl” and Adliver” datasets

Reviewer Comment: As can be seen in this graph generated by FDA statistical review, in general all groups had small changes in TB. Both incremental (shift to right) and decremental movement (shift to left) was seen across all the three treatment groups. The changes were seen in all patients when TB and were within normal reference range. The mean TB reduced by 0.13 mg/dL in OCA titration arm and by 0.17 mg/dL in the OCA 10mg group.

Figure 33 shows TB in the long term safety extension to depict the fluctuations in the TB that were seen when the placebo patients were enrolled to OCA treatment arm.

Figure 33: Changes in total bilirubin over time with OCA treatment



Source: Applicant's AC slide presentation

Reviewer Comment: As can be noted in this graph, when TB is within normal reference range, all three groups had fluctuations in mean TB levels and all treated groups reached pre-treatment baseline value multiple times during this long term safety extension (area shaded in pink is LTSE trial), despite all patients receiving OCA treatment. Natural variability in TB in PBC needs to be analyzed and the trial powered adequately to assess TB reduction. Although the planned confirmatory trial does include patient enrollment criteria of TB > 1 x ULN but < 3 x ULN, AND/OR ALP > 5 x ULN, therefore it may still enroll primarily patients with early stage disease and normal TB, and may still pose the same challenge in interpreting the changes in TB.

Conjugated Bilirubin: For the ITT population, the baseline conjugated bilirubin was elevated (approximately 1.5x ULN to 2x ULN) across treatment arms. 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. In both OCA-treatment arms the mean CB came close to the ULN (3.42 μmol/L), while placebo increased from baseline at all-time points. However, the mean CB did not normalize in any treatment arm.

Figure 34: Conjugated Bilirubin Values and Change from Baseline Over Time: ITT (N = 216) and EE (N = 192) Populations

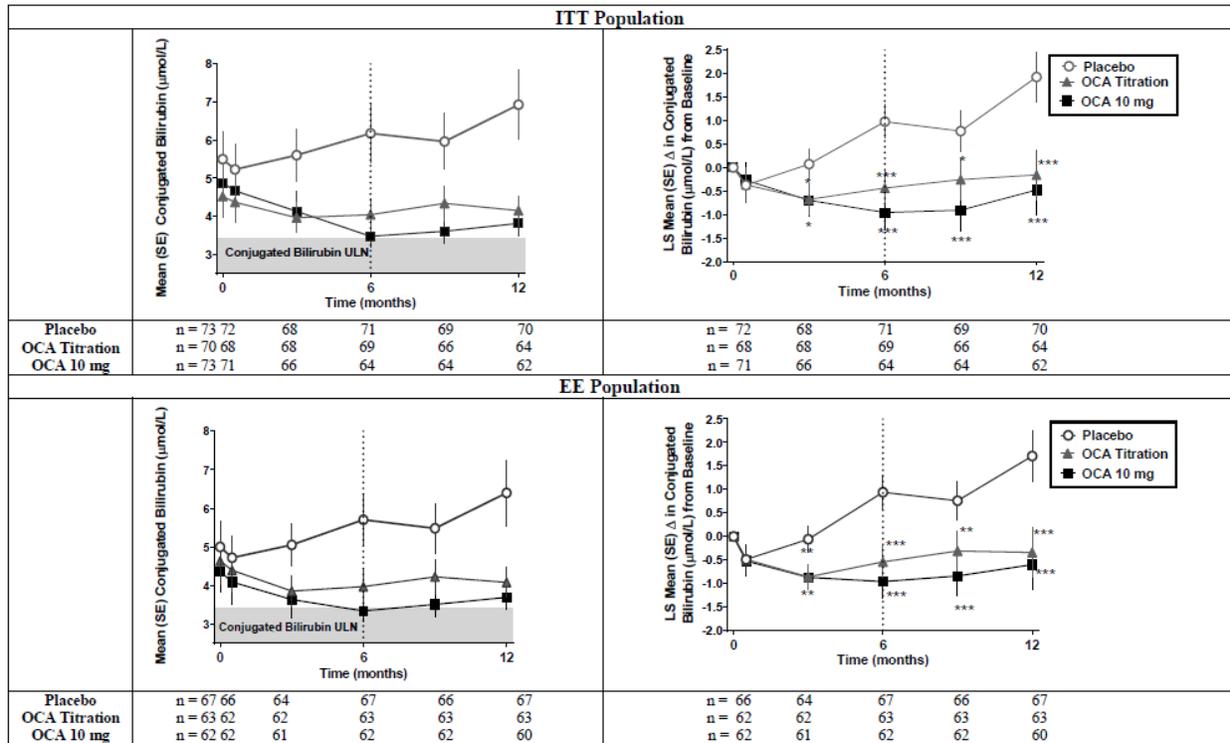
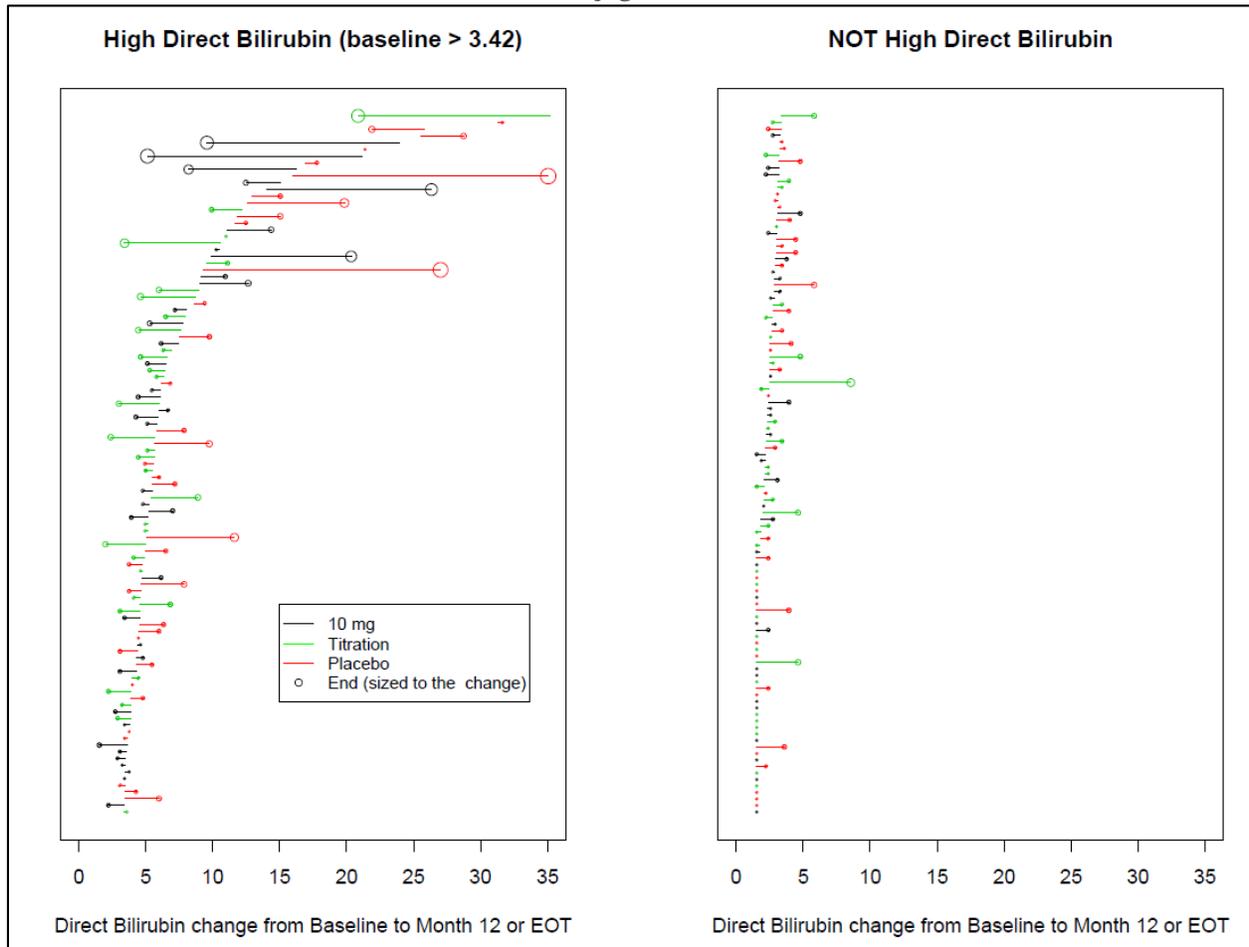


Figure Source: Copied and electronically reproduced from Applicant submission; Clinical Study report page 113-3119; Figure 11
 *p < 0.05, **p < 0.01, ***p < 0.0001; p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Conjugated Bilirubin ULN = 3.42 µmol/L for both females and males.

Figure 35: 747-301-Changes from Baseline to Month 12 in Patients with Elevated Conjugated Bilirubin and Normal Conjugated Bilirubin



Graphs generated by FDA statistical reviewer Andrejus Parfionovas from the Applicants “adsl” and Adliver” datasets

As noted in the graph, on the right shows when CB was not elevated the CB remained mostly within normal range in majority of patient from baseline to end of treatment trial at month 12. When the CB was elevated more patients had increases in the placebo arm (depicted by red line) compared to OCA titration (green line) and OCA 10 mg arm (depicted in black line).

1. On an average placebo arm had higher baseline conjugated bilirubin to begin with (Mean baseline conjugated bilirubin was $5.5 \mu\text{mol/L}$, $4.5 \mu\text{mol/L}$, and $4.9 \mu\text{mol/L}$, for placebo, OCA titration, and OCA 10 mg, respectively). OCA does have an effect on CB reduction (there were some fluctuations in OCA treated arm) but the clinical benefits of these reductions are not known.
2. The conjugated bilirubin values when the TB values are within normal reference range can be erroneous and not reliable.
3. The conjugated bilirubin when excreted in bile a fraction of CB is refluxed into the systemic circulation from the biliary system due to bile duct damage/obstruction. The CB releases into the systemic circulation are affected by local hepatic factors, and micro-circulation around bile ducts. Therefore, CB indeed gives an estimate about hepatic obstruction/cholestatic disease, but does not accurately quantify the burden of liver disease or stage of liver disease.

Other efficacy endpoints: GGT, ALT, and AST

Baseline GGT was elevated across all 3 treatment arms (approximately 9x ULN to 12x ULN) consistent with cholestasis. Mean transaminases (ALT and AST) were also elevated at baseline approximately 2x ULN. Improvements in GGT, ALT and AST were observed as early as 2 weeks, with the largest magnitude of response 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.

Figure 36: GGT change from baseline over time: ITT Population (N = 216); [data presented as mean (SD) ALT (U/L)]

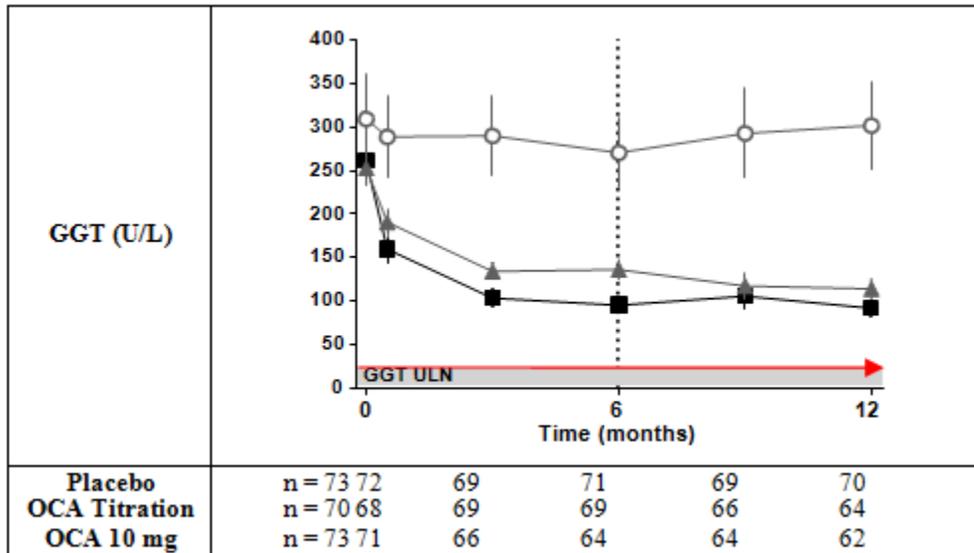


Figure source: Adapted and modified by the reviewer from CSR 747-301 page 116-3119

Figure 37: ALT change from baseline overtime [presented as mean (SD) ALT(U/L)] in ITT population

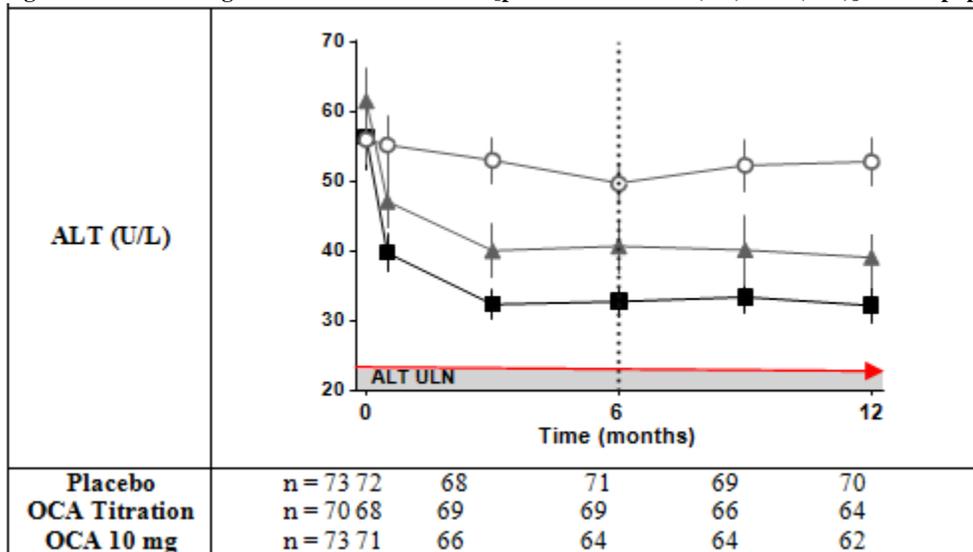


Figure source: Adapted and modified by the reviewer from CSR 747-301 page 117-3119

Figure 38: AST change from baseline overtime [presented as mean (SD) AST (U/L)] in ITT population

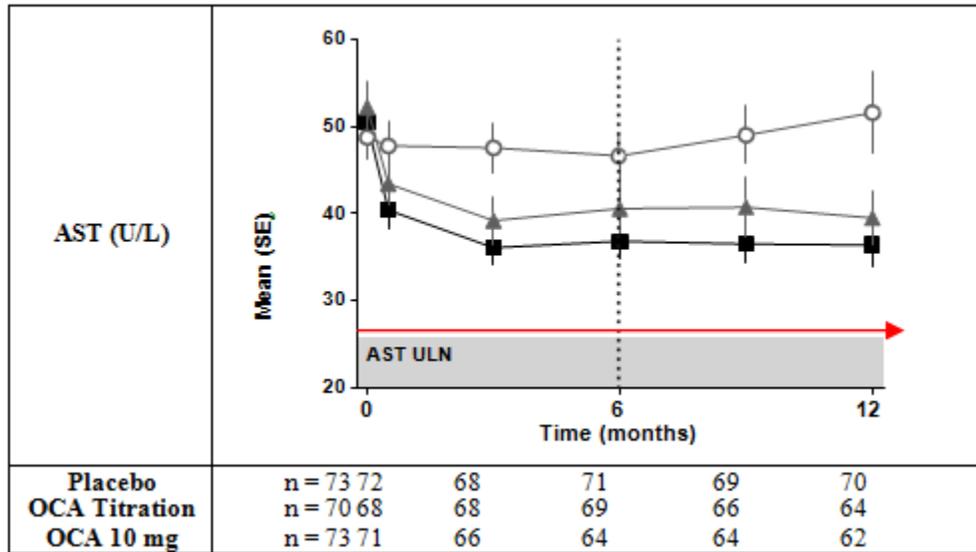


Figure source: Adapted and modified by the reviewer from CSR 747-301 page 117-3119
 Given the majority of the population was female; ULN values are based on criteria for females (i.e., GGT23.6 U/L, ALT 22.9 U/L, and AST 25.7 U/L).

Reviewer comments: There is a mean reduction in absolute and percent change in GGT, ALT and AST over 12 month. None of these parameters normalized to below the normal reference range. The hepatocellular and cholestatic markers decrease over time with use of OCA in 12 month period, and specifically GGT reductions were significant and indicate a decrease in cholestasis. ALT and AST reductions were smaller but also support a reduction in hepatocellular damage. These findings support the primary efficacy endpoint.

Other relevant endpoints:

Albumin, Prothrombin Time, and INR: Baseline albumin, prothrombin time, and INR values were within normal ranges across all 3 treatment arms at baseline, during and after completion of the trial. No statistical differences between placebo and OCA treatment arms were observed; no worsening of these parameters was noted over the 12-month period across all 3 treatment arms.

Table 81: Patients with Low Albumin at Baseline in Trial 747-301

Treatment Group	Baseline				DB Month 12				Change from Baseline			
	Albumin (g/L)	Total Bili (µmol/L)	Direct Bili (µmol/L)	ALP (U/L)	Albumin (g/L)	Total Bili (µmol/L)	Direct Bili (µmol/L)	ALP (U/L)	Alb (g/L)	Total Bili (µmol/L)	Direct Bili (µmol/L)	ALP (U/L)
Placebo	32.5	18.70	11.80 H	745.9 H	36.0	22.74 H	15.05 H	537.6 H	3.5	4.05	3.25	-208.3
Titration OCA	33.0	7.18	1.54	539.4 H	27.7 L	5.64	1.54	260.1 H	-5.3	-1.54	0.00	-279.3
	34.0	11.29	7.61 H	371.5 H	36.0	7.70	4.45 H	137.7 H	2.0	-3.59	-3.16	-233.8

Table source: Applicant submission to NDA Serial0057 (58)

Three patients had elevated albumin at baseline did not change much in any group. However the sample size is too small and precludes any interpretation.

6.3 10 Responder Analyses:

Percentage Reduction in ALP from baseline

Table 82: ALP at Baseline and Month 12

Time Point/Statistics	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)
Baseline ALP Concentration (U/L)			
N	73	70	73
Mean (SD)	316.3 (103.88)	325.9 (116.24)	327.5 (115.01)
Median	271.3	281.3	311.9
Min, Max	207, 620	187, 811	144, 746
Month 12 ALP Concentration (U/L)			
N	63	64	70
Mean (SD)	191.2 (61.38)	219.5 (99.76)	321.3 (142.88)
Median	181.7	196.6	270.5
Min, Max	95, 444	116, 690	149, 733
Absolute Change from Baseline to Month 12 (U/L)			
N	63	64	70
Mean (SD)	-117.1 (72.84)	-103.5 (87.03)	-7.7 (87.96)
Median	-99.0	-85.5	-15.8
Min, Max	-346, 0.3	-402, 127	-208, 308
Percentage Change from Baseline to Month 12 (%)			
N	63	64	70
Mean (SD)	-36.4 (14.88)	-30.5 (18.97)	-2.5 (23.82)
Median	-38.3	-31.5	-4.7
Min, Max	-72, 0.1	-74, 23	-45, 80
Decrease in ALP \geq 10% at Month 12 – n (%) [1]	61 (83.6%)	55 (78.6%)	29 (39.7%)
Decrease in ALP \geq 20% at Month 12 – n (%) [1]	54 (74.0%)	49 (70.0%)	17 (23.3%)
Decrease in ALP \geq 40% at Month 12 – n (%) [1]	25 (34.3%)	21 (30.0%)	1 (1.4%)
Baseline ALP Concentration (\timesULN)			
N	73	70	73
Mean (SD)	2.658 (0.878)	2.747 (0.9851)	2.760 (0.9732)
Median	2.293	2.378	2.607
Min, Max	1.68, 5.23	1.58, 6.86	1.22, 6.31
Month 12 ALP Concentration (\timesULN)			
N	63	64	70
Mean (SD)	1.606 (0.5161)	1.851 (0.8449)	2.705 (1.1987)
Median	1.527	1.661	2.286
Min, Max	0.80, 3.75	0.98, 5.84	1.26, 6.19

Source: Statistical Reviewer's Table generated from ADLIVER dataset.

Note: Denominators for percentages are N.

[1]: Patients with missing data at these time points were designated as non-responders.

ALP normalization was seen in

- 1 patient in OCA titration arm
- 5 patients in OCA 10 mg arm and

- Zero patients in placebo arm.

≥40% ALP reduction

1. one patient in the placebo arm reached
2. 21 patients in the OCA titration arm and
3. 25 patients in the OCA 10mg arm achieved this reduction.

These results are statistically significant and this reviewer believes it indicates a positive effect of OCA on the surrogate, i.e., ALP.

Percentage of Patients Achieving Primary Endpoint by Baseline ALP Tertile:

About 1/3 of patients had ALP >3 x ULN the Applicant analyzed the effect of OCA based on baseline ALP tertiles (lower tertile <250.5 U/L, middle tertile ≥250.5 U/L to <339.6 U/L, and upper tertile ≥339.6 U/L). Patients reaching primary endpoint are as follows

1. Lower Tertile: 18% placebo arm, 71% OCA titration arm, and 65% OCA 10 mg arm
2. Middle Tertile: 13% placebo arm, 50% OCA titration arm, and 50% OCA 10 mg arm
3. Upper Tertile: 0% placebo arm, 17% OCA titration arm, 19% OCA 10 mg arm.
- 4.

No placebo-treated patient with the upper ALP baseline tertile achieved the composite endpoint. The difference in the percentage of patients achieving the primary composite endpoint between the OCA 10 mg arm and placebo was statistically significant for all tertiles at both Month 6 and Month 12, while for the OCA titration arm, statistically significant differences from placebo were observed at Month 6 for the lowest tertile and at Month 12 for all tertiles.

Reviewer Comment: Numerically fewer patients who were in upper tertile baseline ALP responded to OCA. In the upper tertile the ALP reduction response further diminished with 0%, 17% and 19% patients enrolled to placebo, OCA titration and OCA 10 mg treatment arm respectively. In middle tertile: about 50% patients in OCA titration arm and OCA 10 mg arm achieved reduction in ALP patient with baseline ALP in middle tertiles. Majority of response was seen in patients who had ALP in lower tertiles (<250 U/L)

In clinical trial 747-201 OCA monotherapy the baseline ALP tertile categories were: lower (≤277.5 U/L), mid (>277.5 to ≤465.5 U/L), and upper (>465.5 U/L). The patients in the ALP mid tertile category seemed to have responded better than placebo, however, this effect could have been magnified due to small number of patients as well as less patients with ALP in lower tertile randomized to the lower tertile category versus OCA monotherapy may be better in patients who have higher baseline ALP.

Responders Based on Biochemical Treatment Response Criteria:

Table 83: Percentage of Responders and Odds Ratios of Biochemical Treatment Response Criteria in Patients who were Non-Responders at Baseline: ITT Population

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						
Non-responders at Baseline, N	34		36		35	
Responders, n (%)	6 (18)	6 (18)	20 (56)	23 (64)	18 (51)	20 (57)
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)
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)

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 (%)
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)
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)

Table Source: Adapted from Applicant's submission; Clinical Study report 747-301 page 127 & 128 of 3119

Reviewer Comment:

Numerically higher numbers of patients treated with OCA achieved the Paris I, Paris II, Mayo II and the Toronto II criteria relative to placebo at month 6 and month 12.

Very few patients met the Rotterdam criterion across three treatment arms; majority patients reached this endpoint by improvement in TB. The Applicant has not been able to show a positive improvement in albumin in any PBC trial.

Responders Based on Demographic and Baseline Characteristics:

Efficacy data based on demographic (age, age at diagnosis, gender, race, and geographical site) and baseline characteristic (baseline BMI arm, ALP category >3 x ULN and ALP ≤3 x ULN, UDCA use, total bilirubin level, years since PBC diagnosis, and UDCA use) sub group were evaluated by the Applicant. The analyses were performed on the ITT population.

Table 84: Responder Based on Demographics and Geographical Regions

Statistics	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)
Age Subgroups			
<i>Age < 65</i>	n=56	n=60	n=60
Response at Month 12 – n (%) [1] [2]	29 (51.8%)	28 (46.7%)	7 (11.7%)
<i>Age ≥ 65</i>			
	n=17	n=10	n=13
Response at Month 12 – n (%) [1] [2]	5 (29.4%)	4 (40.0%)	0
Geographical Region Subgroups			
<i>Europe</i>	n=51	n=45	n=49
Response at Month 12 – n (%) [1] [2]	23 (45.1%)	23 (51.1%)	3 (6.1%)
<i>North America/Australia</i>	n=22	n=25	n=24
Response at Month 12 – n (%) [1] [2]	11 (50.0%)	9 (36.0%)	4 (16.7%)

Source: Reviewer generated from “adsl” and Adliver” dataset submitted by the Applicant

This reviewer notes that for most sub group analyses for the above mentioned categories the numbers of patients in each arm were small, precluding meaningful interpretation.

Of all the subgroups, analyses for the age <65 and ≥65 years and geographical location are relevant. Similar percentage of patients responded to OCA treatment in age categories ≥65 and <65 years of age.

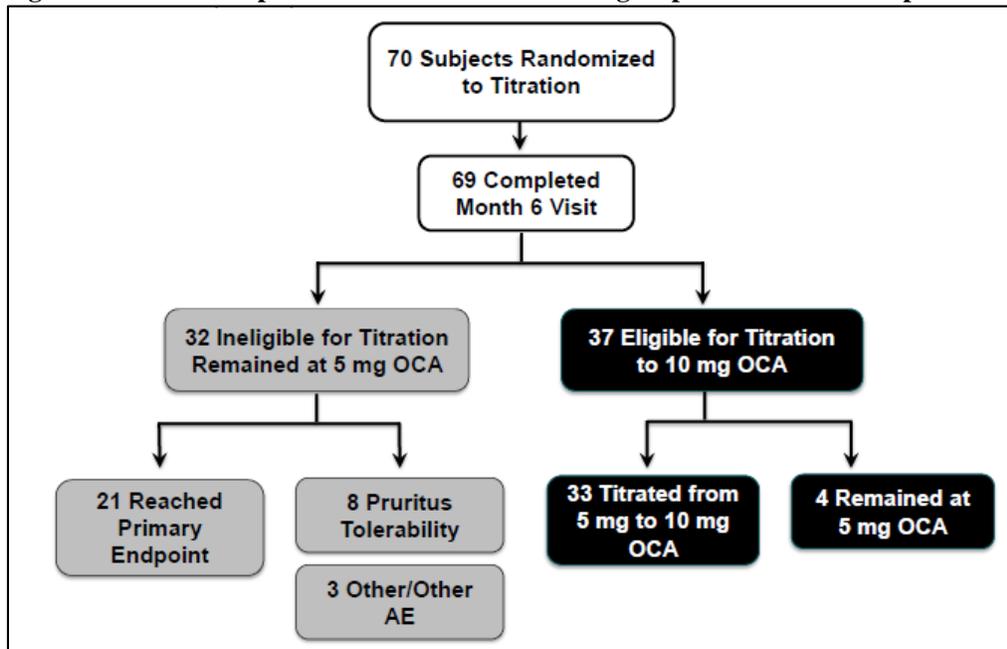
Of note the statistical reviewer makes a note the geographical region did not make much difference, and percent of patients responding were similar to European sites. This reviewer agrees with the assessment.

6.3.11 Effect of Dosing via Titration on Efficacy

Per protocol, OCA titration arm could be titrated from 5 mg to 10 mg at Month 6, if they did not meet the following at 6 month assessment:

ALP ≥1.67x ULN, and/or total bilirubin >ULN, or <15% ALP reduction at Month 6 versus the mean double-blind, pretreatment value(s) and, no evidence of tolerability issues that limits the administration of a higher dose (10 mg)

Figure 39: Patient Disposition for OCA Titration Sub groups: Subset of IIT Population (N = 70)



Source: Copied and electronically reproduced from CSR 747-301 page 141 of 3119

As shown in **Figure 38**, 36 patients were not up-titrated, 21 (58%) of patients achieved the primary endpoint at month 6; and 8 (22%) of patients had pruritus and could not be up-titrated. The 3 patients with other AE include: one patient experienced AE of plicated tongue, second patient had severe pruritus and third patient had an SAE of congestive heart failure not related to OCA therapy. Of the 33 patients titrated 13 achieved the primary endpoint.

Demographic and Baseline characteristics for patients from the OCA titration sub group (OCA 5 mg versus titration OCA 10 mg arm) who completed the month 6 visit were similar across majority of demographic categories (age, region, UDCA use).

Baseline ALP and total bilirubin were lower in the 36 patients who remained at 5 mg. Mean baseline ALP was 306.7 U/L for patients who remained at OCA 5 mg compared to 348.1 U/L for those who up-titrated to OCA 10 mg. Similarly, mean total bilirubin was also lower for those patients remained at 5 mg (9.6 $\mu\text{mol/L}$ versus 11.1 $\mu\text{mol/L}$). The percentage of patients with a Baseline ALP >3x ULN was 22% for those remaining at 5 mg compared with 33% for those who up-titrated to 10 mg. Measures of synthetic liver function (albumin and INR) were within normal ranges in the 2 sub-group.

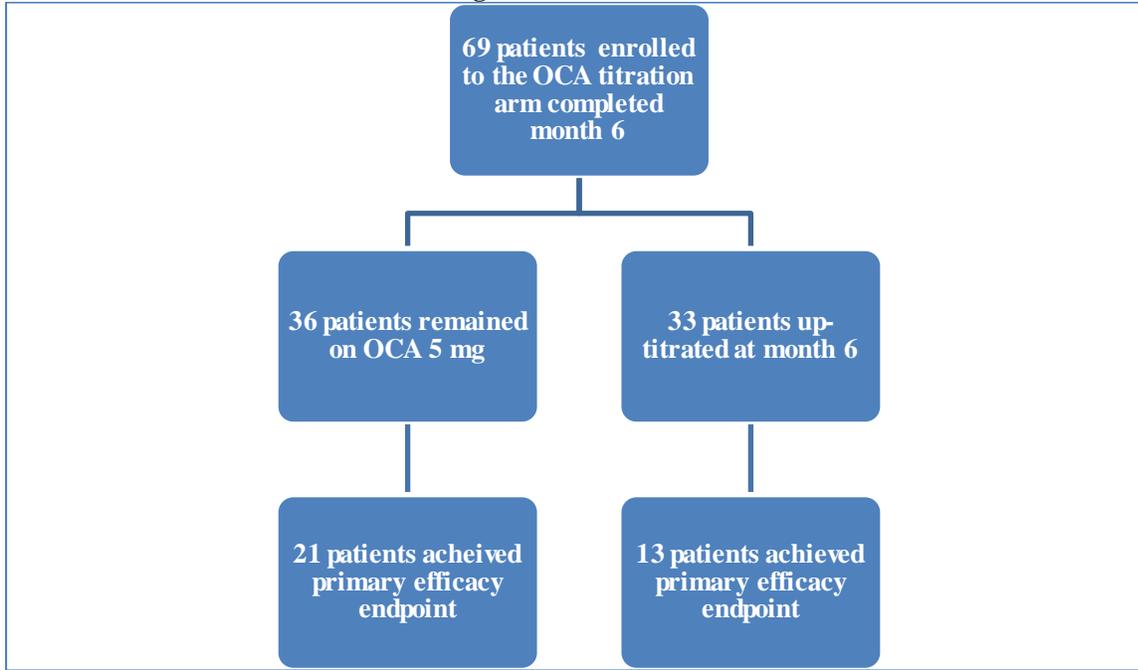
Overall, characteristics were similar with the exception of baseline pruritus and fatigue. The severity of the most recent pruritus event (mild, moderate, or severe) prior to baseline was generally similar between sub groups. A higher percentage of patients who remained at 5 mg (62%) had pruritus ongoing at baseline compared with patients who up-titrated to 10 mg (42%), of which severity of the pruritus was greater for patients who remained at 5 mg (moderate pruritus was 24% versus 3%). No patients from either titration sub groups had severe pruritus.

A 2-fold greater percentage of patients in the 5 mg sub group had a history of fatigue, compared with those patients who up-titrated to 10 mg (70% versus 36%). For these patients, mild, moderate, and severe fatigue-related events were 54%, 35%, and 12%, respectively, for patients who remained on 5 mg compared with 25%, 58%, and 17% for those who up-titrated to 10 mg.

Reviewer comments: It appears baseline fatigue may also limit dose up-titration.

Composite Endpoint for the titration arm: A total of 46% patients achieved the primary efficacy endpoints at month 12. The up-titration schema is presented below.

Figure 40: OCA Titration arm



Source: reviewer generated graph from the data presented in the CSR 747-301

Sub-groups within the OCA Titration Arm:

A total of 69 patients from the OCA titration arm completed Month 6. Of these, 36 (52%) remained at 5 mg for the duration of the 12-month treatment period.

Remained at 5 mg: Of the 36 patients in the OCA titration arm who remained on 5 mg, 21 (58%) achieved the composite endpoint at Month 6 and this response was maintained throughout the latter 6-month treatment period. Fifteen patients remained on 5 mg OCA due to tolerability issues (namely pruritus), other AEs, or other reasons (4 patients were eligible for titration but remained at 5 mg).

Titrated to 10 mg: A total of 33 patients in the OCA titration arm were up-titrated from OCA 5 mg to OCA 10 mg at Month 6. As per protocol, these patients showed no evidence of tolerability issues and were non-responders (i.e., 0% achieved the composite endpoint at Month 6). Thirteen (39%) of these patients met the composite endpoint at Month 12 demonstrating significant incremental benefit with titration of OCA from 5 mg to 10 mg.

Reviewer Comment:

For patients who do not have an optimal response within 6 months of treatment with OCA 5 mg, additional incremental benefit was gained by titrating to OCA 10 mg.

A subset of PBC patients achieved primary endpoint with OCA 5 mg, and in patients who achieved a suboptimal biochemical response at month 6, additional biochemical efficacy was seen in at least 1/3rd of the patients' up-titrated to OCA 10 mg. Therefore the reviewer agrees with the Applicants suggested up-titration approach.

The Applicant is proposing titration at 3 months. The biochemical response of mean ALP decline was seen as early as 2 weeks with a further decline at 3 months. After 3 months patients who were on the OCA titration arm had a

plateauing of the response; there were minimal biochemical gains in ALP reduction further with OCA 5 mg. The predominant effect in the biochemical response quantified at the 3 month mark appears to be the maximum achievable for OCA 5 mg dose. Therefore the titration at 3 months is a reasonable strategy.

The lower incidence of pruritus in patients up-titrated to OCA 10 mg at month 6 may also be a result of selection bias in addition to “tolerating” effect of the OCA. Patients who had tolerability issues with pruritus were not up-titrated to OCA 10 mg arm. Therefore the observation of low incidence of pruritus may be due to exclusion the subset of patients who experience AE of pruritus.

6.3.12 Dose/Dose Response

Dose response: The design of this study allows an evaluation of a dose relationship between OCA 5 mg and OCA 10 mg during the initial 6-month treatment period.

Figure 41: Dose Response – Composite Endpoint Using Observed Data: ITT Population (N = 216)

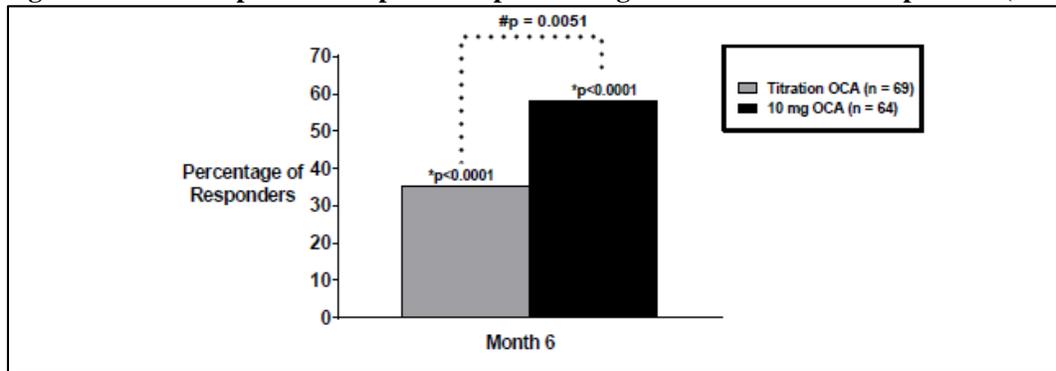


Figure Source: 747-301 CSR; page 154-3119

* p-values for comparing OCA titration to OCA 10 mg are obtained using CMH General Association test stratified by randomization strata factor. A statistically significant difference in the percentage of patients achieving the primary endpoint between the OCA titration (i.e., 5 mg) and OCA 10 mg arms was observed at Month 6 prior to up-titration in the OCA titration arm.

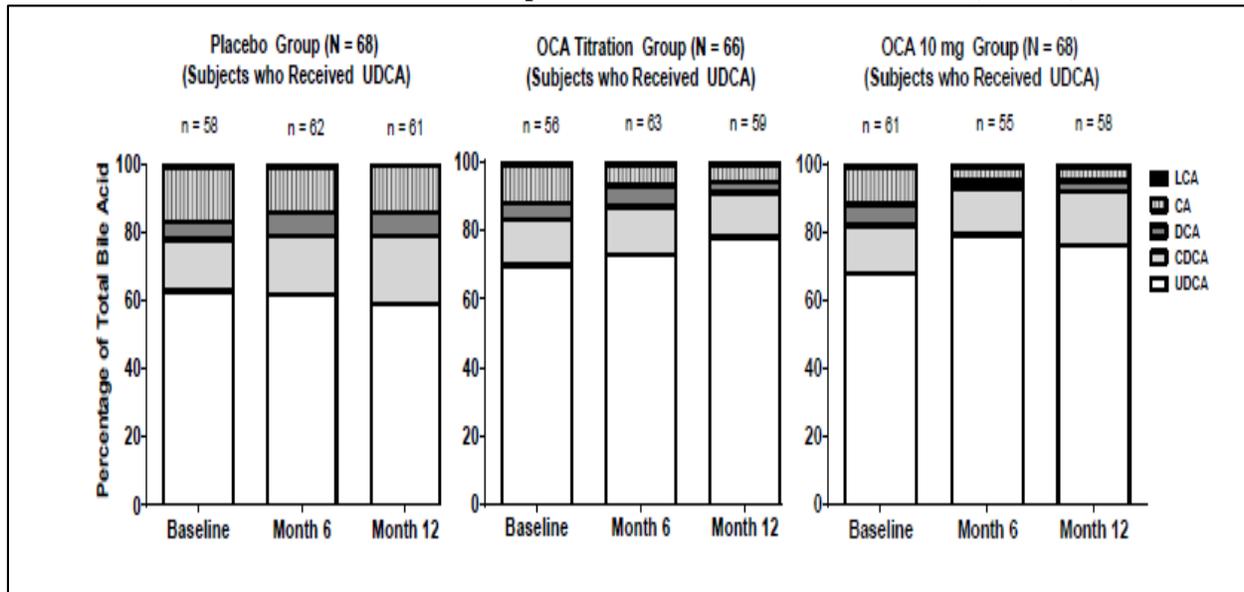
A dose relationship was observed in the percentage of patients who achieved the composite endpoint at each time point during the initial 6-month treatment period. At Month 6, the percentage of patients achieving the composite endpoint was 35% and 58%, for the 5 mg and 10 mg doses, respectively.

Endogenous Bile acids:

The mean baseline levels of total endogenous bile acids were similar for placebo (6.63 μmol) and the OCA titration (7.06 μmol) arms, while higher in the OCA 10 mg arm (9.48 μmol). At month 12, the mean total endogenous bile acid concentrations were 14.59 μmol , 3.77 μmol , and 3.86 μmol for the placebo, OCA titration, and OCA 10 mg arms, respectively.

Statistically significant mean absolute changes 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). In contrast, increases in total bile endogenous concentrations from baseline were observed for the placebo arm at Month 12 (3.16 μmol ; p = 0.2261).

Figure 42: Proportion of Total Bile Acid by Bile Acid Component in Patients Receiving Investigational Product in Combination With UDCA: ITT Population Patients who Received UDCA (N = 202)



Source: CSR 747-301, copied and electronically reproduced from the Applicant CSR 747-301 page 162-3119.
 UDCA = ursodeoxycholic acid, CDCA = chenodeoxycholic acid, DCA = deoxycholic acid, CA = cholic acid, LCA = lithocholic acid, bile acid = bile acid OCA not included in the percentage calculation.

Based on the mechanism of action of OCA the pharmacodynamic effect of OCA was observed, there was suppression of total endogenous bile acid production. The degree and the magnitude of these reductions required to produce a clinical benefit are not currently established. However it is well known stasis of bile acids cause hepatic damage.

Effect of Bile acid sequestrants (BAS) on OCA exposure and efficacy:

The Applicant states at both month 6 and month 12, median OCA trough concentrations were lower for both OCA treatment arms in patients who received BAS compared with patients who did not receive bile acid sequestrants.

The Applicant notes the mean baseline values for ALP, TB and CB values for all 3 parameters were higher across all 3 treatment arms for patients receiving BAS compared with those not receiving BAS making the comparison to the placebo arm in the different cohorts (i.e., BAS use or not) more appropriate. For all 3 treatment arms, the sample size was smaller for patients using BAS compared with those not using BAS (10 versus 63 patients for placebo, 16 versus 54 patients for OCA titration; and 23 versus 50 patients for OCA 10 mg) and thus confounds interpretation.

1. For patients in the OCA titration arm, less improvement in the percent change in ALP was observed for patients using BAS compared with those patients not using BAS. In addition, efficacy was less for this subgroup using BAS at month 6 (OCA 5 mg) compared with Month 12 (OCA 5 mg or OCA 10 mg), reflective of a dose relationship. Thus for the OCA titration arm, the use of BAS appeared to modestly attenuate achievement of biochemical response from baseline to month 6 and month 12 for ALP and total bilirubin. For patients from the OCA titration arm who did not receive BAS, statistically significant differences were observed when compared to placebo across all 3 parameters both at month 6 and 12.
2. For patients receiving OCA 10 mg, similar percent changes from baseline in ALP were observed at month 6 and month 12 irrespective of BAS use. Thus, the lower OCA trough concentrations appeared to have a modest effect on the efficacy of the OCA titration arm, while efficacy was not altered for the OCA 10 mg arm.

Reviewer comment:

These results further support a dose-relationship response given that the effect of BAS does not impact OCA 10 mg

but attenuates biochemical response of OCA 5 mg. This suggests a patient who is on BAS and on 5 mg OCA and had not achieved biochemical response, and dose titration to OCA 10 mg may be helpful to achieve biochemical response.

Other Clinical Outcomes: The Applicant reported the following

1. Death (all-cause),
2. Liver transplant
3. Model of end stage liver disease (MELD) score ≥ 15
4. Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
 - a. Variceal bleed
 - b. Encephalopathy (as defined by a West Haven score of ≥ 2)
 - c. Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
5. Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
6. Hepatocellular carcinoma (HCC) confirmed by 2 complimentary imaging modalities

Reviewers comment:

No patient had liver related death. There were no patients that required liver transplant during the trial. MELD scores increased in few patients across trials however, these findings were not clinically significant in most patients. No patient met the end point of HCC.

The following were noted during the trial:

The patient 186003 who experienced cardiac failure was not associated with the use of investigational agent and the narrative is described in the patient disposition section.

The patient 162005 who experienced one event of esophageal variceal bleeding was not considered be related to the IP (placebo), this reviewer concurs with the Applicant's assessment.

The patient 139003 experienced ascites, hepatic encephalopathy and peripheral edema 360 days after starting the IP (OCA 5 mg). Patient had cirrhosis at enrollment. Causality association with OCA cannot be ruled out.

The fourth patient 139003 noted to have hepatic encephalopathy is the same patient (139003) noted above, who had HE during the same SAE reporting while she developed ascites the second time. Causality association with OCA cannot be ruled out.

Table 85: Clinical Outcomes – MELD Score: Safety Population (N = 216)

Patient Number	Treatment	Baseline MELD Score	Score	Visit
MELD (≥ 15 and Baseline < 12)				
105002	Placebo	6.4	15.8	Week 2
			17.1	Month 3
			21.7	Month 6
134001	Placebo	6.4	21.7	Week 2
			17.1	Month 6
			17.6	Month 9
			20.1	Month 12
162005	Placebo	8.5	23.6	Month 9
174011	Placebo	6.8	20.8	Month 6
153003	OCA 5 mg	8.8	16.6	Month 3
180310	OCA 5 mg	6.4	17.5	Week 2

129002	OCA 10 mg	6.7	18.0	Unscheduled
146004	OCA 10 mg	11.3	16.0	EOT

Source: Adapted from the CSR 747-301 page 170-3119.

Reviewer comments: The SAE narratives were reviewed for all patients.

1. Placebo:

- a. **174011:** there was a finding of isolated INR elevation at 6 month, more than likely a laboratory error, or vitamin K deficiency since TB and creatinine were unchanged. The INR normalized spontaneously without treatment. Therefore the reviewer does not think this is truly elevation of MELD of clinical concern.
- b. **134001:** This patient was on Fenprocoumon (PHENPROCOUMON) which is a long-acting oral anticoagulant drug, a derivative of coumarin. It is expected for this patient to have elevated INR. Additionally serum creatinine and TB were normal throughout the trial duration.
- c. **105002:** The patient had INR elevation with chest pain, and no cause for chest pain or INR elevation was found after extensive evaluation. The Investigator assessed the chest pain as moderate in severity and the dyspnea as severe in severity. Both events were assessed as unlikely related to investigational product. Additionally it is not clear if the patient was anti-coagulation therapy leading to elevated INR. It appears from narrative the patient might have been on some anticoagulation as the narrative said the patient was transitioned to low molecular weight heparin.
- d. **162005:** the circumstances of the INR elevations were not provided in the CSR or narrative. One time elevation in MELD could be due to laboratory error or isolated INR elevations contributing to one time abnormal MELD score and repeat MELD scores were normal in this patient.

2. OCA 10 mg and 5 mg

- a. 146004: narrative does not mention about the INR elevation, only pruritus was described as a case for discontinuation.
- b. 129002, 180310, and 153003: isolated INR elevation was seen which improved spontaneously and patient finished treatment for 12 month. Repeat measure did not show INR elevations and MELD score normalized spontaneously. Again, it appears these were isolated INR elevations and did not contribute to a true rise in MELD score.

Reviewer comment:

These were isolated findings; no other laboratory parameters changed other than abnormal INR reporting in majority of patients. The INR normalized on repeat testing and the MELD score declined to inactive status.

In future negotiations with the Applicant with phase 4 protocols, MELD score increase should be examined to understand what laboratory parameter is giving weight to MELD. If the MELD score is contributed by isolated INR elevation, the laboratory test must be repeated preferably after adequate Vitamin K administration

Liver Fibrosis Assessed by Noninvasive Assessments - Direct and Indirect Biomarkers

1. **ELF Score:** The 3 markers that contribute to the ELF score are HA, P3NP, and TIMP-1. ELF scores for fibrosis range as follows: 7.7 for a high sensitivity exclusion of fibrosis, 9.8 for a high specificity identification of fibrosis (sensitivity 69%, specificity 98% for moderate fibrosis), and 11.3 to discriminate cirrhosis (sensitivity 83%, specificity 97%).
There was no statistical difference in the absolute changes in the ELF score from baseline to month 12.
2. **Hepatic stiffness using Fibroscan TE device:** Change from baseline to month 12 in hepatic stiffness was assessed at a subset of sites using the Fibroscan TE device. Limitation of this test was it was done a subset of patients (34, 32 and 26 patients in placebo, OCA titration and OCA 10 mg treatment arm).

There was no statistical improvement in the hepatic fibrosis over the study duration of 12 months in any treatment arms.

FGF-19

As shown in Phase 2 studies in patients with PBC (747-201 and 747-202), FXR activation by OCA induced a dose-related increase in serum levels of FGF-19, a primary FXR-responsive gene product. This study evaluated the change in FGF-19 over a longer time period and at lower doses, compared with the Phase 2 trials. The baseline FGF-19 levels were well balanced across all 3 treatment arms.

The FXR-mediated activation of the enterohepatic axis to release FGF-19 from the intestine and down regulate bile acid synthesis in the liver by direct induction of the transcription factor small heterodimer partner (SHP) and a direct repression in CYP7A1 expression and bile acid synthesis. Therefore an increase in FGF-19 correlates with the activity of the drug, i.e., higher the FGF-19 the greater is the downregulation of primary bile acid synthesis.

Table 86: FGF19 changes from baseline to Month 12

	Placebo		OCA Titration		OCA 10 mg	
	N = 73		N = 70		N = 73	
FGF-19 (pg/mL)	n		n		n	
Baseline (Median [Q1, Q3])	69	96.0 (62.0, 143.0)	67	92.0 (58.0, 163.0)	70	90.0 (57.0, 179.0)
Month 12 (Median [Q1, Q3])	65	91.0 (62.0, 161.0)	58	157.5 (88.0, 262.0)	63	207.0 (120.0, 351.0)
FGF-19 LLN = 31 pg/mL (males/females) and ULN = 554 pg/mL (males/females)						

Source: Adapted from CSR 747-301 page 176 of 3119

Reviewer comment:

There is a dose related increase in FGF-19 was found in 747-301.

C4 was not measure in this trial. In Trial 747-202 the patients dosed with OCA 10 mg showed a downward trend in the C4 but was statistically significant relative to placebo.

CRP: CRP is an acute-phase protein synthesized by the liver. The level of CRP found in the blood increases in response to inflammation, although significant liver failure impairs CRP production.

Reduction in CRP were noted in both OCA treated groups relative to placebo.

TNF- α There was very minor decline in TNF α (OCA 10 mg > OCA titration arm), however, neither treatment group reached normalization.

The clinical benefits of reductions in TNF- α in PBC are not clear. Again this is a nonspecific marker and the changes observed were relatively small.

TGF- β and IL-6: no changes were observed from baseline to month 12 in any treatment arm.

Immunoglobulin levels: In PBC, common feature is high levels of IgM, in addition to cholestasis and presence of anti-mitochondrial antibodies.

Mean IgM was elevated across all treatment arms. (Normal reference range: IgM = 0.4 g/L to 2.3 g/L for both males and females). IgM reductions were seen in both OCA 10 mg and OCA titration arm relative to placebo, but normalization in IgM was not achieved in any treatment arm.

IgM is elevated in PBC, but is not the cause of PBC, as immunosuppression therapies have failed to change the pathogenesis of disease. The clinical benefits of these reductions in IgM that are still not normalized remain unclear.

6.3.12.1 Efficacy Conclusions

- 1. The primary efficacy endpoint was based on solely ALP in majority of patients enrolled in the trial 747-301. The composite endpoint was evaluated only in subset (8%) patients who had elevated bilirubin at baseline at enrollment. Based on ALP <1.67 ULN or a \geq 15% reduction as a responder definition 47% patients in OCA 10 mg arm (p-value <0.0001), 46% patients (p-value <0.0001) in OCA titration arm were responder compared with 10% responder in the placebo arm.*
- 2. Based on the clinical response, initiating patients on OCA 5 mg and titrating to 10 mg appears to be an appropriate dosing strategy.*
 - a. Patients who were on OCA 5 mg at month 6: 35% (N=69), achieved ALP reduction below the pre-specified threshold.*
 - b. For patients who did not achieve an optimal response within 6 months of treatment with OCA 5 mg, additional incremental benefit was gained by titrating to OCA 10 mg, about 1/3 patients achieved primary efficacy endpoint.*
- 3. Changes in TB when elevated and normalized with OCA show a beneficial effect of OCA. However, when TB is within normal reference range the clinical benefit of changes in TB are not clear, given the natural variability of the TB over time.*
- 4. For patients who received BAS, efficacy was modestly attenuated in patients receiving OCA 5 mg but was not affected in patients receiving OCA 10 mg.*
- 5. There was a reduction in CB in patients treated with OCA and this response was observed better in patients who had abnormal CB at baseline. For patients who had normal CB at baseline these changes were not significant.*
- 6. Decline in liver biochemical markers GGT, ALT and AST were seen. A parallel improvement in ALP with liver biochemistry further supports the slowing of the disease progression with use of FXR activation over a 12-month period. The reductions in GGT, ALT and AST support the primary endpoint.*
- 7. There was a dose relationship observed between OCA 5 mg and OCA 10 mg with regard to changes in biochemical biomarkers (IgM reduction, CRP) and an increase in FGF19.*
- 8. There were reductions (but not normalization) in IgM, CRP were seen relative to placebo. FGF19 was numerically higher in OCA treated patients compared to placebo but still was in normal reference range.*

6.3.12.2 Durability of Response

The biochemical response was durable throughout the study period; the response in ALP was observed at weeks 2 and was durable at month 12. The patients in the OCA titration arm who did not achieve primary efficacy endpoint at 6 month, when titrated to higher dose, at least 1/3 of those patients responded by achieving primary efficacy endpoint. The biochemical response was seen as early as 2 weeks and biochemical response plateaued month 6 in OCA titration arm; and the biochemical response plateaus at month 6 when patient was dosed with OCA 10 mg arm.

6.3.12.3 Persistence of Effect

The response was persistent during the therapy in all three trials.

There was no off treatment follow up of the patients in trial 747-301 to understand persistence of response after treatment discontinuation. However, as seen in Phase II trials, the biochemical response sustained for at least 2 weeks despite discontinuation of the treatment in trial 747-201 and 747-202 study results.

Additionally, the data from the long terms safety extension (LTSE) shows response is durable and persistent for ALP reduction as shown in the graph below for ALP. Once the decline in mean ALP was achieved the mean ALP response was durable as present in Figure 43 shown as ALP durability (data cut-off of 29 June 2015).

Figure 43: Mean (SD) ALP by DB Randomized Treatment Group over Time in Study 747-301 (All Patients)

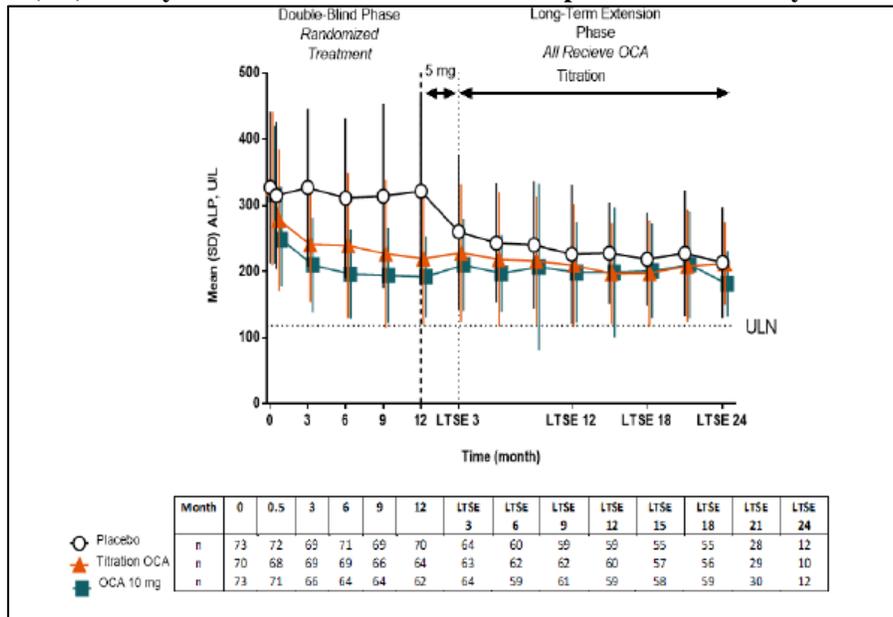


Figure Source: Copied and electronically reproduced from the Applicant submission 120 safety update page 13 of 1033

Post Advisory Committee meeting FDA asked the Applicant to clarify the intra-patient variability as seen in this trial and the independent effect of OCA on ALP response. Response is summarized:
 ALP variance and rise: ALP variance was seen in patients who were on alternate day dosing schedule or receiving bile acid sequestrants. The ALP elevations were seen in patients along with increases in total bilirubin and transaminases, consistent with liver injury, which the Applicant said were transient. The Applicant did not provide numbers of the patients who experienced these liver biochemical elevations but made a note that these elevations were transient and not associated with hepatic decompensations.

Intra-patient ALP variability: The higher intra-patient variability in mean (SD) was noted at week 2, and month 6. However, at month 12 the mean (SD) intra-patient variability was small in both the OCA treated arms as shown in Table 90. Most patient had ALP variability <40U/L but 15% of patients had SD of ALP >60 u/L and these outliers were present in each treatment arm (12/10/13 in placebo, OCA 10 mg and OCA titration arm) that had ALP >60 u/L variance.

Additionally, OCA does not have independent effect on ALP reduction as seen in human PK study 747-105 where OCA was given for 2 weeks and changes in ALP were not seen in the patients at relevant OCA doses.

Finally, at this time we do not have granular data on kinetics of ALP in decompensated cirrhosis and biochemically advanced stage disease.

Table 87: Summary of Within Patient Standard Deviation (SD) of Alkaline Phosphatase (U/L)

Parameter	Placebo		Overall (N=73)	Titration OCA (N=70)	10 mg OCA (N=73)
	Treated with Placebo Only (N=64)	Inadvertently Treated with OCA (N=9)			
Within Patient SD of ALP for All Post-Baseline Visits ^[1]					
n	64	9	73	69	71
Mean (SD)	37.57 (32.203)	44.37 (27.286)	38.41 (31.547)	39.48 (28.563)	33.86 (20.044)
SEM	4.025	9.095	3.692	3.439	2.379
Median	27.87	37.88	29.60	31.27	30.26
(Q1, Q3)	(18.0, 42.0)	(26.9, 49.3)	(18.2, 42.3)	(19.9, 48.2)	(21.1, 39.7)
Min, Max	4.0, 176.2	17.7, 104.3	4.0, 176.2	5.5, 157.0	3.5, 110.6
Within Patient SD of ALP for Week 2, DB Month 3, and DB Month 6A					
n	62	9	71	69	67
Mean (SD)	26.94 (22.351)	41.49 (32.665)	28.79 (24.105)	35.54 (30.834)	32.40 (23.633)
SEM	2.839	10.888	2.861	3.712	2.887
Median	22.07	25.29	22.55	28.26	28.04
(Q1, Q3)	(12.1, 32.7)	(22.6, 38.7)	(12.5, 34.5)	(15.1, 39.3)	(16.4, 41.9)
Min, Max	2.6, 113.3	15.4, 112.9	2.6, 113.3	1.6, 150.6	2.7, 126.8
Within Patient SD of ALP for DB Month 9 and DB Month 12					
n	61	8	69	64	62
Mean (SD)	28.54 (29.760)	22.82 (16.821)	27.88 (28.536)	15.95 (24.858)	17.40 (21.777)
SEM	3.811	5.947	3.435	3.107	2.766
Median	16.90	19.45	17.18	8.80	12.13
(Q1, Q3)	(9.8, 37.1)	(9.7, 33.7)	(9.8, 37.1)	(4.7, 19.6)	(4.0, 24.8)
Min, Max	0.2, 142.1	3.5, 53.5	0.2, 142.1	0.1, 190.9	0.4, 155.3

Source: Applicant's NDA submission Sequence 0060 (63) submitted on 4-29-2016

Additional Analyses Conducted by the Applicant (post hoc data): The Applicant conducted analyses of specific isoforms of ALP including liver, bone and other by fractionating available blood samples as part of an exploratory ad hoc assessment. Blood samples were analyzed in a subset of OCA-treated patients whom had samples of sufficient volume for testing at both baseline and at month 12. A total of 17 patients from the OCA titration arm and 19 patients from the OCA 10 mg arm had samples available for ALP isoform analyses. No samples were analyzed from placebo patients. For both the OCA titration and OCA 10 mg groups, the principle ALP isoform at baseline was liver (>80%). Bone isoform accounted for the remainder of the baseline ALP composition for both OCA groups.

Table 88: ALP (Bone, Liver, and Other) Isoform Levels and Total ALP Levels for Patients on OCA Titration arm: Baseline and Month 12 – ANCOVA Using Observed Data

	OCA Titration (N=70)			
	Bone	Liver	Other	Total
Baseline				
N	17	17	17	17
Mean (SD)	61.5 (24.55)	288.1 (170.45)	0.0 (0)	349.5 (187.34)
Median	56.0	224.0	0.0	267.0
Min, Max	20, 117	160, 809	0, 0	180, 909
Month 12				
N	17	17	17	17
Mean (SD)	51.6 (12.61)	220.6 (131.75)	0 (0)	273.2 (137.70)
Median	51.0	192.0	0.0	230.0
Min, Max	29, 75	80, 673	0, 0	121, 740
LS Mean (SE) Change From Baseline	1.13 (6.33)	-71.53 (17.88)	-1.11 (7.62)	-69.48 (24.07)

95% CI	-11.81, 14.08	-108.22, - 34.84	-16.67, 14.46	-118.70, - 20.25
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Table source: Applicant's clinical submission- serial0049 (50) and Module 5.3.5.1, Section 14, Post Hoc Table 14.2.22

Table 89: ALP (Bone, Liver, and Other) Isoform Levels and Total ALP Levels for Patients on OCA 10 mg arm: Baseline and Month 12 – ANCOVA Using Observed Data

	OCA 10 mg (N=73)			
	Bone	Liver	Other	Total
Baseline				
N	19	19	19	19
Mean (SD)	49.3 (15.27)	253.2 (77.30)	0.0 (0)	302.5 (89.73)
Median	45.0	217.0	0.0	259.0
Min, Max	31, 84	177, 425	0, 0	221, 500
Month 12				
N	17	17	17	17
Mean (SD)	45.7 (17.02)	149.9 (46.50)	11.5 (34.02)	189.5 (54.06)
Median	40.0	149.0	0.0	206
Min, Max	19, 78	73, 223	0, 126	100, 295
LS Mean (SE) Change From Baseline	-0.70 (6.32)	-112.55 (20.77)	9.97 (9.29)	-110.63 (26.46)
95% CI	-13.62, 12.23	-155.18, -69.93	-9.02, 28.95	-164.75, - 56.51

Table source: Applicant's clinical submission- serial0049 (50) and Module 5.3.5.1, Section 14, Post Hoc Table 14.2.22

The mean baseline liver ALP was elevated, 288 U/L for the OCA titration arm and 253 U/L for the OCA 10 mg arm (upper limit of normal [ULN] = 94 U/L).

Mean baseline bone ALP was 62 U/L for the OCA titration arm and within normal limits i.e., 49 U/L for the OCA 10 mg arm (ULN for bone ALP= 55 U/L).

The LS mean change from baseline to month 12 for the liver ALP isoform was 72 U/L for the OCA titration arm and 113 U/L for the OCA 10 mg arm (Table 89, Table 90). In contrast, the LS mean changes from baseline to Month 12 were minimal for the bone and other ALP isoforms. On average, the change in liver ALP isoform contributed to 91% change in total ALP with the OCA treatment.

Only OCA treated patient had the ALP isoform fractionation analyses. None of the placebo patients had these analyses to compare the results. We can rely on these data and that the changes with OCA treatment are seen predominately in liver ALP fraction. This evidence suggests that the high ALP at baseline was mainly due to liver ALP and reduction of ALP after OCA treatment was the liver fraction. These results are reassuring that the drug's main action is on the liver ALP.

6.3.13 Trial 747-301-Safety Assessment

OCA treatment appeared safe and was generally well tolerated. Across treatment arms, a similar number of patients reported TEAEs (66 patients [90%] from the placebo arm reported 452 TEAEs, 65 patients [93%] from the OCA titration arm reported 471 TEAEs, and 69 patients [95%] from the OCA 10 mg arm reported a total of 467 TEAEs). Pruritus was the most common TEAE associated with OCA treatment.

The number of patients with mild TEAEs was higher in the placebo arm compared to the OCA treatment arms; the number of patients with moderate TEAEs was well-balanced across treatment arms, and the number of patients with severe TEAEs was higher in the OCA treatment arms. The incidence of TEAEs assessed as severe, related, serious, or leading to study discontinuation was higher in OCA-treated patients compared with placebo-treated patients. With the exception of SAEs, these imbalances were predominantly attributed to pruritus.

The safety population included all patients (N=216) who received at least one dose of investigational product. 73 patients received placebo and 73 patients received OCA 10 mg for the duration of the study. In the OCA titration arm, 70 patients received at least 1 dose of OCA 5 mg from Day 0 to month 6. Of the 70 patients in the OCA titration arm, 69 patients completed Month 6 (1 patient [Patient 104003] discontinued prior to Month 6). Of these, 36 patients remained at 5 mg for the duration of the 12-month treatment period and 33 patients 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.

Table 90: Exposure to Investigational Product: Safety Population (N = 216)

		OCA Titration			
	Placebo (N = 73)	OCA Titration (N = 70)	Remained at 5 mg (N = 37)	Titrated to 10 mg (N = 33)	OCA 10 mg (N = 73)
Number of Days on Investigational Product					
N	73	70	37	33	73
Mean (SD)	346.0 (58.55)	341.7 (60.77)	326.4 (80.09)	358.8 (13.24)	308.9 (105.47)
Median	361.0	360.0	356.0	361.0	355.0
Min, Max	16, 378	7, 378	7, 378	296, 375	9, 378
Average Daily OCA Dose (mg)					
N	73	70	37	33	73
Mean (SD)	0 (0.0)	6.2 (1.27)	5.0 (0.0)	7.5 (0.2)	10.0 (0.0)
Median	0.0	5.0	5.0	7.5	10.0
Min, Max	0, 0	5, 8	5, 5	7, 8	10, 10

Table source: Copied and electronically reproduced from CSR 747-301 page 188 of 3119

The median number of days on investigational product was similar across treatment arms (361, 360, 356, and 355 days in the placebo, OCA 5mg, OCA 5 mg → up-titrated to OCA 10 mg, and OCA 10 mg treatment arms, respectively). The mean duration of exposure was higher for placebo arm compared to OCA treated patients. This was due to dosing interruptions or alternative dosing.

6.3.13.1 Treatment emergent AE

TEAEs that occurred at an incidence of $\geq 5\%$ and were reported with an incidence of $> 3\%$ more frequently in

patients receiving OCA compared with placebo were limited to pruritus, fatigue, hypothyroidism, oropharyngeal pain, arthralgia, abdominal discomfort, sinusitis, peripheral edema, pyrexia, palpitations, eczema, bronchitis, and nasopharyngitis.

Table 91: Treatment-Emergent Adverse Events Occurring in ≥5% of Patients 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 (%)	Patients ^a (%)	Patients ^a (%)	Patients ^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)
Edema peripheral	2 (3)	2 (3)	5 (7)
Pyrexia	1 (1)	0	5 (7)
Infections and Infestations			
Naso pharyngitis	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)
Diarrhea	8 (11)	2 (3)	8 (11)
Constipation	4 (5)	5 (7)	5 (7)
Abdominal pain upper	5 (7)	5 (7)	4 (5)
Gastro esophageal 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)
	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
System Organ Class/ Preferred Term, n (%)	Patients ^a (%)	Patients ^a (%)	Patients ^a (%)
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 patients; n = number of patients 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), patients 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 patients (Patients 105002, 174018, and 186005); in the OCA titration group, 2 fractures (1 wrist fracture and 1 ulna fracture) were experienced by 2 patients (Patient 162002 and Patient 172002); 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 patients (Patients 159003, 161001, 142022, and 180007). The pubis fractures experienced by Patient 174018 were the result of an accidental fall. One patient (Patient 192003) had a sternal fracture that occurred -32 days prior to initiation of investigational product that is not included in the incidence.

Table 92: Relevant Medical History in Patients Experiencing Serious or Non-Serious Adverse Events of Fractures: Safety Population (N = 216)

Patient (Gender/ Age/ Race/ BMI)	Injury, Poisoning, and Procedural Complications AE	SAE	Relevant Medical History
Placebo			

105002 (Female/67 y/white/32.5 kg/m ²)	Tibia fracture (2x)	Yes No	Lumbar spine osteopenia Osteopenia Costochondritis Height loss Hyperparathyroidism Postmenopausal Vitamin D deficiency Right clavicle fracture
174018 (Female/76 y/white/18.2 kg/m ²)	Pubis fracture (2x)	No (2x)	Fracture humerus Osteoporosis
186005 (Female/51 y/white/22.7 kg/m ²)	Upper limb fracture	No	Osteopenia
OCA Titration			
162002 (Female/62 y/white/26.4 kg/m ²)	Wrist fracture	No	Hypothyroidism
172002 (Female/63 y/Cuban/27.5 kg/m ²)	Ulna fracture	No	Post-menopause
OCA 10 mg			
142022 (Male/34 y/white/27.6 kg/m ²)	Clavicle fracture (2x)	No Yes	None
159003 (Female/53 y/white/22.8 kg/m ²)	Radius fracture (2x)	Yes (2x)	Thyroid part resection Subtotal hysterectomy Hysterectomy (2005)
161001 (Female/51 y/white/24.7 kg/m ²)	Wrist fracture (2x)	No Yes	Post-menopausal
180007 (Female/61 y/white/22.1 kg/m ²)	Skeletal injury	No	Osteopenia Hashimoto disease

Table source: Copied and electronically reproduced from CSR page 194-3119

A consult was placed for the Division of Bone, Reproductive and Urologic Products (DBRUP) for recommendation for assessment of fractures. A summary of the consult is noted below.

Reviewer comment:

The reviewer agrees with this assessment and thinks OCA is unlikely to cause these fractures. The standard medical care should be appropriate to assess bone monitoring, so specific postmarketing bone monitoring is warranted with OCA use. The following is the summary in which this reviewer has additional comments embedded. For details the reader is referred to read the clinical consult review placed in DARRTs by Dr. John T. Stinson.

The reviewer notes, discounting one patient in the OCA 10 mg group who sustained a sternal fracture before dosing, 3.4% of patients treated with OCA had fractures, as did 4% of placebo treated patients. These rates are consistent with background fracture rates (in age and sex-matched) general population.

For the placebo group, 4 fractures (1 tibia fractures, 2 pubis fractures [same patient], and upper limb fracture) were experienced by 3 patients (Patients 105002, 174018, and 186005); in the OCA titration group, 2 fractures (1 wrist fracture and 1 ulna fracture) were experienced by 2 patients (Patient 162002 and Patient 172002); in the OCA 10 mg group, 7 fractures were listed.

These included 2 clavicle fractures, 2 radius fractures, 2 wrist fractures, and 1 skeletal injury [sternal fracture] that were experienced by 4 patients (Patients 159003, 161001, 142022, and 180007).

The pubis fractures experienced by Patient 174018 were the result of an accidental fall. One patient (Patient 192003) randomized to OCA 10 mg, had a sternal fracture that occurred 32 days prior to initiation of investigational product, and withdrew study consent.

None of these fractures were considered by investigators to be study-related.

Radius, wrist and pubis fractures are generally considered fragility fractures due to loss of bone quality. The 2 pubis fractures in one patient (174018) were due to falling, and qualify as fragility fractures. There is no narrative for this patient, and the timeframe is unclear. Fractures of 2 pubic rami sustained simultaneously could be looked at as one fracture.

These 2 pubic fractures were reported only 8 days apart and most likely represent one fracture.

Therefore there were 5 fragility fractures in 4 patients out of 8 patients with fractures. The other fractures, (clavicle, ulna, arm and tibia) were most likely traumatic in origin. This fracture incidence (4%) is less than reported historically with PBC.

When compared with the general population, the absolute increase in fracture risk in patients with PBC is increased with an absolute excess fracture rate of 12.5 per 1,000 person-years.

This reviewer sees no evidence of a safety signal for bone health or fracture risk for OCA. The

DXA scan results are generally consistent with the disease state, although they indicate less osteoporosis than reported in earlier series of PBC patients. The rate of bone loss is comparable to the age-related general population. The fracture incidence is consistent with clinical experience with PBC and with background rates in the general population. Aside from routine DXA monitoring of PBC patients, as recommended by in the AASLD and EASL cholestatic liver disease clinical practice guidelines (AASLD 2009 and EASL 2009), no focused postmarketing bone monitoring for OCA is warranted.

Table 93: Incidence of Treatment-Emergent Adverse Events by Maximum Severity: Safety Population (N = 216)

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
Maximum Severity	n (%)	n (%)	n (%)
Mild	29 (40)	16 (23)	19 (26)
Moderate	28 (38)	27 (39)	29 (40)
Severe	9 (12)	22 (31)	21 (29)

Table source: Copied and electronically reproduced from CSR page 195-3119

Note: A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. At each level of summation (overall, preferred term), patients reporting more than one AE are counted only once using the highest severity.

The incidence of severe TEAEs was higher in OCA treated patients~30% relative to placebo 9%.

6.3.13.2 Deaths

One death was reported during the double-blind phase of the study.

Intensity: Severe; Causality: Unlikely; Outcome: Fatal; SAE occurred 257 days after initial investigational product (IP) dosing (OCA 5 mg)

Patient 186003 (male, age 82, OCA Titration): The patient's medical history included PBC, deep vein thrombosis (DVT), heart failure, atrial fibrillation (b) (6) myocardial infarction x2, hypertension, intermittent pleural effusions (b) (6) generalized nonspecific rash of unknown etiology, gout, gastrointestinal symptoms, insomnia, and chronic renal impairment since 1995. The patient had an implantable cardioverter defibrillator at study entry. The patient was randomized to the titration arm (OCA 5 mg) and initiated IP dosing on (b) (6)

The patient did not uptitrate to OCA 10 mg at month 6 due to general progression of his medical history of heart failure. On Day 219 (b) (6) after initiation of IP, the patient experienced an SAE of cardiac failure and was hospitalized. Peripheral edema and pleural effusion were noted upon admission. The event of worsening heart failure was considered resolved on (b) (6).

On Day 257 (b) (6), the patient had a second event of cardiac failure and was hospitalized. The patient was treated diuretics. The patient was placed on palliative care for the management of shortness of breath and fatigue and many of the patient's heart failure medications were withdrawn, 3 doses of IP were missed during this event. UDCA dosing was discontinued on (b) (6). The patient was discharged to home and readmitted to the hospital on (b) (6) for worsening symptoms of heart failure. IP dosing was discontinued (b) (6). The patient died on (b) (6). The primary cause of death was noted as congestive cardiac failure and ischemic heart disease, prior myocardial infarction. Secondary causes of death were listed as chronic kidney disease and PBC.

This patient had elevated serum creatinine (1.76 mg/dL) during screening period and patient was not a good candidate for enrollment in trial. The bilirubin, ALT, AST and GGT were relatively stable throughout the trial period. On Day 219 the albumin declined from 4 gm/dL to 2.7 g/dL and INR was elevated to 7.47 (possibly as the patient was on warfarin), and his MELD was elevated due to both increases INR and serum creatinine. The serum creatinine was reported to be 3.6 mg/dL on day 257.

Reviewers conclusion: Even if the death occurred due to cardiac event this patients should have not been enrolled (due to high baseline serum creatinine) in trial or discontinued after the first cardiac failure event.

6.3.13.3 Serious Adverse Events

The incidence of SAEs in the OCA treatment arms compared to the placebo arm was higher. There was no clear dose-related pattern (11 patients [16%] in the OCA titration, 8 patients [11%] in the OCA 10 mg treatment arm)

Table 94: Incidence of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Reported: Safety Population (N = 216)

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
System Organ Class Preferred Term	Patients (%) Events (a)	Patients (%) Events	Patients (%) Events
All Serious Adverse Events	3 (4) 8	11 (16) 15	8 (11) 11
Injury, Poisoning and Procedural Complications	1 (1) 1	0	4 (5) 5
Clavicle fracture	0	0	1 (1) 1
Post procedural hemorrhage	0	0	1 (1) 1
Radius fracture	0	0	1 (1) 2
Tibia fracture	1 (1) 1	0	0
Wrist fracture	0	0	1 (1) 1
Musculoskeletal and Connective Tissue Disorders	0	1 (1) 1	3 (4) 3
Osteoarthritis	0	0	2 (3) 2
Intervertebral disc protrusion	0	0	1 (1) 1
Rotator cuff syndrome	0	1 (1) 1	0
Infections and Infestations	0	1 (1) 1	2 (3) 2
Erysipelas	0	0	1 (1) 1
Parotitis	0	1 (1) 1	0
Pneumonia	0	0	1 (1) 1
Blood and Lymphatic System Disorders	0	0	1 (1) 1
Anemia	0	0	1 (1) 1
Gastrointestinal Disorders	1 (1) 3	4 (6) 4	0
Upper gastrointestinal hemorrhage	1 (1) 1	1 (1) 1	0
Abdominal wall hematoma	0	1 (1) 1	0
Ascites	0	1 (1) 1	0
Splenic artery aneurysm	0	1 (1) 1	0
Varices esophageal	1 (1) 2	0	0
Nervous System Disorders	0	2 (3) 3	0
Hepatic encephalopathy	0	1 (1) 2	0
Syncope	0	1 (1) 1	0

Table continued: Incidence of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Reported: Safety Population (N=216)

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
System Organ Class Preferred Term	Patients (%) Events (a)	Patients (%) Events (a)	Patients (%) Events (a)
Vascular Disorders	0	2 (3) 2	0
Varicose vein	0	2 (3) 2	0
Cardiac Disorders	1 (1) 1	1 (1) 2	0
Cardiac failure	0	1 (1) 2	0
Sick sinus syndrome	1 (1) 1	0	0
General Disorders and Administration Site Conditions	2 (3) 2	1 (1) 1	0
Chest pain	1 (1) 1	0	0
Non-cardiac chest pain	1 (1) 1	0	0
Edema	0	1 (1) 1	0
Respiratory, Thoracic and Mediastinal Disorders	1 (1) 1	1 (1) 1	0
Dyspnea	1 (1) 1	0	0
Interstitial lung disease	0	1 (1) 1	0

Table source: copied and electronically reproduced from CSR page 201 of 3119 and page 202-3119

^a At each level of summation (overall, system organ class, preferred term), patients reporting more than one AE are counted only once.

SAEs:

All SAEs resolved with or without sequelae except for the SAE of cardiac failure (Patient 186003, OCA titration), which was fatal. Another patient (Patient 142004, OCA titration) had an SAE of interstitial lung disease that resulted in study discontinuation. Both these SAEs were assessed as not related to investigational product, and the reviewer agrees with the Applicant's assessment.

Patient 139003 enrolled to the **OCA titration arm** (dosed with 5 mg) relevant medical history include Stage 4 fibrosis (cirrhosis) with regenerative nodules at baseline, but very important to note, she had not history of decompensation events prior to this event.

9th June 2012: The patient was started on IP (OCA 5 mg)

23rd March, 2013: Patient experienced diarrhea (acquired as a result of being on cruise travel)

9th April 2013: Patient complained of bilateral pitting edema, colonoscopy was done, no etiology for diarrhea found. Her albumin was 3.1 and platelets were 159; patient started gaining weight and complained of edema

14th May 2013: Her albumin was 2.7 and platelets count 188 and her OCA treatment was discontinued.

23rd May 2013: Patient required Furosemide for abdominal distension and leg swelling.

3rd June 2013: continued to complain of weight gain and required medical care: Abdominal US showed: enlarged cirrhotic liver with nodularity, moderate ascites and splenomegaly; patient reported 20 lbs weight gain since mid-April 2013

4th June 2013: Experienced hepatic encephalopathy last 4 days, and improved

21st June 2013: Patient experienced 2nd episode of hepatic encephalopathy+ severe ascites with significant worsening as noted by CT scan; IV diuretics were given; her serum creatinine was 0.9 mg/dL; serum albumin was 2.9 g/dl and platelet count was 88 k/uL

Patient's symptoms began while she was on OCA 5 mg dose (mid-April 2013) and actual decompensation occurred after OCA discontinuation. The pharmco-dynamic action of the drug persists for a long period after OCA discontinuation because of long half-life of OCA and its conjugates.

Even if one assumes the patient developed protein losing enteropathy (PLE), and developed edema, her edema continued despite improvement in diarrhea and led to medically refractory ascites and hepatic encephalopathy. This is not a phenomenon seen in patients with PLE.

Patient 174004 enrolled to **OCA 10 mg** treatment arm developed anemia the event was coded as severe and causality not associate with OCA. Relevant medical history includes: patient had hepatomegaly and splenomegaly (patient already had portal hypertension at the time of enrollment). Patient had congestive gastropathy noted on (b) (6). The reviewer notes the patient experienced massive gastrointestinal hemorrhage while on OCA 10 mg and required 5 trans fusions on two separate days. (b) (6): Start date-i.e., dosed with OCA 10 mg; (Screening lab hemoglobin was 11.8 g/dL and platelet count was 59 K/uL) (b) (6): 14 days after OCA dosing patient's hemoglobin dropped to 6.5g/dL and dark stools (b) (6) EGD showed grade 1 varices and mild congestive gastropathy; hemoglobin was 7 g/dL and she was transfused with 2 units of blood (b) (6) she received 3 units of blood transfusion hemoglobin was 9.5 g/dL; an abdominal ultrasound was performed which showed mild ascites. A colonoscopy was performed on (b) (6) and showed no indication of bleeding. A gynecological examination to further investigate the potential source of bleeding was normal. (b) (6) hemoglobin 12.7 g/dL

The Investigator noted that the patient's cause of anemia was not due to hemolysis or lack of production and concluded that the only possible explanation was that the anemia was probably due to congestive gastropathy. During hospitalization and follow up, the underlying cause of the patient's anemia was not discovered. The patient's platelet count was very low at Screening and Day 0. There was no increase in indirect bilirubin. Other sources of bleeding were ruled out.

Bleeding due to congestive gastropathy in setting of portal hypertension (esophageal varices grade 1, splenomegaly and ascites) is likely a non variceal hemorrhage. They typically present as melena and require transfusions. However, in presence of portal hypertension, the hemodynamics of blood flow is altered, and the reviewer thinks these portal circulatory changes may contribute to bleeding. This reviewer considers the causality with OCA use cannot be ruled out. Notably, she did not discontinue from the trial at this time and re-challenge with OCA use for next 74 days did not lead to second episode of gastrointestinal hemorrhage. However, the patient discontinued from the trial on Day 86 due to severe pruritus.

Placebo Patient 162005

SAE Criteria: Hospitalization, Life-Threatening. The Investigator considered the esophageal varices with a start date of 12 Feb 2013 as mild in severity and unlikely related to investigational product.

One event of variceal bleeding that occurred 75 days after dosing with investigational product. The second and third; the second and third events were elective variceal banding which are coded as esophageal varices.

Upper gastrointestinal bleeding; Intensity Severe; Causality Unlikely; Action Taken Non-drug treatment, medication, hospitalization, diagnostic upper endoscopy and therapeutic upper endoscopy with rubber band ligation; Outcome: Resolved

41-year-old white female with primary biliary cirrhosis (PBC) was randomized to placebo. The patient was hospitalized on (b) (6), approximately 2.5 months after initiation of investigational product, due to upper gastrointestinal hemorrhage. An upper endoscopy was performed which revealed Grade 2 to 3 esophageal varices with no signs of active bleeding. The patient remained stable during hospitalization without blood transfusions. Abdominal ultrasound revealed a cirrhotic liver and enlarged spleen. On (b) (6), the patient underwent elective

endoscopy with rubber band ligation for the esophageal varices. The report conclusion indicated Grade 3 varices with cherry red spots which were banded. On [REDACTED] (b) (6), the patient was admitted to the hospital for elective upper endoscopy and repeat banding of Grade 2 to 3 esophageal varices

The event of upper gastrointestinal bleeding was considered resolved with sequelae on [REDACTED] (b) (6). The Investigator assessed the event of upper gastrointestinal bleeding as severe in severity and unlikely related to treatment.

Reviewer Comment: The reviewer agrees with investigator's assessment.

Serious adverse events but not related to OCA use:

Patient 169001 (OCA titration arm): The patient was treated with doxycycline for bronchitis contributing to an elevated INR of 3.74. Patient was hospitalized due to abdominal pain. Computed tomography (CT) of the abdomen revealed a mass of the right rectus abdominis muscle with likely hematoma, and intra-abdominal hematoma breakthrough. The patient's hemoglobin had decreased to 4.8 mmol/L and was transfuse 3 units of blood. The hemoglobin and the INR normalized. The event of hematoma, right muscle rectus abdominis (abdominal wall hematoma) was no longer considered serious. The Investigator assessed the hematoma, right muscle rectus abdominis (abdominal wall hematoma) as severe in severity and unlikely related to investigational product.

This reviewer agrees with the Investigator's assessment, however, thinks concomitant antibiotics use should trigger testing for coagulation profile a few days' post antibiotics use in patients with PBC to assess for vitamin K deficiency leading to coagulopathy. This might be more relevant in patients with advanced liver disease.

Patient 118008 (OCA titration arm): 66 y/white/female/PBC experienced upper GI bleed, 210 days after initial investigational product dosing. Intensity: sever, causality: not related, outcome: resolved.

On [REDACTED] (b) (6) approximately 7 months after the initiation of investigational product, the patient presented to the Emergency Room with complaints of light-headedness and melena beginning 2 days prior, and her hemoglobin dropped from 12.6 g/dL to 8.3g/dL. The patient received 2 units of packed red blood cells. Her esophagogastroduodenoscopy revealed erosive gastritis and a 3 mm antral ulcer. No blood was seen; however, the gastritis and ulcer were considered possible causes of the melena and anemia. Of note, the patient had recently started taking oral alendronate sodium weekly for osteoporosis on [REDACTED] (b) (6).

On 10 May 2013, the event of upper gastrointestinal bleed was considered resolved. The patient continued participation in the trial and resumed investigational product on 11 May 2013. The Investigator assessed the upper gastrointestinal bleed as severe in severity and not related to investigational product.

RC: This reviewer agrees, antral ulcers can bleed and resulting melena can cause a drop in hemoglobin. This SAE this is not likely related to OCA use.

Other Significant Adverse Events

Table 95: Treatment-Emergent Adverse Events Leading to Discontinuation from Trial

Treatment Group	Preferred Term	Time to Onset (D) ^a	Duration (days)	Severity	Relationship to Study Treatment	SAE	Outcome
Placebo^b							
129001	Headache	43	29	Mild	Not Related	No	Recovered, Resolved
	Abdominal distension	66	6	Moderate	Not Related	No	
	Nausea	66	6	Moderate	Not Related	No	
	Vomiting	66	6	Moderate	Not Related	No	
183008	Rash	2	34	Moderate	Probable	No	Recovered, Resolved
OCA Titration							
104003	Hallucination	7	2	Moderate	Unlikely	No	Recovered, Resolved
111003	Pruritus	221	32	Severe	Definite	No	Recovered, Resolved
139003	Diarrhea	288	82	Moderate	Possible	No	Recovered, Resolved

142004	Interstitial lung disease	218	10	Moderate	Not Related	Yes	Resolved
186003	Cardiac failure	257	37	Severe	Unlikely	Yes	Fatal
OCA 10 mg^c							
133004	Pruritus	47	27	Severe	Possible	No	Recovered, Resolved
136002	Pruritus	82	38	Severe	Definite	No	Recovered, Resolved
146004	Pruritus	9	153	Severe	Possible	No	Recovered, Resolved
170004	Pruritus	6	11	Severe	Definite	No	Recovered, Resolved
	Pruritus	16	Ongoing	Mild	Definite	No	Patient discontinued for prior severe event of pruritus/ Ongoing DB ^d
174004	Pruritus	86	40	Severe	Probable	No	Recovered, Resolved
174012	Pruritus	11	9	Severe	Possible	No	Recovered, Resolved
178001	Contusion	67	6	Mild	Definite	No	Recovered, Resolved
182001	Pruritus	52	18	Severe	Probable	No	Recovered, Resolved with Sequelae

Table source: Copied and electronically reproduced from CSR 747-301: page 209-3119

Footnote: D = Day

a For adverse events that start on or after the first dose of study drug, the time to onset of the adverse event is calculated as the start date - date of first dose of investigational product + 1. For adverse events that occur prior to the first dose of study drug, the time to onset is calculated as the start date - first dose of study drug.

b Patient 165001 (placebo) experienced a TEAE of osteoarthritis that resulted in withdrawal of investigational product. The patient was discontinued from the study, which was determined by the Investigator to be the result

c. Two patients (3%) in the placebo arm, 5 patients (7%) in the OCA titration arm, and 8 patients (11%) in the OCA 10 mg arm, experienced at least 1 TEAE leading to study discontinuation.

The majority of TEAEs leading to study discontinuation were attributed to pruritus and occurred in the OCA 10 mg treatment arm (7 patients [10%]). One patient (1%) in the OCA titration arm experienced a TEAE of pruritus that resulted in study discontinuation. No placebo-treated patients withdrew due to pruritus.

One patient in each treatment arm discontinued from trial due to withdrawal of consent.

Two (3%) placebo patients had mild to moderate AE which resolved with IP discontinuation. Patients: 129001 experienced headaches abdominal bloating,

nausea and vomiting, causality not related as assessed by the investigator. Patient 183-008 experienced rash on face after 2 days of dosing, IP discontinued, moderate in intensity and the causality assessment was considered probable by the investigator. All the AEs were resolved on discontinuation of the IP.

Five patients (7%) in the OCA titration arm reported TEAEs that resulted in study discontinuation (Patient 186003 [SAE cardiac failure, fatal], Patient 142004 [SAE interstitial lung disease], Patient 111003 [pruritus], Patient 139003 [diarrhea/ascites], and Patient 104003 [hallucination]). None of the patients with TEAEs resulting in study discontinuation had titrated to 10 mg after 6 months of treatment; Patient 186003 did not uptitrate due to general progression of his medical history of heart failure; Patient 142004 did not uptitrate due to pruritus (moderate); Patient 111003 did not uptitrate due to pruritus (moderate); Patient 139003 did not uptitrate due to pruritus (moderate); and Patient 104003 was discontinued prior to the 6-month visit due to a TEAE of hallucination.

APPEARS THIS WAY ON ORIGINAL

In the OCA 10 mg arm, 8 patients (11%) reported TEAEs that resulted in study discontinuation; 7 patients (Patients 133004, 136002, 146004, 170004, 174004, 174012, and 182001) were discontinued due to pruritus. Six of 7 TEAEs that resulted in study discontinuation due to pruritus were considered severe and all 7 TEAEs were considered related to OCA. TEAEs of pruritus recovered with or without sequelae in 6 of 7 patients.

Patient 178001 (OCA 10 mg) had a TEAE of contusion 67 days after initiation of treatment. The patient had a numerous bruises on lower extremities at the EOT visit. The TEAE was considered mild in severity and had a definite relationship to investigational product. The patient had normal platelets and INR at screening and through the follow-up visit (range: 235 to 307 x 10⁹/L and 1.0 to 1.1, respectively). Investigational product was withdrawn 69 days after initiation of treatment and the patient was discontinued from the study 106 days after initiation of treatment.

6.3.13.4 Pruritus

Pruritus: Baseline pruritus incidence was similar across all treatment groups. There was a dose dependent increase in the incidence of pruritus, TEAE during this 12 month treatment trial are noted

Placebo (38%),
 OCA titration (56%) and,
 OCA 10 mg arms (70%).

Table 96: Display of Treatment-Emergent Pruritus: Safety Population (N = 216)

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
	Patients (%)	Patients (%)	Patients (%)
History of Pruritus	47 (64)	45 (64)	45 (62)
Pruritus Ongoing at Baseline	47 (64)	37 (53)	44 (60)
Patients reporting at least 1 TEAE Pruritus Event ^a , n (%)	28 (38)	39 (56)	51 (70)
Discontinuations due to Pruritus ^e	0	1 (1)	7 (10)
Pruritus Events by Maximum Severity^a			
Mild	16 (22)	11 (16)	15 (21)
Moderate	7 (10)	15 (21)	19 (26)
Severe	5 (7)	13 (19)	17 (23)
Patients with Interventions for Pruritus Events^b			
Patients with any intervention due to pruritus ^c	14 (50)	24 (62)	30 (59)
Patients who received any intervention for pruritus and did not discontinue from the study due to pruritus ^d	14 (100)	23 (96)	25 (83)

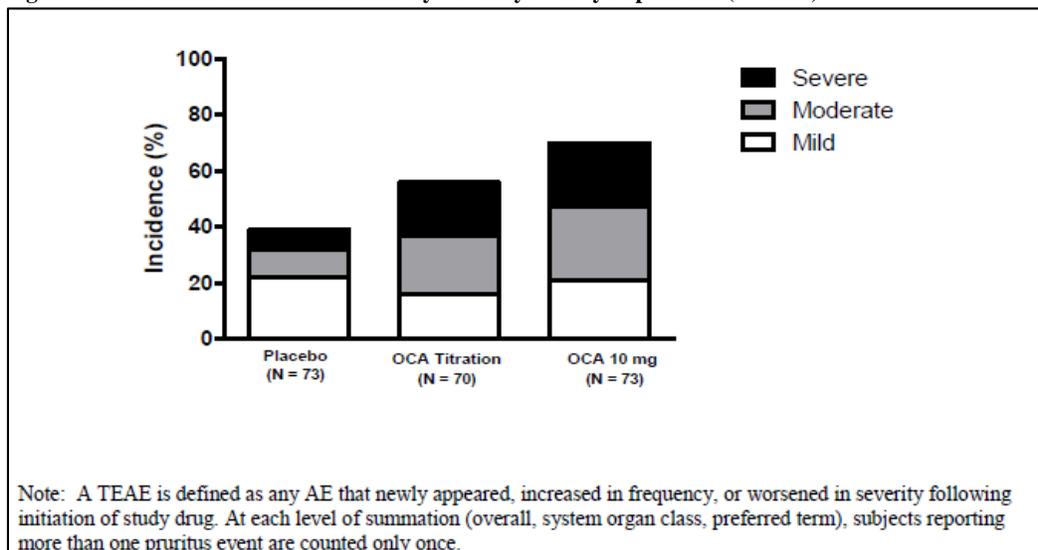
Table source: Copied and electronically reproduced from Applicant Submission 747-301 CSR 212 of 3119 Note: A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug.

- ^a Incidence is calculated using the number of patients randomized per treatment group as the denominator. Treatment-emergent pruritus events included the MedDRA PTs of Pruritus, Rash pruritic, Prurigo, Pruritus generalised, Eye pruritus, Ear pruritus, Anal pruritus, and Vulvovaginal pruritus.
- ^b Interventions for pruritus included one or more of the following: Receiving concomitant medications for pruritus, dosing interval change (i.e., decrease in study drug frequency), investigational product interruption, or non-drug treatment.
- ^c Incidence is calculated using the number of patients with a TEAE of pruritus per treatment group as the denominator.
- ^d Incidence is calculated using the patients who received any intervention for pruritus per treatment group as the denominator.
- ^e Incidence based on total number of patients randomized per treatment group.

Reviewer comments:

1. The incidence of mild and moderate TEAE for pruritus was similar across all treatment arms.
2. Higher incidence was noted for TEAE for moderate pruritus events in OCA treated patients relative to placebo.
3. Numerically higher number of patients required medical interventions for pruritus i.e., 14 patients in placebo arm; 24 patients in OCA titration arm and 30 patients in OCA 10 mg arm.
4. There was higher incidence of severe pruritus during the treatment trial in OCA treated patients, despite the exclusion of the patients with severe baseline pruritus. The incidence of severe pruritus was 7% in placebo arm, 19% in OCA titration arm and 23% in OCA 10 mg treatment arm.

Figure 44 Incidence of Pruritus Events by Severity: Safety Population (N = 216)



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New Onset or Worsening of Pruritus

Please note that the baseline disease-related pruritus, pruritus events that were reported as TEAEs but were at the same or lower severity as that reported at baseline were not included in the analysis of the incidence of pruritus events. Pruritus events used for the analysis were categorized as new onset or worsening pruritus events.

Patients were considered to have new or worsening pruritus based on the following criteria:

1. Any mild, moderate, or severe treatment-emergent pruritus event in patients with no pruritus at Baseline
2. Any worsening of the severity of the pre-treatment condition in patients with pruritus at Baseline
3. TEAEs of pruritus that occurred between Day 0 and month 6, and were ongoing during the month 6 to month 12 were not counted during the latter period.

The reviewer notes that the incidence of new or worsened pruritus during the second 6-month study period was consistently lower compared to the first 6-month study period in all treatment arms: 16% versus 11% in the placebo arm, 31% versus 20% in the titration arm, and 52% versus 16% in the 10mg arm respectively.

Time to First Onset of Pruritus:

1. The median time to first onset of pruritus in the OCA treatment arms occurred within the first month, and was 9 days for OCA 10 mg treatment arm.
2. OCA titration mitigated the time to first onset of pruritus and severe pruritus. The median time to onset of severe pruritus was 158 days in OCA titration arm compared to 11 days in OCA 10 mg arm.

Table 97: Summary of Time to First Onset of Treatment-Emergent Pruritus and Time to First Onset of Severe Treatment-Emergent Pruritus by Treatment Arm (Safety Population (N = 216))

Days	Placebo N = 73	OCA Titration N = 70 ^a	OCA 10 mg N = 73
n ^b , n ^c	28, 5	39, 13	51, 17
Mean (SD) Time to First Onset of Pruritus	81.4 (98.72)	62.6 (82.41)	47.3 (84.53)
Median Time to First Onset of Pruritus	50.5	24.0	9.0
Min, Max Time to First Onset of Pruritus	1, 344	1, 302	1, 332
Mean (SD) Time to First of Severe Pruritus	102.6 (94.49)	160.2 (138.26)	46.1 (72.87)
Median Time to First Onset of Severe Pruritus	75.0	158.0	11.0
Min, Max Time to First Onset of Severe Pruritus	7, 259	3, 362	1, 300

Table Source: Copied and electronically reproduced from the Applicant's submission CSR 219-3119

Note: Descriptive statistics in this Table are based on the number of patients within each treatment group who experienced pruritus.

^a All patients randomized to OCA titration group

^b Number of patients with event of pruritus

^c Number of patients with event of severe pruritus

Patient Reported Outcome: Pruritus Questionnaire

The disease-specific measure for PBC showed no clinically significant improvements in comparison to placebo for the global score or individual scores of general symptoms, cognitive function, and emotional/social domains; however, a difference in itch scores was observed in the earlier treatment months. Results from the VAS and 5-D pruritus questionnaire are described below.

Visual Analog Scale

Figure 45: Pruritus VAS - ANCOVA Scores over Time Using Observed Data: Safety Population (N = 216)

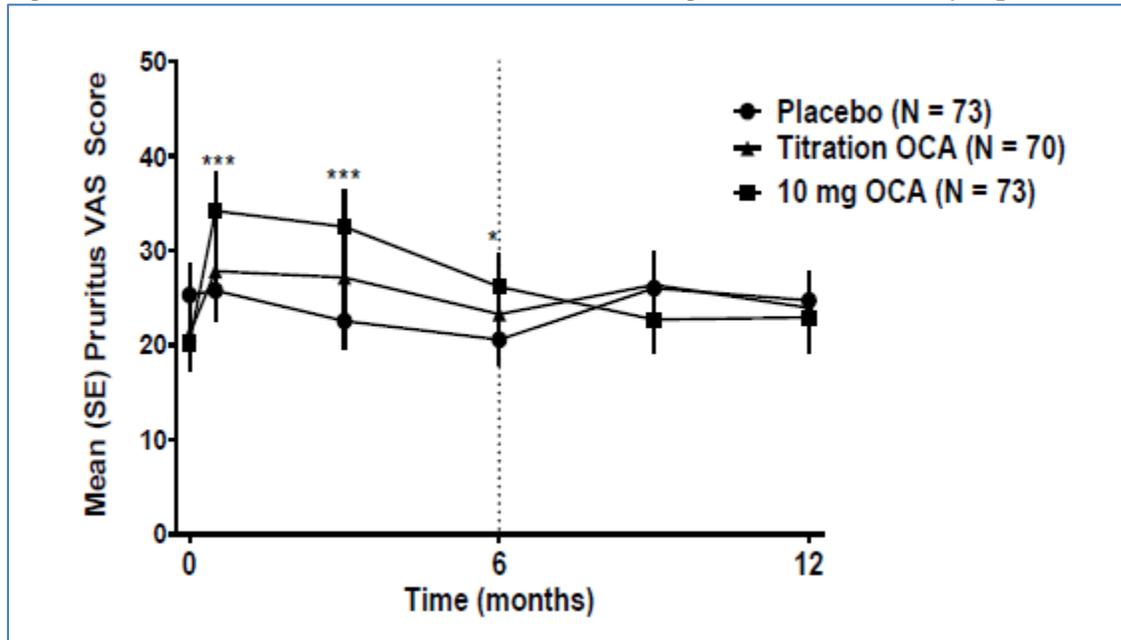


Table Source: Copied and electronically reproduced from the Applicant's submission CSR page 221 of 3119

Pruritus VAS

A 0-10 VAS was used, where "0" indicates "no itching" and "10" indicates "worst possible itching."
As the reviewer noted earlier data collection methodology was not optimal and may have under-represented the incidence of pruritus.

5-D Pruritus Questionnaire

The 5-D Pruritus Scale is a multidimensional measure that quantifies pruritus. The scale consists of five domains: duration (1 item), degree (1 item), direction (1 item), disability (4 items), and distribution (16 locations of itch). The scores of each of the five domains are achieved separately and then summed together to obtain a total 5-D score. 5-D scores can potentially range between 5 (no pruritus) and 25 (most severe pruritus). Single-item domain scores (duration, degree, and direction) are equal to the value indicated below the response choice (range 1-5). For the distribution domain, the number of affected body parts is tallied (potential sum 0-16) and the sum is sorted into five scoring bins: sum of 0-2 = score of 1, sum of 3-5 = score of 2, sum of 6-10 = score of 3, sum of 11-13 = score of 4, and sum of 14-16 = score of 5.

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Reviewer comment:

The main results of the 5-D Itch scores were contributed by dimension of “Disability” and “Degree” at Month 3; and at month 6 “Distribution” contributed the main weight.

Management of Pruritus

Per SAP (version 3; 24 September 2012, page 30-391 the management of pruritus was as follows:

1. Use of Bile acid sequestrants: such as cholestyramine, colestipol, colestimide, or colesvelam
2. Dose frequency modification: e.g., on alternate days
3. Drug holiday: For patients with severe pruritus, instruct the patient to stop taking study medication until the pruritus subsides to an acceptable level at which time it should be restarted (likely, on a modified, alternate day dosing schedule). Patients with drug holidays of > 28 days total during the DB phase should be discontinued from the trial.
4. UDCA discontinuation
5. Antihistamines
6. Other therapies may be tried as deemed clinically appropriate.

Number of Patients, n (%)	Placebo (N = 73)		OCA Titration (N = 70)		
	Patients (%)		Patients (%)		
Patients reporting at least 1 TEAE of pruritus ^a	28 (38)		39 (56)		
Patients with any intervention due to pruritus ^b	14 (50)		24 (62)		
Successful interventions: patients who received any intervention for pruritus and did not discontinue from the study due to pruritus ^c	14 (100)		23 (96)		
Patients who had an intervention for pruritus and discontinued due to pruritus ^c	0		1 (4)		
Patients who had no intervention for pruritus ^b	14 (50)		15 (38)		
Patients who did not discontinue the study due to pruritus ^c	14 (100)		15 (100)		
Patients who discontinued the study due to pruritus ^c	0		0		
Method of Intervention	Total Interventions ^d	Successful Interventions for Pruritus ^f	Total Interventions ^d	Successful Interventions for Pruritus ^f	Total Interventions ^e
Dosing interval change	1 (7)	1 (7)	0	0	4 (13)
Investigational product interruption	0	0	1 (4)	1 (4)	0
Dosing interval change and investigational product interruption	0	0	0	0	0

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Number of Patients, n (%)	Placebo (N = 73)		OCA Titration (N = 70)		
Investigational product interruption and concomitant medication	0	0	3 (13)	3 (13)	5 (17)
Dosing interval change and concomitant medication	2 (14)	2 (14)	4 (17)	3 (13)	2 (7)
Dosing interval change, investigational product interruption, and concomitant medication	0	0	1 (4)	1 (4)	1 (3)
Patients who had only non-drug treatment	2 (14)	2 (14)	2 (8)	2 (9)	2 (7)
Patients who received any concomitant medication	7 (50)	7 (50)	11 (46)	11 (48)	14 (47)
Only received BAS	3 (21)	3 (21)	5 (21)	5 (22)	5 (17)
Only received antihistamines	2 (14)	2 (14)	4 (17)	4 (17)	2 (7)
Only received BAS and antihistamines	1 (7)	1 (7)	2 (8)	2 (9)	4 (13)
Only received "other" concomitant medication	1 (7)	1 (7)	0	0	1 (3)

Note: A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug. Percentages are based on the number of patients who received any intervention for pruritus and did not discontinue the study due to pruritus. Interventions for pruritus included one or more of the following: receiving concomitant medications for pruritus, dosing interval change (ie, decrease in study drug frequency), investigational product interruption, or non-drug treatment.

- ^a Incidence is calculated using the number of patients randomized per treatment group as the denominator.
- ^b Incidence is calculated using the number of patients with a TEAE of pruritus per treatment group as the denominator.
- ^c Incidence is calculated using the number of patients with an intervention for pruritus as the denominator.
- ^d Incidence is calculated using the patients who received any intervention for pruritus per treatment group as the denominator.
- ^e Incidence is calculated using the number of patients who did not receive an intervention for pruritus.
- ^f Incidence is calculated using the number of patients who received any intervention for pruritus and did not discontinue from the study due to pruritus.

Applicant noted the following:

1. OCA-related pruritus was manageable.
2. Concomitant medications including BAS and antihistamines, changes in dosing frequency, and investigational product holidays were used to treat pruritus.
3. There was no one preferred intervention utilized for pruritus management.
4. Concomitant management was utilized in ~50% patient across the three treatment arm.
5. Regardless of the type of intervention used to manage pruritus, all methods appeared to be similarly successful.
6. A total of 100%, 96%, and 83% of patients in the placebo, OCA titration, and OCA 10 mg treatment arms, respectively, who received an intervention to treat a pruritus event did not discontinue from the study due to that pruritus event.

Pruritus by OCA Titration Sub group

Overall, initiating OCA at the 5 mg dose level followed by up-titration to OCA 10 mg improved tolerability of pruritus resulted in fewer discontinuations in the titration arm.

Table 98: Time to onset of severe pruritus in OCA titration arm

	Patients who Remained at OCA 5 mg dose (n=39)	Patients who Uptitrated Non-Responders (n = 33)
Severe Pruritus Mean duration	22 days	339 days
Severe pruritus Median duration	72	301 days
Median time for TEAE of pruritus	24	20
Mean time for TEAE of pruritus	61.9	63.3

Source Reviewer generated Table

Table 101 shows the time to onset of severe pruritus, which was earlier in patients who remained on OCA 5 mg compared to patients who got up-titrated.

The incidence of ongoing pruritus at baseline was higher for patients who remained at OCA 5 mg compared with those who uptitrated (62% and 42%, respectively).

Over all the titration regimen seems to help selecting patients who would tolerate up-titration as well a tolerize to the drug and have less pruritus related AE.

2. Hepatic-Related Effects

In this trial the hepatic related adverse events were well balanced across all treatment arms. OCA 5mg and OCA 10 mg seem appropriate doses for early stage disease patients who have not had hepatic decompensations.

Serious AEs: There was no dose-dependent trend in the incidence of hepatic-related events. Hepatic-related SAEs were experienced by 1 patient in the placebo arm and 1 patient in the OCA titration arm and 1 patient in the CA 10 mg arm:

- 1 patient (Patient 162005, placebo) had one hepatic-related SAEs (1 SAE of upper gastrointestinal hemorrhage); *Patient 162005 who had one event of variceal bleeding. After which the patient had elective banding and therefore coded as varices esophagus, and they were not variceal bleeding events.*
- 1 patient (Patient 139003, OCA titration) had a total of 4 hepatic-related SAEs (2 SAEs of hepatic encephalopathy, 2 SAEs of ascites with peripheral edema. OCA conjugates have a long half-life, therefore causality assessment cannot be ruled out.
- 1 patient (Patient 174004, OCA 10 mg) had 1 SAE of gastrointestinal hemorrhage (probably due to portal gastropathy) and ascites. In setting of portal hypertension, the bleeding from congestive portal gastropathy may be secondary to increased portal pressures therefore the underlying liver disease as a cause of bleeding.

In this reviewer opinion the serious hepatic related AE were the three mentioned above in the SAE discussion.

Non serious AEs:

Rest other AEs presented across different treatment arms such as increase in aPTT, MELD (discussed earlier), mild AE of liver test abnormalities noted as resolved spontaneously in placebo arm patient, hepatic pain and feces discolored were not clinically significant. Since the AEs were balanced across all treatment arms. Two patients in the trial had elevation of INR due to anti-coagulation therapy.

Additionally as noted patient 118008 had antral ulcer therefore the likely source of bleeding was the ulcer and OCA is not related to this event, the reviewer concurs.

2 patients 149006 (day 52 of treatment) and 171001 (day 356 of treatment) both in the OCA titration arm experienced AE of gallstones and cholelithiasis which were AE of moderate severity.

6.3.13.5 Lipid-Related Effects

Clinical studies evaluating OCA for the treatment of PBC have shown that OCA treatment is associated with early and sustained reduction in HDL cholesterol. Mild and generally transient increases in LDL have also been observed.

Findings published by Crippin et.al., 1992 are as follows: the incidence of atherosclerotic death in patients with primary biliary cirrhosis was not statistically different when compared with an age-matched and sex-matched U.S. control population. Findings included progressive increases in total cholesterol and low-density lipoprotein cholesterol with an increasing histological stage or severity of disease. High-density lipoprotein cholesterol was elevated in all stages, with the highest levels in histological stage 2 and 3 disease. Triglycerides were normal or slightly elevated in all stages. Apoprotein A-I was elevated in all but histological stage 4 disease. The conclusion of the study proposed hyperlipidemia associated with primary biliary cirrhosis does not place PBC patients at risk for atherosclerotic death.

However, further studies and meta-analyses have shown mixed results. Therefore, the long term clinical implications of hyperlipidemia at baseline and reductions in HDLc observed in OCA trials in patients with PBC⁹ are unknown at this time.

Table 99: Changes in Mean HDL Cholesterol in Trial 747-301

	OCA 10 mg	OCA titration	Placebo
Mean HDLc (mg/dL)			
Baseline	81.2	81.2	69.6
Month 12	61.8	69	69.6
Mean change at month 12	-19.4	-12.2	0

Table source: Reviewer generated from the data submitted to the NDA

Changes in mean HDLc (mg/dL) at baseline to month 12 as noted in Table 104: A 19 point mean HDLc reduction was noted in OCA 10 mg arm, 12 points reduction in HDLc was observed in OCA titration arm and no change in the placebo arm. The HDLc reductions were seen in 3 month trial as well as in this 12 month trial, the duration of OCA exposure does not diminish the HDLc reduction in PBC patients

Table 100: HDLc Reductions seen in Trial 747-301

Patients with HDLc \geq 2 SD reduction (44 mg/dL)	
Placebo	0
OCA titration	4
OCA 10 mg	5
Patients with HDLc \geq 1 SD but \leq 2 SD reduction (between 22 to 44 mg/dL)	
Placebo	1
OCA titration	14
OCA 10 mg	16

Table source: Reviewer generated from the data submitted to NDA

Table 105 shows total of 4 patients in OCA titration arm, 5 patients in OCA 10mg arm had an HDLc reduction > 2 SD (i.e. 44 mg/dL) and 1 patient in placebo arm; 14 patients in OCA titration arm and 16 patients in OCA 10mg arm had HDLc reduction > 1 SD but < 2 SD that is between 22-44 mg/dL

⁹ Crippin JS, Lindor KD, Jorgensen R, et al. Hypercholesterolemia and atherosclerosis in primary biliary cirrhosis: what is the risk? Hepatology. 1992 May;15(5):858-62.

There were outliers in the trial and some patients had HDLc reduction as much as 86 mg/dL as shown in Table below:

Table 101: HDLc Reductions Seen Among the Outliers

Baseline HDLc (mg/dL)	Month 12 or end of treatment HDLc (mg/dL)	Decrease in HDLc (Month 12-Baseline) (mg/dL)
OCA 10 mg		
119.5	34	-85.5
112.1	34	-78.1
95.1	35.9	-59.2
75	29	-46
75	37	-38
40.9	8.1	-32.8
62.2	32.8	-29.4
35.1	6.9	-28.2
42.2	25.9	-16.3
OCA titration arm		
75	22	-53
68.5	22	-46
90.5	50	-40.5
64	38	-26
49.5	31	-18.5
56	37.8	-18.2
Placebo arm		

93.5	54	-39.5
75.5	58	-17.5

Table Reviewer generated from data submitted to the NDA

Each row is a unique patient designated as an outlier.

OCA 10 mg: Out of 64 patient who completed the trial 57 patients had HDLc reduction. Those reductions are listed in the Table above in patients who had reduction >2 SD and between 1 SD and 2 SD. Additionally Table 106 shows, the patients who had significant HDLc reduction to 8 mg/dL and 7 mg/dL and reduction are much as -85.5 and 59 mg/dL were seen over 12 month duration. Nine patients in the OCA 10 mg arm had reduction <40 mg/dL.

OCA titration arm: Out of 69 patients who completed the trial, 42 patients had HDLc reduction. Those reductions are listed in the Table 106 in patients who had reduction >2 SD and between 1 SD and 2 SD. Again few examples are noted in this Table. Again HDLc as low as 22 mg/dL were noted with exposure to OCA with lower doses, that is 5 mg. Six patients in the OCA 10 mg arm had reduction <40 mg/dL.

Placebo: Of the 70 patients who completed the trial 36 patients had HDLc reduction. 9 patients were dosed with OCA inadvertently; therefore those patients are not included in Table 105 and Table 106. 3 patients had HDLc reduction that were <LLN (40 mg/dL).

Cardiovascular Treatment-Emergent Adverse Events

The distribution of patients with a history of cardiovascular conditions at the start of treatment was comparable across treatment arms (40%, 34%, and 42% for placebo, OCA titration, and OCA 10 mg, respectively). Five patients (7%) in the placebo arm, 6 patients (9%) in the OCA titration arm, and 12 patients (16%) in the OCA 10 mg had a cardiovascular TEAE. Most patients with a cardiovascular TEAE had a history of prior or ongoing cardiovascular disease.

Other than the 2 events of cardiac failure, which were severe in severity, all other cardiovascular TEAEs were mild or moderate in severity. With the exception of an event of palpitations in the OCA 10 mg arm that was considered to have a possible relationship to investigational product, all cardiovascular TEAEs were considered to be unlikely or not related to treatment. Approximately half of the events were resolved at the end of the double-blind treatment period.

A total of 4 cardiovascular SAEs were reported by 2 patients: Patient 105002 (placebo) experienced an SAE of sick sinus syndrome and an SAE of chest pain. Abnormal ECG results were reported throughout the study for both patients. All 4 SAEs were assessed by the Investigator as unlikely related to investigational product.

Occurrence of Chest pain was seen across all treatment arms at similar rates.

Pregnancies

One pregnancy occurred during the 12-month, double-blind phase.

Patient 182002 (OCA titration), a 33-year-old female, with no prior pregnancies, who was randomized to the OCA titration arm, and notified the site approximately 59 days after initiation of investigational product that she had become pregnant. Investigational product administration was interrupted 3 days later. The patient experienced a spontaneous abortion while awaiting a planned abortion 87 days after initiation of investigational product and 26 days after IP interruption. Following the spontaneous abortion, the patient resumed participation in the study. The patient withdrew consent after 266 days of participation in the double-blind phase of the study and received the last dose of investigational product on Day 239.

The spontaneous abortion was considered unlikely related to study drug and resolved without sequelae. The patient was not taking any contraception at the time of the pregnancy. Patient 182002 (OCA titration) had a visit schedule deviation per the Investigator; however, it is the Applicant's assessment the patient had a deviation from inclusion criterion 5 (any measure of contraception).

MO comments: The Applicant should continue to maintain a pregnancy registry and follow the outcomes of the pregnant patient and outcomes of the pregnancy. Especially signal was noted in the non-clinical studies OCA caused an increase in the incidence of benign granulosa cell tumors in the ovaries and benign granular cell tumors in the cervix and vagina of female rats.

These findings were TEAE for pruritus by demographics and baseline characteristics in ITT population: The large imbalance in sample size in the sub group of age, gender, race, baseline total bilirubin, and UDCA use versus no UDCA use at baseline that precludes any meaningful interpretation for TEAEs.

Psychiatric symptoms: One Patient 104003 enrolled in OCA titration arm experienced hallucinations. The narrative read, patient had relevant medical history of depression, anxiety and forgetfulness. The patient experienced hallucinations 7 days after starting the OCA 5 mg. The patient never had hallucinations in the past and the hallucinations stopped as soon as OCA was discontinued. The temporal association makes it likely in this particular patient OCA might have triggered hallucinations, however this is the lone case.

The reviewer notes these adverse events which were noted in line listings:

Patient 162004 had worsening of depressive mood, and the causality was assessed possible by the investigator. This must be monitored during phase 3b (confirmatory trial).

Patient 147001 experienced depression and it was deemed as a possible adverse reaction secondary to OCA 5 mg (day 48)

At least 2 patients had either new onset depression or worsening of depression. Again, more data are required before a causality association can be made.

There were four events of neoplasms detection during the trial, and was a well-balanced across treatment arm. These are 4 separate patients discussed below:

- *Basal cell carcinoma (Placebo)*
- *Lung neoplasm (placebo)*
- *Colon adenoma: OCA 10 mg the event was severe and occurred on Day 336 of dosing with OCA 10 mg, the patient was diagnosed with colon adenoma and was thought to be possibly related to the drug.*
- *Thyroid neoplasm: OCA 10 mg - the relationship is possible with OCA 10 mg dosing, Patient 149002; was diagnosed with as moderate severity and occurred on Day 187 of OCA ingestion, and required resection. Further details were not provided.*

These events must be followed in future trials to assess if these are events are similar to background rates or occur at higher incidence than general population.

Clinical Laboratory Evaluation:

1. Hematology Parameters Change Over Time:

Across treatment arms, the majority of patients were in the normal range for most hematology parameters. No clinical meaningful differences in shifts from Normal to High were observed for any hematology parameter between the treatment arms.

This reviewer notes the hemoglobin decline seen in patients during the trial and required transfusion were not accounted in these analyses, please note the narratives for hemoglobin decline and the management.

Coagulation: A few patients had changes in aPTT and INR, however, these were seen equally among all the

treatment arms. *Of note, there were isolated changes in INR across all treatment arms.*

2. Serum Chemistry Parameters Change Over Time

No meaningful differences in absolute mean changes in serum chemistry parameters from baseline to each assessed time-point were observed across treatment arms, with the exception of analytes expected to be affected by OCA. In addition, compared with placebo, more patients in the OCA treatment arms with normal glucose levels at baseline developed high glucose levels at Week 2 and Month 3.

A Clinical IR was sent and the Applicant stated:

Given that patients were not consistently fasted during screening, an analysis of the number of patients with normal Day 0 glucose values who subsequently developed high glucose values was conducted and demonstrated similar results in all three treatment arms: placebo n=15, titration n=18, 10 mg n=17.

None of the patients that experienced changes in serum glucose reported an AE that was clinically associated with the finding or received specific treatment with the exception of 2 patients.

Patient 145008, an 83 year old black female with a history of insulin dependent type II diabetes randomized to the Titration arm and who experienced an SAE described by the Investigator as mild, unrelated syncope after developing urinary tract infection, becoming dehydrated and in the setting of preexisting cardiomyopathy (SAE Case Number: 2013-747-301-02).

Patient 174011, a 63 year old white female patient randomized to placebo and with a prior history of insulin resistance continued to receive Metformin 1000 mg TID, a medication she had initiated prior to enrollment.

Narrative of both patients read and the reviewer agrees with the Applicant's assessment. At this time, with these data a signal could not be identified that glucose control is being altered by OCA.

3. Hepatic and Renal Biochemistry Markers:

Mean reductions in ALP, total bilirubin, and conjugated bilirubin were observed for both OCA treatment arms, compared with placebo treatment arm. Patients treated with OCA had 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.

Only 1 patient in OCA titration arm and 5 patients in OCA 10 mg arm demonstrated ALP normalization while no placebo-treated patients had an ALP value within the normal limits by month 12.

The majority of patients across treatment arms were in the normal albumin category at baseline; no changes were observed at month 12.

Renal (protein, BUN, and creatinine) parameters: mean protein, BUN, and creatinine values were stable for the duration of the double-blind treatment phase across all treatment arms and no clinically meaningful shifts from baseline were observed during the study.

Table 102: Patients with ALT, AST, and/or GGT >2 Times Baseline Value and >ULN During the Double-Blind Treatment Period

Patient	Analyte	Baseline ^a	Day 0	Week 2	Month 3	Month 6	Month 9	Month 12
Placebo								
119001	ALT (U/L)	49.4	39.8	44.8	30.7	52.7	44.9	113.9*
	AST (U/L)	41.5	33.9	38.7	27.9	43.7	41.9	276.4*
161003	GGT (U/L)	302.6	328.7	359.2	277.3	614.5*	508.5	554.5

164003	ALT (U/L)	31.3	33.4	172.5* Uns: 239.4*	42.1	33.7	31.0	30.3
	AST (U/L)	29.3	31.5	112.3* Uns: 174.2*	38.5	33.0	31.4	33.1
	GGT (U/L)	188.3	180.6	483.7* Uns: 814.4*	310.3	214.1	150.3	175.8
175006	GGT (U/L)	197.8	247.5	193.0	262.5	273.4	398.8*	369.3
179006	GGT (U/L)	379.9	343.4	695.3	924.2*	946.8*	922.3*	906.1*
OCA Titration								
138003	ALT (U/L)	22.8	23.1	NA	21.4 Retest: 53.3*	19.7	26.8	16.2
OCA 10 mg								
118003	ALT (U/L)	30.5	28.1	26.9	23.0	22.3	64.2*	32.3

Table source: CSR 747-301 page 252 of 3119

ALT = alanine aminotransferase, AST = Aspartate aminotransferase, GGT = gamma-glutamyl transferase, LLN = lower limit of normal; NA = not available; OCA = obeticholic acid, ULN = upper limit of normal; Uns = unscheduled.

^a Baseline was defined as the mean of all available evaluates prior to treatment.

* Indicates an increase in liver enzyme >2 times baseline value and >ULN when converted to ULN value. Actual values with < were imputed by multiplying the value by 0.9.

Reference range females: ALT: 6.6 U/L LLN, 22.9 U/L ULN; AST 11.8 U/L LLN, 25.7 U/L LLN, GGT: 23.6 LLN, 3.9.

A total of 5 patients had elevations in AST, ALT and GGT in the 12 month period. PBC is relatively slowly progressive disease. One patient (Patient 164003, placebo) experienced elevations in ALT, AST, and GGT > 2 times Baseline values and a laboratory abnormality that was assessed as a TEAE of abnormal liver function test.

No other TEAEs related to liver enzyme elevations were reported.

Urinalysis

In all treatment arms, transient individual variations in urinalysis parameters were observed. No trends in changes in parameters emerged and no apparent clinical meaningful differences were observed between treatment arms in any of the urinalysis parameters.

Vital Signs

There were no apparent differences in the mean change from baseline for systolic and diastolic

Two patients in the OCA 10 mg arm experienced a TEAE considered to be related to vital signs (Patient 198001 [BP increased] and Patient 105003 [heart rate irregular]).

One patient (1%) in the placebo arm and 5 patients (7%) in the OCA 10 mg arm reported TEAEs of pyrexia. No other individual vital sign results were reported as a TEAE by Investigator.

Body Weight and BMI:

Overall, no clinically meaningful mean changes from baseline to month 12 in body weight or BMI were observed in any of the treatment arms.

Physical Examination:

Clinically significant treatment-emergent physical examination findings were similar between treatment arms.

More patients in the placebo arm experienced abnormal QTcF measurements; 12 patients in the placebo arm, 6 patients in the OCA titration arm, and 7 patients in the OCA 10 mg arm had abnormal QTcF measurements of QTcF >450 msec or change in QTcF >30 msec at Month 6, Month 12, EOT, or at an unscheduled visit. No patients treated with OCA experienced a QTcF of >500 msec throughout the treatment period.

Two patients treated with placebo and 1 patient treated with OCA, experienced cardiovascular TEAEs and an ECG abnormality during the conduct of the study. The narrative of the placebo patient had pre-existing cardiac condition of cardiomyopathy, aortic stenosis, aortic valve replacement, implantable defibrillator in one patient and atrial fibrillation that was ongoing and a surgical ablation for a cardiac arrhythmia in 1999 in second patient. The reviewer considers the ECG abnormality was attributable to the pre-existing medical condition.

Patient 180004 (OCA 10 mg) had an abnormal potentially clinically significant ECG at month 12 with sinus bradycardia, non-specific intraventricular conduction defect, left axis deviation, anterolateral myocardial infarction (MI). The patient had a medical history of hyperlipidemia and Hashimoto disease that were ongoing. A TEAE of hypertension was noted 83 days after study initiation. The TEAE was considered unlikely related to investigational product and was ongoing at the end of the double-blind treatment period.

This reviewer agrees that the causality assessment is appropriate and the AEs are unlikely to be caused by OCA. Serious cardiovascular events (such as MI in this patient) should be monitored in post approval settings.

Mayo Risk Score

The MRS is a mathematical model predicting survival in non-transplanted patients suffering from PBC and was the first disease-specific algorithm to assess risk of clinical. This model allows the calculation of a risk score including 5 variables (patient's age, serum bilirubin and albumin concentrations, prothrombin time, and presence of peripheral edema and antidiuretic therapy). Higher scores are indicative of worse disease severity, with a MRS of 7.8 defined as an optimal time point for liver transplantation.

The baseline MRS were low and comparable across treatment arms, which is not unexpected in this study population given their relative early stage of disease (i.e., the majority of patients had albumin values >LLN, Baseline INR <1.3, and total bilirubin <ULN and patients with clinically significant hepatic decompensation were excluded).

Mean MRS remained generally stable for all treatment arms throughout the 12-month treatment period with similar mean score pre- and post-treatment.

MELD Score

The MELD scoring system is a system used to assess the severity of chronic liver disease. It was initially developed to predict death within 3 months of surgery in patients who had undergone a TIPS procedure and was subsequently used in determining prognosis and prioritizing patients for receipt of a liver transplant regardless of their diagnosis. An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk.

For reference: a MELD score <9 is correlated with 1.9% 3-month mortality risk; A MELD score of 10 to 19 has a 3 month mortality risk of 6%. MELD score is now used by the United Network for Organ Sharing in the US and Eurotransplants to manage the organ allocation for liver transplantation. The threshold for placement on an organ transplantation queue varies between regions across the globe but a score of 15 results in a place on the transplant waiting list in the US.

The MELD score is useful in assessing patients with significant decompensation. The MELD score is derived from the patient's serum total bilirubin, serum creatinine, and INR to predict survival.

Mean MELD scores were between 6 and 7 for all three treatment arms both at baseline and at the end of trial.

DEXA Scans

In a subset of patients (n = 138 at baseline and n = 122 at Month 12), DEXA scans were done to assess femoral neck bone density and lumbar spine density.

DEXA scans were used to assess femoral neck and lumbar spine bone mineral density at Baseline and Month 12 in approximately 55% of patients from the ITT population (n = 138 at Baseline and n = 122 at Month 12). DEXA scans of the lumbar spine and femoral neck were conducted at a subset of study sites with the capabilities to perform this assessment. At those selected centers, all patients were to undergo the assessment. A total of 40/59 (68%) of study sites indicated they had the capability of performing DEXA scans. Thirty-seven of the 40 sites with DEXA capabilities actually performed DEXA scans. Of these 37 sites, 144 patients were enrolled and the majority (96%) of these patients underwent DEXA assessment. No explanation was provided for why the 6 patients (4%) did not have DEXA scans performed. Of these 6 patients, 2 were in the placebo arm, 3 were on OCA 10 mg, and 1 was on OCA titration 5-10 mg.

For Protocol 747-301 DEXA scans could be scheduled ±2 weeks from each appropriate visit. Patients who had a recent DEXA scan with an available report within 6 months prior to Day 0 did not need to repeat the Baseline DEXA scan. There were no specifications on the type of DEXA device to be used. The protocol did require that the same two bone locations be scanned (i.e., femoral neck and lumbar spine) and that scans be performed with central rather than peripheral devices. Study site personnel recorded the bone location scanned, and for femoral neck scans, the side of the body for the femoral neck scan (left or right) was recorded. Bone density data were read locally from the device and entered directly by the study site into the eCRF. There was no systematic harmonization of DEXA data across sites, nor documentation of quality control measures at each site. That patients could be rescanned on the same machine at follow-up was not specified.

The age-matched reading, known as the Z-score, compares a person's bone density to what is expected in someone of equivalent age, sex, and size. However, among older and elderly adults, low bone mineral density is common; so that comparison with age matched norms can be misleading. The Z-score is useful in premenopausal women, men under the age of 50, and in children.

T-score changes may correlate inaccurately with bone mineral density changes, as varying baseline standards for peak bone mass are used. Important racial, geographic and gender differences exist in average peak bone mass values, often explained by differences in body size. The only bone DEXA-derived endpoint acceptable to FDA is bone mineral density expressed in units of g/cm².

Table 103: DEXA Data: Safety Population (N = 216)

	Placebo			OCA Titration			OCA 10 mg		
	Baseline N=47	Month 12 N=44	Mean Actual Change	Baseline N=49	Month 12 N=42	Mean Actual Change	Baseline N=44	Month 12 N=38	Mean Actual Change
Lumbar (L2-L4) BMD									
g/cm ²	0.97	0.97	0	1.02	1.01	-0.01	1.03	1.00	-0.03
T-Score	-1.16	-1.42	-0.26	-1.10	-1.10	0	-0.82	-1.02	-0.09
Femoral Neck BMD									
g/cm ²	0.79	0.76	-0.03	0.80	0.81	0.01	0.87	0.81	-0.06
T-Score	-1.15	-1.48	-0.33	-1.29	-1.28	-0.01	-0.89	-1.06	-0.17

Table source: Copied and electronically reproduced from the Dr. Stinson consult review (generated by Dr. Stinson)

Reviewer Comment:

Mean changes in lumbar and femoral neck bone mineral density over 12 months appear comparable across the 3 treatment groups. Generally, mild reductions in BMD were observed in all treatment groups. These BMD changes are unlikely to be associated with increased fracture risk. An association with increased fracture risk has been shown only with much higher BMD decreases. For each standard deviation decrease in age-adjusted BMD, the risk for any fracture has been shown to increase by a factor of about 1.5.

Overall, the incidence of osteoporosis in the OCA trial is low compared to that reported in previous PBC studies. It may be that most series in the past included either a small number of patients or the analysis was performed in the eighties or early nineties, when the disease was diagnosed in patients with significant cholestasis with advanced liver damage and more bone loss.

Safety Conclusions:

Overall, administration of OCA 5 mg and OCA 10 mg was safe and generally well tolerated over a 12-month period in patients with PBC.

1. Pruritus:

Pruritus was the most common TEAE with a higher incidence reported in OCA treatment arms (OCA titration [56%] and OCA 10 mg [68%] versus the placebo [38%]).

Based on the rate of treatment discontinuations due to pruritus, treatment was better tolerated in patients treated with OCA who initiated treatment at 5 mg and titrated up to 10 mg after 6 months based on clinical response.

Additionally, the severity of pruritus was mitigated by this dosing strategy compared to starting at OCA 10 mg. There were no discontinuations due to pruritus in the placebo arm, and in the majority of patients who experienced pruritus in this arm, the maximum severity of pruritus was mild or moderate. Pruritus was manageable with concomitant treatments or dosing interval changes. A substantial number of patients in each treatment arm who experienced pruritus did not receive treatment for their pruritus, but were able to remain in the study; supporting tolerability of treatment-emergent pruritus during the study.

The incidence of TEAEs assessed as related, severe, or leading to study discontinuation was higher in patients treated with OCA, compared with placebo. With the exception of SAEs, these imbalances were predominantly attributed to pruritus.

2. Total TEAEs

A total of 66 patients (90%) from the placebo arm reported 452 TEAEs, 65 patients (93%) from the OCA titration arm reported 471 TEAEs, and 69 patients (95%) from the OCA 10 mg arm reported a total of 467 TEAEs.

TEAEs occurring in ≥5% of patients in either of the OCA Arms

TEAEs that occurred with an incidence of ≥5% and were reported more frequently in either of the OCA treatment arms compared with placebo included pruritus, rash, eczema, fatigue, pyrexia, peripheral edema, nasopharyngitis, influenza, bronchitis, sinusitis, diarrhea, constipation, arthralgia, cough, oropharyngeal pain, procedural pain, fractures, palpitations, and hypothyroidism.

TEAEs that occurred at an incidence of ≥5% and were reported with an incidence of >3% more frequently in patients receiving OCA compared with placebo were limited to pruritus, fatigue, hypothyroidism, procedural pain, oropharyngeal pain, arthralgia, sinusitis, peripheral edema, pyrexia, palpitations, eczema, bronchitis, and nasopharyngitis.

Related AEs

As expected based on prior experience with OCA treatment in patients with PBC, the most common related TEAE was pruritus. In all treatment arms, the majority of pruritus AEs were considered related to investigational product. The incidence and number of patients with related TEAEs of pruritus was 27 patients (37%) in the placebo arm, 35 patients (50%) in the OCA titration arm, and 48 patients (66%) in the OCA 10 mg arm. Incidence of fatigue was higher in OCA treated patients.

This reviewer sees no evidence of a safety signal for bone health or fracture risk for OCA. The

DXA scan results are generally consistent with the disease state, although they indicate less osteoporosis than reported in earlier series of PBC patients. The rate of bone loss is comparable to the age-related general population. However, this should be followed post-marketing and in the phase 4 trial to assess long-term effects.

Serious AEs

With the exception of the SAE that was fatal, all SAEs resolved with or without sequelae. In the placebo, OCA titration, and OCA 10 mg arms, 4%, 16%, and 11% of patients experienced an SAE. No clear dose-related pattern was observed in the types of events that were serious in nature. No SAEs were considered by the investigator to be related to investigational product.

3. Hepatic-Related Effects

Well balanced distribution of hepatic related serious AEs were noted across the three treatment arm. One patient each had hepatic related AE across each treatment arm. Although the number of events was higher in OCA treated patients. Placebo (1 event in 1 patient), OCA titration (4 events in 1 patient) and OCA 10 mg (1 event in 1 patient) were noted. Non serious events: Two patients had gall stone during the trial period.

4. Lipid-Related Effects

Lipid changes, were concerning for decrease in HDLc

5. Cardiovascular-Related TEAEs

Cardiovascular events are of special interest in the setting of lipid changes in the OCA treatment arms. No treatment differences were observed for cardiovascular-related AEs or SAEs. A total of 4 cardiovascular SAEs were reported in 3 patients: 1 patient in the placebo arm experienced sick sinus syndrome, 1 patient in placebo arm had SAE of chest pain, and 1 patient in the OCA titration arm had 2 SAEs of cardiac failure, 1 of which was fatal.

Palpitations were seen in 7% patients in OCA 10 mg arm, 3% patients in OCA titration arm compared with 1% patient with placebo arm. In patients on OCA treatment arm in at least 50% patients there was no prior history of cardiac disease and in about half the patients the AE of palpitation was ongoing after completion of the double blind trial duration.

6. Deaths and Other Serious Adverse Events

One death occurred during the double-blind phase (cardiac failure) in a patient from the OCA titration arm that had an extensive history of cardiovascular conditions including cardiac failure.

7. Adverse Events Leading to Study Discontinuation

Two patients (3%) in the placebo arm experienced TEAE that resulted in study discontinuation. In the OCA titration treatment arm and the OCA 10 mg treatment arm, 5 patients (7%) and 8 patients (11%), respectively, experienced TEAEs leading to study discontinuation.

The majority of TEAEs leading to study discontinuation were attributed to pruritus and occurred in the OCA 10 mg treatment arm (7 patients [10%]). One patient (1%) in the OCA titration treatment arm experienced a TEAE of pruritus that resulted in study discontinuation. No placebo-treated patients withdrew due to pruritus.

8. Safety Laboratory Parameters

Other than the lipid and hepatic test results discussed earlier, no clinically meaningful differences between the treatment-arms were observed for any safety laboratory parameters.

Other Safety Evaluations

1. As may be expected, no or minimal changes in MRS and MELD scores were observed in either treatment arm indicating overall stable disease state over the course of the 12-month treatment period.
1. No evidence of a safety signal for bone health or fracture risk for OCA. The DXA scan results are generally consistent with the disease state, although they indicate less osteoporosis than reported in earlier series of PBC patients. The rate of bone loss is comparable to the age-related general population.

- Overall, no clinically meaningful mean changes from baseline to month 12 in body weight or BMI were observed in any of the treatment arms. No clinically meaningful differences in vital signs (with exception of patients in OCA 10 mg arm who experienced hypertension and palpitations as noted in review).
- ECG changes: No patients treated with OCA experienced a QTcF of >500 msec throughout the treatment period. No significant ECGs changes were observed from baseline to month 12 in the OCA treated patients.

7 Integrated Review of Effectiveness

7.1 Assessment of Efficacy across Trials - Monotherapy

The reviewer will present effectiveness of monotherapy OCA use in patients who achieved the composite endpoint in ALP. Since the phase 2 and phase 3 trials utilized different doses and different duration a direct comparison of these trials is not possible. Therefore a pooled data analysis of a comparable duration, and comparable dose, i.e., OCA 10 mg (dose submitted for marketing approval) has been analyzed for this section. These were not pre-specified analyses i.e., analyses are post-hoc assessments.

Population analyzed:

Trial 747-201: A total of 20 patients were enrolled of which 16 completed the trial for duration of 3 months. A total of 8 patients were responders i.e., achieved the biochemical response: ALP <1.67x ULN and Total Bilirubin ≤ULN, and ALP Decrease of ≥15% from baseline to month 3 with OCA monotherapy.

Trial 747-301: A total of 7 patients were enrolled in the trial that were on OCA monotherapy of which all the patients completed the trial for 3 month duration. A total of 2 patients out of 7 patients achieved the responder criteria: ALP <1.67x ULN and Total Bilirubin ≤ULN, and ALP Decrease of ≥15% from baseline to month 3 with OCA monotherapy

Table 104: OCA Monotherapy

Month 3	747-201 (Monotherapy)	
	Placebo (N = 23)	OCA 10 mg (N = 20)
Responder, n (%)	1 (4)	8 (40)

Table: Reviewer generated from NDA submission

Responder criteria: Composite Endpoint: ALP <1.67x ULN and Total Bilirubin ≤ULN, and ALP Decrease of ≥15% from Baseline to month 3

Table 105: Pooled Data of the Double Blind Trial 747-201 and 747-301 Patients achieving the Composite Endpoint

Month 3	Composite Endpoint at Month 3
	Responder (%)
OCA Monotherapy	
Placebo (N = 29)	1 (3)
OCA 10 mg (N = 27)	10 (37)
Combination (+UDCA)	
Placebo (N=106)	5 (5%)

OCA 10 mg (N=105)	43 (41%)
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Table: Reviewer generated from NDA submission

Responder criteria: Composite Endpoint: ALP <1.67x ULN and Total Bilirubin ≤ULN, and ALP decrease of ≥15% from baseline to month 3

Figure 46: Double-Blind Percentage of Patients Achieving Primary Composite Endpoint: ITT Population (N = 54), Monotherapy

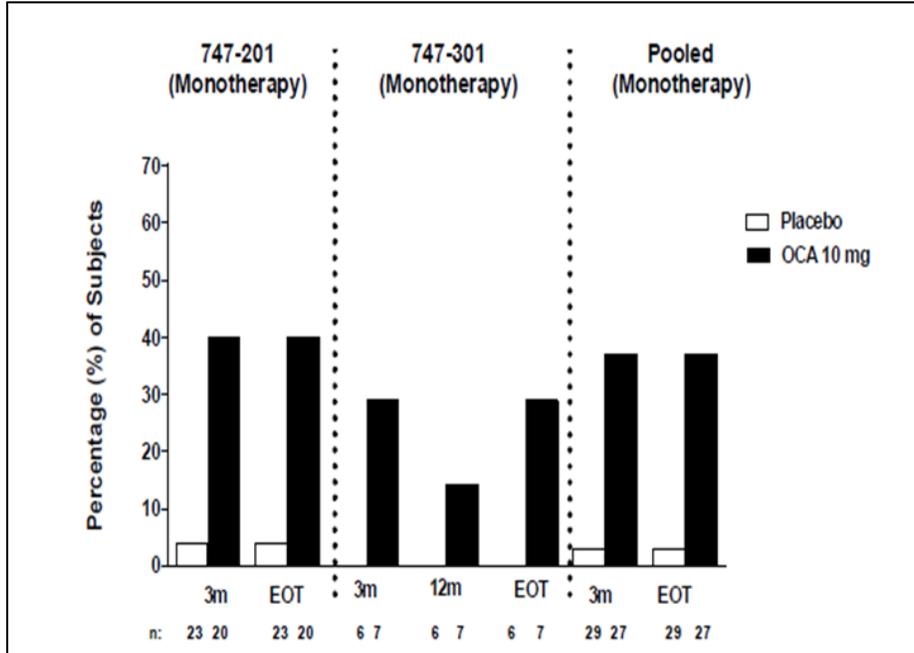


Figure Source: Adapted from the Applicant submission of Summary of clinical efficacy page 145 of 190
 Endpoint: ALP <1.67x ULN and Total Bilirubin ≤ULN and ALP Reduction ≥15%

Figure 47 shows the ALP percent reduction in the trial 747-201 was about 40% ALP reduction. In trial 747-301 the percent reduction at month 3 was about 30% which dropped ~ 15% reduction in the ALP at month 12. Although no patient discontinued from this treatment arm only 2 out of 7 achieved efficacy endpoint. However, at end of treatment the mean ALP reduction was close to 30%.

Figure 47 : Double-Blind Phase LS Mean (SE) ALP Values at Baseline, Month 3, and EOT: ITT Population (N = 54), Monotherapy

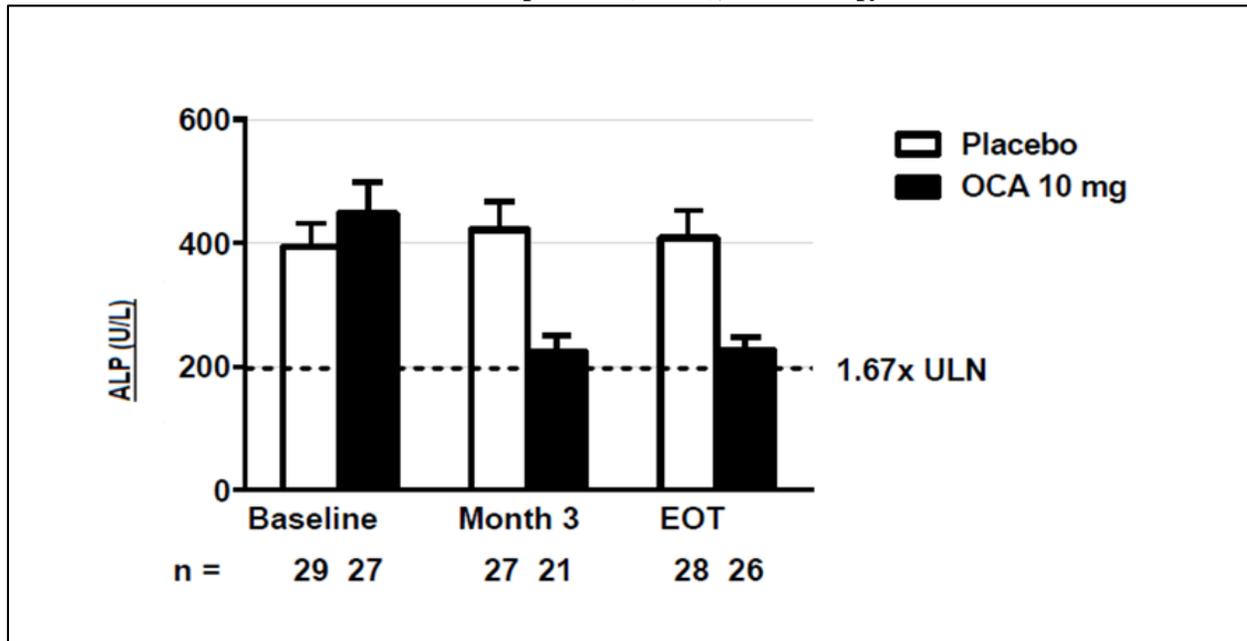
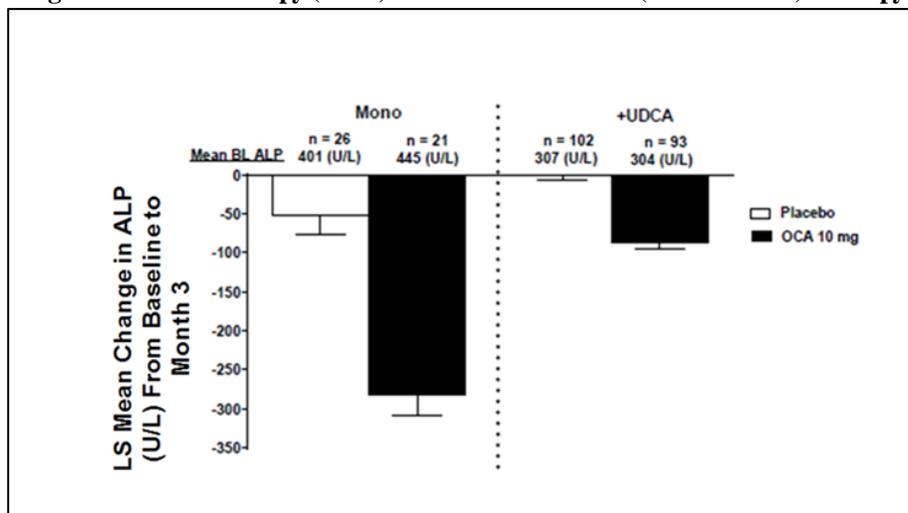


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This graph shows pooled data from trials 747-301 and 747-201. The left graph is the total number of patients i.e., placebo (N=29) and OCA monotherapy 10 mg (N=27). At month 3 mean ALP for placebo arm did not change. Whereas the mean ALP of the OCA treated patients came down to the phase 3 trial pre-specified endpoint. The right graph shows end of treatment (Day 85 and not month 3) as assessment has been plotted separately as trial 747-201 was an 85 day trial.

Figure 48: Monotherapy (OCA) Versus Combination (OCA+UDCA) Therapy



Source: Adapted from the Applicants submission of Clinical Overview page 54 of 86

Monotherapy Summary:

Pooled data from trial 747-201 and 747-301 are not the most optimum method of assessing the effectiveness of use of OCA as monotherapy. However, given the inability to recruit patients who were not on UDCA was a major hurdle leading to a small sample size for analyses for OCA monotherapy effectiveness.

However, these pooled data show numerically greater number of patients responded to OCA relative to placebo at month 3.

1. OCA monotherapy is generally well tolerated. Notably, in trial 747-201 at least 50% patients had moderately advanced stage disease. No major or serious safety signal (other than pruritus) was seen during the trial.
2. Patients who cannot tolerate UDCA have no medical treatment option remaining. OCA will be an alternative to patients who are unable to tolerate UDCA.
3. The baseline ALP in trial 747-201 was higher mean ALP of 448 U/L (~3.8 x ULN) and ~50% patient had ALP > 3 x ULN compared to patients in 747-301 where the mean ALP was 304 (~2.6 x ULN). At month 3, patients treated with OCA monotherapy achieved reductions in ALP levels that were similar to those on combination therapy although the absolute as well as percent reductions with OCA monotherapy were greater in comparison to combination therapy as seen in Figure 48
4. However, more data are required to assess the long term safety and efficacy of OCA use as monotherapy.

The primary endpoint was not pre-specified for the analyses of pooled data. There was no secondary endpoint for the analyses of these pooled data. The reader is directed to Section 6 for details of individual trial results.

The subpopulations were very small and precluded any interpretation.

The onset of response was similar i.e., ALP reduction was seen at 2 weeks and the response was durable for 3 months.

Conclusions:

While the data is sparse, there is enough evidence to approve OCA used as monotherapy in patients intolerant or who do not have an adequate response to UDCA. Additional, safety and clinical efficacy data should be obtained from the phase 4 trial.

7.1.1 Considerations on Benefit in the Postmarket Setting

A PMR has been requested by the FDA to conduct a trial in PBC patients using OCA as monotherapy for assessing long term safety of OCA monotherapy use.

7.1.2 Other Relevant Benefits

The major benefit of OCA that will benefit PBC patients are the UDCA non responders. The patients who do not respond do not have therapeutic alternatives and will benefit with OCA use.

7.2 Integrated Assessment of Effectiveness

Please see Section 6 for review of effectiveness as seen across each trial.

8 Review of Safety

8.1 Safety Review Approach

The safety information for this section has been reviewed from the

1. Clinical Pharmacology Studies
 - a. 16 clinical studies in healthy volunteers
 - i. phase 1 studies evaluated OCA
 - ii. pharmacokinetics (PK) and short terms safety,
 - iii. pharmacodynamics (PD), clinical DDIs,
 - iv. QT prolongation potential (thorough QT study),
 - v. absolute bioavailability, relative bioavailability,
 - vi. hepatic impairment, food-effect, and
 - vii. Agent altering gastric pH on OCA PK.
2. Randomized, Double-Blind, Placebo-Controlled Studies 3
 - a. Two phase 2 trials: 747-201 and 747-202
 - b. One phase 3 trial: 747-301
3. Open-Label, Uncontrolled Studies
 - a. The interim data from open-label, uncontrolled, long-term safety extension (LTSE) phases (747-301 LTSE, 747-201 LTSE, and 747- 202 LTSE),
 - b. Open-label, uncontrolled primary treatment phase (PTP) of 747-205 (also in patients with PBC)
4. Other Indications (only pooled for exposure)
 - a. Type 2 Diabetes Mellitus and NAFLD
 - b. Nonalcoholic steatohepatitis (NASH)
 - c. Alcoholic cirrhosis with portal hypertension
 - d. Bile Acid Diarrhea
 - e. Bariatric and Gallstone Surgery

8.2 Review of the Safety Database

8.2.1 Overall Exposure

Across the clinical studies that were pooled for exposure, 1325 male and female patients were exposed to at least 1 dose of OCA. Of those, 1147 patients (87%) had ≥ 1 week of exposure and 232 patients (18%) had ≥ 1 year of exposure. Of all patients treated with OCA, 152 patients (11%) had ≥ 1.5 years of exposure and 70 patients (5%) had ≥ 2 years of exposure to OCA. Across all clinical pharmacology studies, 819 patients were exposed to OCA and 88 patients were exposed to placebo.

Figure 49: Cumulative Investigational Product Exposure (All OCA-Treated Patients, N= 1325)

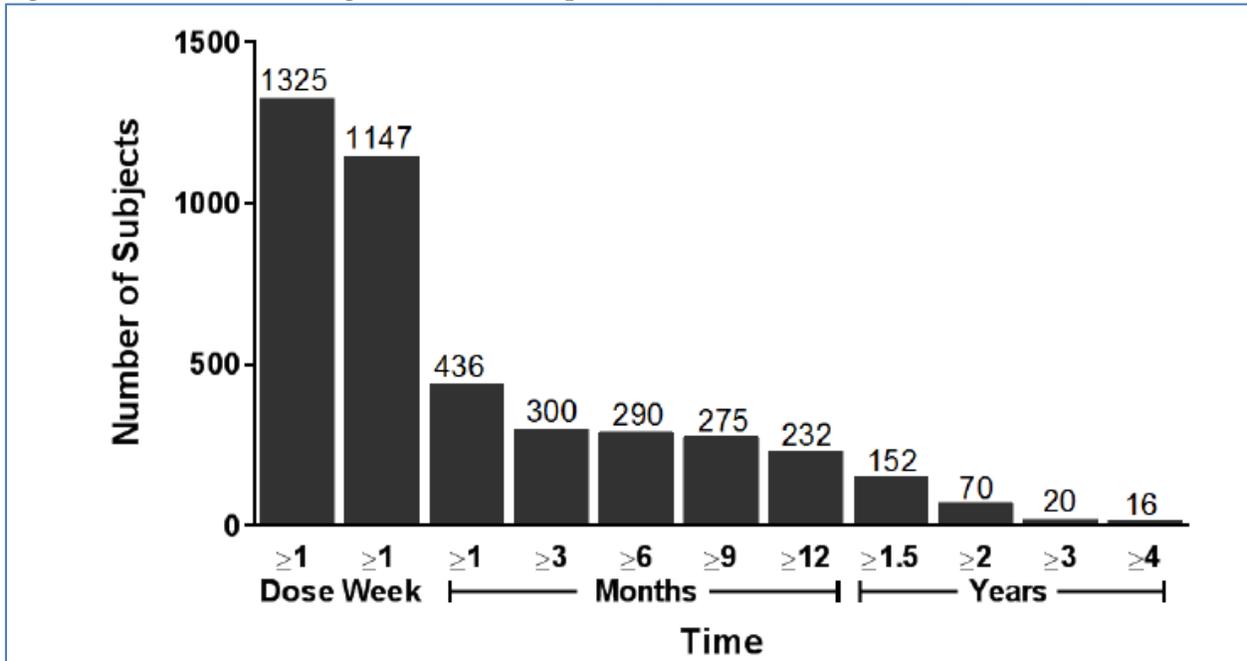


Figure source: Copied and electronically reproduced from the Clinical summary of safety page 41 of 162

Cumulative exposure data are based on all pooled patients exposed to OCA over time; exposure was calculated at each timepoint from the following studies: D8601002, 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, 747-201 Double-Blind Phase, 747-202 Double-Blind Phase, 747-301 Double-Blind Phase, 747-201 LTSE Phase, 747-202 LTSE Phase, 747-301 LTSE Phase, 747-203, 747-204, and 747-205 PTP. Cumulative exposure data for FLINT, OBADIAH1, OCABSGS, and DSP862001 are not available and are therefore not included. Exposure for Study 747-113 was not included; the study used a radiolabeled oral and intravenous formulation of OCA.

Table 106: Patients/Healthy Volunteers exposed to OCA during the Drug Development Program

Studies Conducted by the		
Clinical Pharmacology Studies		
	OCA	Placebo
Human PK/Bioavailability ^a	44	NA
Comparative Bioavailability and Bioequivalence (Healthy Patients) ^b	320	NA
Human PK/Safety Tolerance ^c	124	24
Human PK/Intrinsic Factors ^d	32	NA
Human PK/Drug Interaction ^e	236	NA
Human PD and PK/PD ^f	63	64
Study 747-113 ^g	13	NA
Phase 1 Subtotal	832	88
Controlled, Double-Blind Studies in Patients with PBC		
747-201	36	23
747-202	127	38
747-301	143	73
Phase 2 and Phase 3 Subtotal	306	134
Uncontrolled, Open-Label Studies in Patients with PBC		
747-201 LTSE ^h	28	NA
747-202 LTSE ^h	78	NA
747-301 LTSE ^h	193	NA
747-205 PTP	27	NA
Uncontrolled, Open-Label Studies in Unique Patients with PBC^{j,k}	126ⁱ	NA
Total Number of Patients Exposed to OCA in Patients with PBC	432	NA
Completed Studies in Other Indications Conducted by the Applicant		
747-203 (T2DM and NAFLD)	41	23
747-204 (Alcoholic Cirrhosis)	33	
Total Number of Patients Exposed to OCA and Placebo in Studies Conducted by the Applicant^l	1325	245
Ongoing and Completed Investigator of Partner Initiated Trials		
FLINT (NASH)	141	142
D8602001 (NASH) ^m	150	50
OBADIAHI (Bile Acid Diarrhea)	28	
OCABSGS (OCA in patients undergoing planned bariatric surgery or gallstone surgery)	14 ^o	14 ^o

Table source: Copied and electronically reproduced from the Summary of Clinical Safety page 46 of 162

NAFLD = non-alcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; T2DM = diabetes mellitus type 2 a Study 747-104, D8601002¹¹

b Study 747-115, 747-116

c D8601002 SAD/MAD, 747-101, 747-102, 747-105, 747-107

d Study 747-103

e Study 747-109, 747-110, 747-111, 747-112, 747-114

f Study 747-108

g Study not pooled for exposure.

h Includes 16 patients exposed to OCA during the Study 747-201 double-blind, 57 patients exposed to OCA during 747-202 double-blind, and 127 patients exposed to OCA during 747-301 double-blind.

i Patients who were randomized to placebo in the double-blind, placebo-controlled studies and rolled over into the LTSE phase and patients from Study 747-205.

j Ninety-nine patients who received OCA during the double-blind, placebo-controlled studies also received OCA and are therefore subtracted from the total number of unique patients who participated in all studies.

k Study 747-201 LTSE, Study 747-301 LTSE, and Study 747-205 LTSE are ongoing.

l Studies pooled for exposure included all clinical pharmacology studies (with the exception of Study 747-113), Study 747-201 double-blind, 747-202 double-blind, 747-301 double-blind, and their LTSEs, Study 747-205 PTP, Study 747-203, and Study 747-204.

m Study D8602001 is still blinded. The number of patients exposed to OCA and placebo are estimates.

n Including 747-203, 747-204, D8602001, FLINT, OBADIAH1, and OCABSGS o OCABSGS is still blinded. The number of patients exposed to OCA and placebo are estimates.

p Includes estimated exposure of 150 patients in Study D8602001 and 14 patients in Study OCABSGS and 13 patients exposed to OCA in Study 747-113.

q Excluding estimated exposure in Study D8602001 Study OCABSGS, but including Study 747-113.

¹¹D8601002 had two parts: A double-blind, placebo-controlled, randomized, ascending single dose and multiple dose study (SAD/MAD) to investigate the safety and pharmacokinetics of DSP-1747 and open-label, single-dose, two-period, crossover study to determine the effect of food on the pharmacokinetics of DSP-1747 in health Japanese male patients.

OCA exposure during the double-blind treatment period in patients with PBC includes:

1. 300 (98%) patients for at least a week.
2. 142 patients (87%) with at least 3 months of exposure
3. 37 patients (45%) with ≥ 12 months of exposure;

Patient in 747-301 completed the 12-month trial; most patients had their last study visit prior to Day 365 (due to protocol visit windows) and were therefore not included in the calculation of exposure for at least 12 months.

OCA exposure in the open-label studies in patients with PBC is limited to those patients who enrolled in the LTSE phase of studies 747-201, 747-202, and 747-301, and in the PTP of Study 747-205 and includes:

1. 324 patients (99%) with ≥ 1 week of exposure (from the start of the LTSE period or the start of the PTP of 747-205);
2. 279 patients (86%) with ≥ 6 months of OCA exposure
3. 148 patients (45%) with ≥ 1 year exposure.
4. Twenty-three patients (7%) had at least 2 years of exposure during the LTSE phase (747-201 LTSE Phase, 747-202 LTSE Phase, 747-301 LTSE Phase, and 747-205 PTP Phase).

Figure 50: OCA Exposure in Patients with PBC (N = 432)

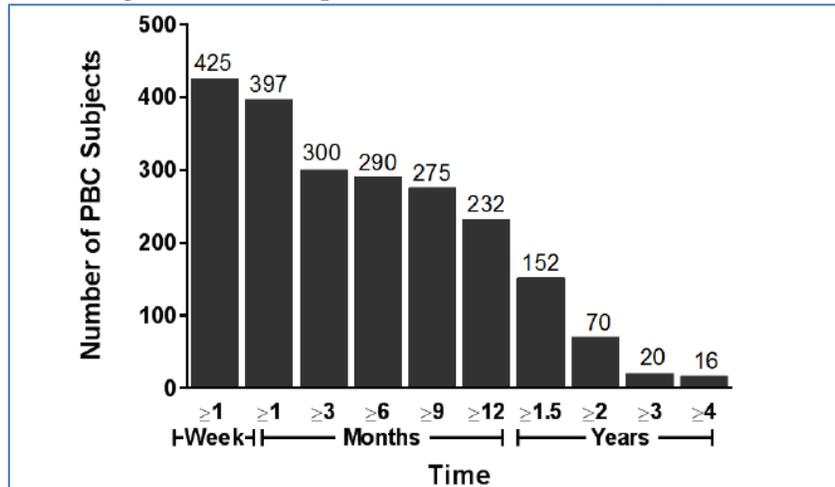


Figure Source: Copied and electronically reproduced from the Clinical summary of safety page 44 of 162
Includes patients from Studies 747-201, 747-202, 747-301, 747-201 LTSE, 747-202 LTSE, 747-301 LTSE, and
747-205 PTP. The figure above also include placebo patients therefore the total number of patients exposed reflect
N=425.

Patient disposition: Subject Disposition by Dose - Double- Blind, Placebo- Controlled Studies in Subjects with PBC (All Randomized Subjects, N = 442)

	747-201				747-202					747-301			
Number of Subjects (n, %)	PBO	OCA 10 mg	OCA 50 mg	Total OCA	PBO	OCA 10 mg	OCA 25 mg	OCA 50 mg	Total OCA	PBO	OCA Titration	OCA 10 mg	Total OCA
Subjects Randomized	24	20	16	36	38	38	48	41	127	73	71	73	144
All Treated	23	20	16	36	38	38	48	41	127	73	70	73	143
Completed DB Study													
Yes	23 (96)	16 (80)	9 (56)	25 (69)	37 (97)	32 (84)	42 (88)	25 (61)	99 (78)	70 (96)	64 (90)	64 (88)	128 (89)
Overall Subject Discontinuations	0	4 (20)	7 (44)	11 (31)	1 (3)	6 (16)	6 (13)	16 (39)	28 (22)	3 (4)	6 (8)	9 (12)	15 (10)

Table source: Summary of Clinical Safety (NDA/MAA) page 53-162

PBO = placebo

^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.

The OCA treated patients had a higher discontinuation rate compared to the placebo across all OCA trials. The discontinuations were higher at OCA doses >10 mg. Pruritus was the main reason of discontinuations. Liver related serious adverse reactions (PBC flare, jaundice, ascites) were higher in OCA >10 mg dose. In Studies 747-201 and 747-202 of OCA in the PBC patient population, a 3-fold rise in AST and/or ALT or a 2-fold rise in conjugated bilirubin required mandatory discontinuation (provided the values were above the normal range). A total of 4 OCA-treated patients developed mandatory protocol discontinuation criteria in Study 747-202 (3 patients [1 OCA 10 mg, 2 OCA 50 mg] due to a 2-fold increase in total bilirubin and 1 patient (1 OCA 50 mg) due to a 3-fold increase in AST/ALT.

Table 107: Subject Disposition: Open-Label, Uncontrolled Studies in Subjects with PBC (Enrolled Subjects, N = 326)

	OCA			Total OCA
	≤5 mg	>5 mg to ≤10 mg	>10 mg	
Enrollment				
Subjects Enrolled	52	180	94	326
Study 205	1	26	0	27
LTSE Phase of 201, 202, 301	51	154	94	299
All Treated Population				
Total Subjects Receiving OCA ^a	52 (100)	180 (100)	94 (100)	326 (100)
2-Year Completer Population				
Subjects Completing 2 Years of OCA Treatment ^b	6 (12)	43 (24)	30 (32)	79 (24)
Subjects Completing the LTSE or OL Phase				
Yes	0	2 (1)	0	2 (<1)
Ongoing ^c	41 (79)	151 (84)	32 (34)	224 (69)
Subjects in Study 747-202 LTSE who Continued until Study was Terminated ^d	2 (4)	7 (4)	50 (53)	59 (18)
Overall Subject Discontinuation prior to Study Termination^e	9 (16)	27 (11)	12 (13)	41 (13)

Source: Table source: Summary of Clinical Safety (NDA/MAA) page 55-162

Open-label, uncontrolled studies include Studies 201 LTSE, 202 LTSE, 301 LTSE, and 205 PTP. Although Study 205 is categorized as a clinical pharmacology study, it is analyzed with the open-label, uncontrolled studies.

^a All randomized subjects who received any amount of OCA. Treatment assignment is based on the actual treatment.

^b All subjects with PBC who were exposed to OCA (including exposure during the double-blind and LTSE phases) for at least 2 years are included in the Completer population.

^c LTSE studies are ongoing. Data for Study 747-201 LTSE and 747-301 LTSE are available as of 31 Aug 2014.

^d Incidence of subject termination due to administrative reasons was based on overall open-label population (n = 326).

^e Incidence of subject discontinuation prior to study termination does not include 59 subjects who were early terminated due to the Applicant stopping the long-term extension phase of Study 747-202 LTSE.

Study 747-202 LTSE was stopped by the Applicant after all ongoing patients had received at least 1 year of open-label treatment. At that point, all patients (n = 59) who remained in the study were terminated (“discontinuation due to administrative reasons”). Since these patients completed all study-related visits and procedures through the study termination date, they are not included in the total incidence of study discontinuations.

Reviewer comments: In the OCA arm: 2 patients died (one in 747-301 DB phase and one in 747-301 LTSE phase). Both deaths were related to cardiovascular reasons, and in patients >65 years of age. 15 patients withdrew consent and were discontinued from trial, 47 discontinued due to AE of pruritus. There were 31 laboratories or clinical adverse event leading to discontinuations. Laboratory abnormality of elevations of ALT/AST/TB occurred in 4 patients treated with OCA. 3 patients were lost off follow up. No patient in placebo arm was discontinued for any of the reasons stated.

Demographic and Baseline Characteristics – All Pooled Studies:

Demographics and baseline line characteristics are not described, as they similar to what was observed in trials 747-201, 747-202 and 747-301. The demographics of clinical pharmacology trials are not described here. Of the PBC patients enrolled in trial, 82% were age <65 years, and 91% females, 97% white. 50% were enrolled in North America, remaining in Europe and Australia. 84% patients were on concomitant UDCA.

Table 108: Most Commonly Reported (≥20%) Baseline Medical History - Double-Blind, Placebo-Controlled Studies in Patients with PBC (All Treated Patients, N = 440)

	OCA					Total OCA (N = 306)
	Placebo (N = 134)	Titration ^a (N = 70)	10 mg (N = 131)	25 mg (N = 48)	50 mg (N = 57)	
Pruritus	43 (32)	15 (21)	44 (34)	21 (44)	29 (51)	109 (36)
Fatigue	30 (22)	8 (11)	29 (22)	14 (29)	21 (37)	72 (24)
Hypertension	29 (22)	14 (20)	38 (29)	8 (17)	10 (18)	70 (23)
Osteopenia	34 (25)	20 (29)	29 (22)	9 (19)	12 (21)	70 (23)
Post menopause	25 (19)	5 (7)	26 (20)	15 (31)	18 (32)	64 (21)
Drug hypersensitivity	27 (20)	5 (7)	21 (16)	23 (48)	15 (26)	64 (21)
Hysterectomy	21 (16)	14 (20)	28 (21)	11 (23)	8 (14)	61 (20)

Table source: Copied and electronically reproduced from Summary of Clinical Safety page 62-162

^a In Study 747-301 (747-301 Double-Blind Phase), 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 up-titrate to OCA 10 mg.

Reviewer Comment: Baseline history of fatigue prior to enrollment in trial was well balanced (22-29%) across all treatment arms except the OCA titration arm (11%) and patients in OCA 50 mg (37%). The baseline incidence of drug hypersensitivity was higher in patients treated OCA 25 mg arm. Baseline distribution for was well balanced for osteopenia, hypertension, and hysterectomy.

Baseline Characteristics – Open-Label, Uncontrolled Studies in Patients with PBC:

Baseline characteristics for the patients enrolled in LTSEs of Studies 747-201, 747-202, 747-301 are described in Section 6. Baseline and the open-label, uncontrolled PTP of Study 747-205 was similar to those observed at baseline in the corresponding controlled phase of the studies.

Baseline characteristics for the patients in the LTSE phase: for patients who had previously been treated with OCA, liver biochemistries at LTSE baseline were notably lower than the placebo-treated patients.

8.2.2 Adequacy of the safety database:

Appropriate safety evaluations were performed as part of the drug development program.

The safety of OCA was assessed throughout the clinical development program. Individual clinical trial protocols outlined safety monitoring and included assessment of AEs, serious AEs, and deaths, and the following specific safety related testing:

- Physical examinations
- Clinical laboratory evaluation: hematology, serum chemistry, urine chemistry, and lipoprotein analytes
- Vital sign measurements
- 12-lead electrocardiograms (ECGs)
- Body weight (including BMI)
- Dual-emission x-ray absorptiometry (DEXA) scans (selected patients)
- Patient questionnaires: 5-D Pruritus and Pruritus VAS
- AEs of special interest: pruritus, hepatic disorders, dyslipidemia, and cardiovascular disorders.
- Mayo Risk Score (MRS) and Model for End Stage Liver Disease (MELD)

Reviewer Comments:

The Applicant's safety database exceeds the ICH E1A minimum recommendations for drugs that are to be used chronically (reference: ICH E1A Guidance "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073083.pdf>). The overall exposure to OCA and duration of clinical trials during clinical development were acceptable to assess the safety of the product.

APPEARS THIS WAY ON ORIGINAL

Patient Disposition - Clinical Pharmacology:

Table 109: Patient Disposition - Clinical Pharmacology Studies (All Enrolled/Randomized Patients, N= 819)

	PK/Bioavailability ^{a,c}	Subject PK and Initial Safety and Tolerability ^{b,c}		Intrinsic Factors PK ^d	PK (Drug Interaction) ^e	Secondary Pharmacology ^f	
		PBO	OCA			PBO	OCA
	OCA	PBO	OCA	OCA	OCA	PBO	OCA
Subjects enrolled/randomized	44	24	124	32	236	64	64
All Treated Subject Population ^h	44 (100)	24 (100)	124 (100)	32 (100)	231 (98)	64 (100)	63 (99)
Completed							
Yes	40 (91)	24 (100)	120 (97)	32 (100)	231 (98)	63 (98)	62 (99)
Discontinuation from Study	4 (9)	0	4 (3)	0	5 (2)	1 (2)	1 (2)

Table source: 2.7.4 Summary of Clinical Safety page 51-261

PBO = placebo

Note: Percentages are based on the number of subjects randomized/enrolled. Study 747-113 is not included in the analysis.

a 747-104, D8601002 Food Effect

b D8601002 SAD/MAD^c, and 747-101, 747-102, 747-105, and 747-107

c D8601002 had 2 parts: A double-blind, placebo-controlled, randomized, ascending single dose and multiple dose study (SAD/MAD) to investigate the safety and pharmacokinetics of DSP-1747, and open-label, single-dose, two-period, crossover study to determine the effect of food on the pharmacokinetics of DSP-1747 in healthy Japanese male subjects.

d 747-103

e 747-109, 747-110, 747-111, 747-112, and 747-114

f 747-108 g 747-115 and 747-116

h All randomized subjects who received any amount of investigational product.

i An AE of liver enzyme elevations was experienced by Subject 203-1024 (Study 747-108) and was included even though the AE was considered non-TEAE as it started prior to the first dose.

Across clinical pharmacology studies, the majority of patients (97%) receiving OCA completed the studies compared with 99% placebo patients completed the studies. No patients were discontinued due to pruritus. Nine (1%) patients were discontinued due to “Other reason.” Seven patients (<1%) randomized to OCA discontinued from the study due to a TEAE and 1 patient (1%) randomized to placebo discontinued due to a TEAE in the clinical pharmacology studies.

8.2.3 Issues Regarding Data Integrity and Submission Quality

No issues were found in regards with the Data Integrity and Submission Quality.

Categorization of Adverse Events

Applicant states AE were restricted to TEAEs, which are defined as any AEs that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product.

Summaries were displayed by system organ class (SOC) and preferred terms, ordered by descending order of incidence of SOC and preferred term within each SOC in the total OCA arm.

TEAEs were assessed by crude incidence rates, cumulative incidence rates, exposure-adjusted incidence rates, placebo-adjusted incidence rates, and by most commonly occurring TEAEs ($\geq 5\%$ in patients treated with OCA [total OCA arm]), and by relationship and severity. SAEs, AEs leading to study discontinuations or investigational product withdrawals, and adverse events of special interest (AESIs) were also analyzed and all summaries of TEAEs were analyzed by intrinsic factors. Applicant utilized the TEAEs verbatim terms and mapped to SOCs and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA; version 15.0).

Table 110: Summary of Treatment-Emergent Adverse Events in Clinical Pharmacology Studies and Double-Blind, Placebo-Controlled Studies in Patients with PBC (All Treated Patients, N = 440)

	Clinical Pharmacology		Double-Blind, Randomized, Placebo-Controlled in Subjects with PBC	
	Placebo (N = 88)	OCA (N = 819)	Placebo (N = 134)	OCA (N = 306)
n (%)	n (%)	n (%)	n (%)	n (%)
All TEAEs	14 (16)	173 (21)	119 (89)	288 (94)
Total Number of TEAEs	24	302	632	1527
By Severity, n (%)				
Mild	11 (13)	157 (19)	56 (42)	79 (26)
Moderate	2 (2)	14 (2)	46 (34)	119 (39)
Severe	1 (1)	2 (<1)	17 (13)	90 (29)
TEAE By Relationship, n (%)				
Not Related	4 (5)	48 (6)	48 (36)	52 (17)
Related	10 (11)	125 (15)	71 (53)	236 (77)
At Least One Related and Severe TEAE, n (%)	0	2 (<1)	9 (7)	77 (25)
Subjects reporting at Least 1 SAE	0	1 (<1)	5 (4)	25 (8)
SAE Based on Investigator Assessment of Relationship				
Not Related	0	0	5 (4)	21 (7)
Related	0	1 (<1)	0	4 (1)
Death	0	0	0	1 (<1)

Table source: 2.7.4 Summary of Clinical Safety (NDA 207999) page 66-162

TEAEs were noted for both OCA- and placebo-treated patients.

The incidence of TEAEs in patients treated with OCA or placebo was similar within clinical pharmacology studies (21% and 16%, respectively). The majority of TEAEs were considered to be mild in severity in clinical pharmacology trials. The incidence of “related events” was higher in OCA treated patients, compared to placebo. One OCA-treated patient experienced 2 SAEs (acute Cholecystitis and Cholelithiasis) that were possibly related to OCA treatment.

The incidence of TEAE in the double-blind, the placebo-controlled trials was greater with OCA compared to placebo arm (94% and 89%, respectively). More OCA-treated patients experienced severe TEAEs compared with placebo, which was largely due to dose-related pruritus. The incidence of related TEAEs higher in the OCA arm compared with the placebo arm (77% and 53%, respectively). A greater number of patients treated with OCA (25 patients [8%]) experienced SAEs compared with those treated with placebo (5 patients [4%]). Most SAEs experienced by OCA-treated patients (21 of 25 patients in the double-blind, placebo-controlled studies) were considered not related to investigational product.

One OCA-treated patient died (<1%) in the LTSE phase of the trial.

8.2.4 Routine Clinical Tests

The Applicant conducted routine clinical tests for safety:

Hematology
Coagulation
Serum Chemistry
Vital Signs
Electrocardiogram (ECG)
Adverse event reporting

8.3 Safety Results

8.3.1 Deaths

Across all studies conducted with OCA, a total of 4 treatment-emergent deaths were reported. Two deaths (cardiac failure and sepsis) occurred, both in male patients with PBC, treated with OCA. In addition, there were 2 deaths in two patients with nonalcoholic steatohepatitis (NASH) trial with OCA. This NASH trial out of two deaths, one of these deaths was considered as possibly related to OCA by the investigator.

Deaths in Patients with PBC: In the OCA clinical development program for PBC there were 2 deaths that occurred due to 2 distinct underlying causes.

1. 81 year-old male patient (Patient 186003, OCA titration [OCA 5 mg], Study 747-301 Double-Blind Phase) with a medical history of chronic kidney disease, PBC, and ischemic cardiovascular and congestive cardiac failure died due to worsening congestive cardiac failure and renal failure.

The death was assessed as not related to investigational product. *The details of the narrative has been described in 747-301 trial safety section 6, the reviewer agrees with the investigators assessment, however, considered that the continued patient enrolled after first cardiac failure was not acceptable.*

2. 69-year old male patient (Patient 183004, OCA 10 mg, Study 747-301 LTSE Phase) had a prosthetic aortic valve and the patient died due to sepsis secondary to endocarditis, along with splenic infarction, abdominal wall hematoma, acute renal failure. The patient's last dose prior to the event was OCA 10 mg. The death was assessed as not related to investigational product.

Narrative: 69 year old male; relevant medical history as follows: PBC, hypertension, and aortic valve prosthesis with systolic murmur, dyslipidemia, and osteoporosis.

Initial OCA 10 mg LTSE dosing started on (b) (6) (SAE occurred 1.5 years after the initial investigational dosing) the SAE. On (b) (6) the patient presented to hospital with persistent fever for 4 weeks. He developed vegetation on aortic valve, secondary to malfunctioning of the aortic prosthesis, and moderate-to-severe aortic stenosis. CT scan revealed splenic infarct. He was diagnosed with endocarditis and had positive blood cultures with *Enterococcus faecalis*. OCA was interrupted. During the same hospitalization, the patient developed abdominal hematoma measured 8.5 cm × 6 cm in thickness and extended 22 cm extending in pelvic region; there was also

another abdominal hematoma detected 7 cm under the fascia that was 10 cm × 4.5 cm in thickness. The patient's hemoglobin was low at 8.1 g/dL; treatment included a transfusion with 4 units of blood. On [REDACTED] (b) (6), his condition worsened the patient developed multi-organ failure including progressive renal insufficiency (increased creatinine with anuria [laboratory result not specified]) that required hemodialysis, pulmonary insufficiency with a need for artificial respiratory support and endotracheal intubation, progressive increase in bilirubin and international normalized ratio (results not available), and hemodynamic instability requiring pharmacological support with increasing doses of dopamine and adrenaline/noradrenaline. Further laboratory work up was not provided the patient died on [REDACTED] (b) (6), autopsy was not performed.

The investigator assessed the events of abdominal wall hematoma as moderate in severity; splenic infarction as severe; and, endocarditis, sepsis, and acute renal failure as severe and none of the three events were assessed as related to the investigational product.

The reviewer agrees with the investigators assessment. Although this is the second case report in a patient who had large abdominal hematoma (requiring blood transfusion), however the patient was critically ill with elevated INR. This reviewer does not consider hematoma an adverse event due to OCA.

8.3.2 Serious Adverse Events

Other Serious Adverse Events In total, 31 patients experienced SAEs in the clinical pharmacology and double-blind, placebo-controlled studies.

Serious Adverse Events - Clinical Pharmacology Studies

In the clinical pharmacology studies, a male patient (Patient 9011, OCA 25 mg, 747-110) without a prior history of liver disease was discontinued from the study due to a TEAE of abdominal pain. Eight days after discontinuation, the patient experienced 2 SAEs (acute Cholecystitis, and Cholelithiasis). The SAEs were assessed as definitely related to treatment by the Investigator.

The reviewer agrees with the assessment and this SAE (cholecystitis/cholelithiasis) has been reported in patients who are on OCA for other liver disease (NASH trials with OCA). This is an SAE of concern and physicians should keep a high index of suspicion.

Serious Adverse Events – Double-Blind, Placebo-Controlled Studies in Patients with PBC

A total of 25 patients (8%) treated with OCA in the double-blind, placebo-controlled studies in patients with PBC experienced 33 SAEs compared with 5 patients (4%) treated with placebo that experienced 10 SAEs. The incidence of SAEs did not appear to be dose-related. The majority of patients (n = 21) experienced SAEs that were assessed as unlikely or definitely not related to treatment and the majority of patients who experienced an SAE during the double-blind phase did not discontinue treatment or discontinue from the study.

Table 111: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term - Double-Blind, Placebo- Controlled Studies in Patients with PBC (All Treated Patients, N= 440)

MedDRA System Organ Class Preferred Term ^a	OCA				TOTAL ^a	
	Titration ^b (N=70)	10 mg (N=131)	25 mg (N=48)	50 mg (N=57)	Placebo (N=134)	OCA (N=306)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All Serious Adverse Events	11 (16)	8 (6)	1 (2)	5 (9)	5 (4)	25 (8)
Gastrointestinal disorders	4 (6)	0 (0)	0 (0)	1 (2)	1 (<1)	5 (2)
Abdominal wall hematoma	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Ascites	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Gastrointestinal hemorrhage	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (<1)
Splenic artery aneurysm	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Upper gastrointestinal hemorrhage	1 (1)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)
Varices esophageal	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)
Injury, poisoning and procedural complications	0 (0)	4 (3)	0 (0)	0 (0)	1 (<1)	4 (1)
Clavicle fracture	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Post procedural hemorrhage	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Radius fracture	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Wrist fracture	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Tibia fracture	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)
Musculoskeletal and connective tissue disorders	1 (1)	3 (2)	0 (0)	0 (0)	0 (0)	4 (1)
Osteoarthritis	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	2 (<1)
Intervertebral disc protrusion	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Rotator cuff syndrome	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Infections and infestations	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)	3 (<1)
Erysipelas	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Parotitis	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Pneumonia	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Cardiac disorders	1 (1)	0 (0)	0 (0)	1 (2)	1 (<1)	2 (<1)
Angina Pectoris	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (<1)
Cardiac failure	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)

Sick sinus syndrome	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)
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Table source: Summary of Clinical Safety (NDA/MAA) page 77-162

Footnote:

a SAEs are displayed by system organ class and preferred term, ordered by descending order of incidence of system organ class and preferred term within each system organ class in the total OCA arm. If there was a tie in incidence, alphabetical ordering was done.

b In Study 747-301, patients randomized to OCA 5 mg were assessed at Month 6 for clinical response and tolerability. Patients who did not achieve the primary composite endpoint and did not have tolerability issues were able to uptitrate to OCA 10 mg.

Table 112 Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term- Double-Blind, Placebo- Controlled Studies in Patients with PBC (All Treated Patients, N= 440) (Continued)

MedDRA System Organ Class Preferred Term ^a	OCA				TOTAL ^a	
	Titration ^b (N=70)	10 mg (N=131)	25 mg (N=48)	50 mg (N=57)	Placebo (N=134)	OCA (N=306)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
General disorders and administration site conditions	1 (1)	0 (0)	0 (0)	1 (2)	2 (1)	2 (<1)
Chest pain	0 (0)	0 (0)	0 (0)	1 (2)	1 (<1)	1 (<1)
Edema	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Non-cardiac chest pain	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)
Hepatobiliary Disorders	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	2 (<1)
Primary Biliary cirrhosis Flare	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (<1)
Jaundice	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (<1)
Nervous system disorders	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)
Hepatic encephalopathy	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Syncope	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Vascular disorders	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)
Varicose vein	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)
Blood and lymphatic system disorders	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Anemia	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Neoplasms benign, malignant and unspecified	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (<1)
Salivary gland neoplasm	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (<1)
Respiratory, thoracic and mediastinal disorders	1 (1)	0 (0)	0 (0)	0 (0)	2 (1)	1 (<1)
Interstitial lung disease	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Dyspnea	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)
Skin and subcutaneous disorders	0 (0)	0 (0)	0 (0)	1 (2)	1 (<1)	1 (<1)
Angioedema	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (<1)
Rash	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)

Table source: Summary of Clinical Safety (NDA/MAA) page 78-162

^a SAEs are displayed by system organ class and preferred term, ordered by descending order of incidence of system organ class and preferred term within each system organ class in the total OCA group. If there was a tie in incidence, alphabetical ordering was done. ^b 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.

Clinical Review
 Ruby Mehta
 NDA 207999
 OCALIVA [Obeticholic acid (OCA)]

Please read the Section 6.3.13 for SAEs in clinical trial 747-301 for details.

In Study 747-202 at the OCA 50-mg dose level and within 1 month of initiating treatment (747-202 Double-Blind Phase) three patients experienced hepatic SAEs. One patients experienced SAEs of jaundice, another patient had SAE of worsening of primary biliary cirrhosis clinically as well as laboratory parameters [PBC flare], and third patient experienced gastrointestinal hemorrhage. These three adverse events are very concerning, all these patients quite stable at least one patient with cirrhosis, and experienced sudden hepatic decompensation soon after initiation of treatment with OCA.

Another patient on OCA 50 mg dose experienced chest pain and this was possibly related to the OCA, this is again of concern as OCA will be used in older PBC patients also who may have underlying cardiac disease and discriminating them from drug related AE will be quite difficult.

The AE of pneumonia was seen in a patient on OCA 10 mg (Patient 109003), however, it appears this is not related to the drug.

Analysis of Serious Adverse Events by Intrinsic Factors - Double-Blind, Placebo-Controlled Studies in Patients with PBC

Given the uneven distribution of numbers of patients in sub groups (including sex, race/ethnicity, and baseline total bilirubin) the SAE results could not be interpreted meaningfully. No regional difference in the SAEs was observed.

8.3.3 Dropouts and/or Discontinuations Due to Adverse Effects

Investigational Product Withdrawal or Patient Discontinuation Due to TEAE

The overall incidence of TEAEs leading to study discontinuations was higher in the OCA-treated patients compared with placebo-treated patients.

Investigational Product Withdrawal or Patient Discontinuation from Study Due to TEAE – Clinical Pharmacology Studies

Study ID	Subject ID	Last Dose Prior to AE Start Date	Preferred Term / Verbatim Term	Start Day / Stop Day (Duration)	Seriousness / Severity	Relationship to Study Treatment	Action Taken w Study Treatment / Other Action Taken
Clinical Pharmacology							
747-102	307	250 mg OCA	Rash / Rash	6 / 15 (10)	No / Moderate	Possibly Related	Patient Discontinued From Study /
747-104	0031	10 mg OCA	Vomiting / Vomiting	1 / 1 (1)	No / Mild	Definitely	Drug Withdrawn
747-105	10425	5 mg OCA	Anxiety / Anxiety	4 / 6 (3)	No / Mild	Unlikely	Drug Withdrawn / Termination
747-108	203-1024	100 mg OCA	Hepatic Enzyme Increased Liver Enzyme Elevations	1 / 8 (8)	No / Mild	Not Related	Drug Withdrawn Study
747-108	203-1088	Placebo	Rash Maculo-Papular / Maculo-Papular Rash with Multiple Satellite Lesions on Both Sides of Chest	1 / 8 (8)	No / Severe	Not Related	Drug Withdrawn Concomitant Medication Taken, Study Termination
747-110	9011	25 mg OCA	Abdominal Pain / Abdominal Pain	12 / 13 (2)	No / Severe	Definitely	Drug Withdrawn Patient Discontinued From Study, Concomitant Therapy Given
747-115	200-056	10 mg OCA	Hyperbilirubinemia / Isolated Transient Hyperbilirubinemia	8 / 35 (28)	No / Mild	Unlikely	Drug Withdrawn Study Termination

Clinical Review
 Ruby Mehta
 NDA 207999
 OCALIVA [Obeticholic acid (OCA)]

747-116	200-092	10 mg OCA	Hypertransaminasemia / Hypertransaminasemia	27 / 36 (10)	No / Mild	Possibly Related	Drug Withdrawal Study
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In total there were only 7 healthy volunteers (<1%) who received OCA treatment in the clinical pharmacology studies who were withdrawn from the studies due to a TEAE compared with 1 patient who received placebo. A subset of AEs that resulted in study discontinuation were assessed as possibly or definitely related to treatment and occurred at doses ranging from OCA 5 mg to OCA 250 mg.

In healthy volunteers trial treated with OCA 2 patients:

1. Patient 200-056 OCA 10 mg, trial 747-115 experienced a hyperbilirubinemia (mild in severity and unlikely related to investigational product) and
2. Patient 200-092, OCA 10 mg, trial 747-116 experienced a hypertransaminasemia (assessed as possibly related to investigational product), that resulted in study discontinuation.
3. Patient 2031024, received OCA 100 mg and experienced liver biochemical test elevation.

In double-blind, placebo-controlled PBC trials: Please see Section 6 for full details.

There were 2 patients in OCA 10mg that experienced depression; one patient experienced hallucination, both worsening of depression and hallucinations appeared to be related to OCA dosing.

Significant Adverse Event

Adverse Events of Special Interest in Patients with PBC:

1. **Pruritus:** OCA-related AE
2. **Hepatic Disorders:** dose-limiting toxicities observed in non-clinical animal studies
3. **Cardiovascular events:** such as HDLc decreases and LDLc increases

These three were considered as AEs of special interest, and are discussed below:

Pruritus:

1. The severity of pruritus, and discontinuations due to pruritus were dose-related. However, pruritus has not been known to result in hospitalization or otherwise qualify as a serious event. In addition, the time to first onset of pruritus appeared to be dose-related and on average occurred within the first week of treatment for the OCA 50-mg dose. For the dose used in 747-301 the median time to first onset of pruritus was 9 day in OCA 10 mg arm, 24 days in OCA titration arm and 50.5 days in placebo arm.
2. Across the three double blind trials 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. 34 (11%) discontinuation for OCA-treated patients were due to pruritus that resulted in study discontinuation with most (n = 21) treated OCA >10mg dose. In patients treated with OCA 10 mg, the most frequently reported TEAE leading to study discontinuation was pruritus (n = 12). Of the 12 patients with TEAEs of pruritus that resulted in study discontinuation, 7 occurred in Study 747-301 in the OCA 10 mg arm. In the OCA titration arm, 1 patient withdrew due to a TEAE of pruritus after 221 days in trial 747-301. The highest rate of discontinuation was experienced by patients treated with the 50mg dose.

The reviewer agrees that pruritus is a dose dependent and manageable symptom and that pruritus did not cause hospitalization or SAE. Details on pruritus are presented in individual trial description.

3. **Hepatic Events and Liver Enzyme Changes**

Because of different duration of the trial exposure adjusted incidence was utilized.

Exposure-adjusted incidence in the summary of clinical safety addressed exposures of different duration for a given treatment group. Crude AE incidences are corrected for differences in investigational product exposure by using person-time in the denominator to calculate incidence rates. Adjusted incidence per 100 patient exposure years

(PEY) is the number of subjects with an event for whom person-time is available divided by the total PEY for each treatment group and multiplied by 100. Each subject's PEY was calculated as the last dose date minus the first dose date plus 1 divided by 365.25 days/year.

One PEY is the equivalent of one subject exposed to investigational product for one year. Two subjects who are exposed to investigational product for half a year together contribute one PEY. The total PEY of a treatment group is the sum of the person exposure years of each subject in that treatment group.

With increasing OCA doses, the incidence of serious hepatic adverse reactions increases. This exposure adjusted incidence in PEY was: 2.4 for placebo arm → increased to ~5 in OCA titration arm and OCA 10 mg arm → increased to 19.8 in patients treated with OCA 25 mg → increased to 54.5 in patients treated with OCA 50 mg. The number of patients experiencing these increased in each category with most concerning hepatic decompositions events seen in OCA 50 mg treatment arm.

OCA hepatic exposure is higher in hepatic impaired patients and is quite concerning. These adverse reactions are described in the footnote for each category. This effect was OCA dose dependent. Therefore a recommendation not to exceed the OCA dose > 10 mg is highly advised and is also mentioned in the label.

Table 113: Exposure adjusted Incidence Increase in Hepatic adverse events with OCA

Exposure Adjusted Incidence- 100 persons exposure years (PEY)					
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
2.4	4.5	5.2	19.8	54.5	8.6

Table source: Electronically copied and reproduced from 2.7.4 Summary of Clinical Safety page 91-162

Footnote

^bAt 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 biochemical test abnormality and varices esophageal X1 event (serious).

Adverse events reported for subjects in the Titration and OCA 10 mg groups were: Ascites, hepatic encephalopathy, increased International normalized ratio, and increase in total bilirubin.

Adverse events reported for subjects in the OCA 25 mg and 50 mg groups were: Ascites, medical therapy resistant ascites requiring paracentesis, primary biliary cirrhosis flare, hepatomegaly, jaundice, portal hypertension, and alanine aminotransferase increased, aspartate aminotransferase increased, and increase in conjugated bilirubin.

Dyslipidemia and Cardiovascular Disorders

Lipid abnormalities, including elevations in Total Cholesterol, HDLc and LDLc at Baseline, are commonly observed in patients with PBC. Minimal data is available regarding the cardiovascular risk associated with hypercholesterolemia in PBC. The largest such study found no increased cardiovascular risk compared to age- and gender-matched controls. However, of the 128 total deaths, only 7 events of atherosclerotic death were observed by Crippin et al. 1992. FXR plays a role in lipid homeostasis. Since there are distinct differences in the human and rodent physiology for example mice do not have CETP and as a consequence they have HDL as major cholesterol carrying lipoproteins animal model trials are not very informative.

In Section 6 for individual trials to review HDLc changes.

OCA has been observed to reduce HDLc, as noted in the FLINT trial conducted in patients with nonalcoholic steatohepatitis and was also seen as soon as 2 weeks and the effects are sustained at 8 week as seen trial 747-205 (dedicated lipid trial in patients with PBC) is summarized below.

8.3.3.1 Phase 2 Trial 747-205: To evaluate lipid metabolism in PBC patients

Open label trial to evaluate effects of OCA 10 mg on lipoprotein was conducted, enrolling 26 patients for 8 weeks in patients with PBC. UDCA use was allowed. Change in diet or exercise was not allowed during the trial. Patients with presence or history of clinically significant cardiac arrhythmias were excluded.

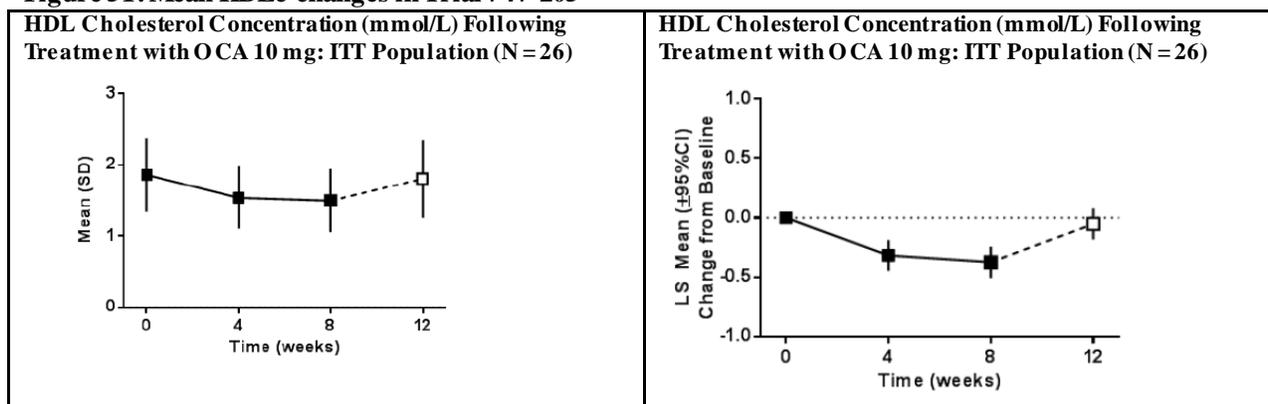
Prohibited medications were as follows (before and during the trial duration):

1. 28 days before Day 0 and throughout the trial period:: BAS
2. 3 months before Day 0 and throughout the trial period: Serum lipid modifying drug: HMGCoA reductase inhibitors, nicotinic acid and derivatives, ezetimibe, or Vitamin E (other than as standard dietary supplement)
3. 6 months prior to Day 0 and throughout the trial period:: azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline; budesonide and other systemic corticosteroids; potentially hepatotoxic drugs (including α -methyl dopa, sodium valproic acid, isoniazide, or nitrofurantoin)
4. 12 months before Day 0 and throughout the trial period: antibodies or immunotherapy directed against interleukins or other cytokines or chemokines
5. Prohibited 3 months before Day 0 and throughout the trial period as well as during LTSE Phase: fenofibrate or other fibrates.

Following dosing with OCA 10 mg the results were as follows:

HDL cholesterol: A statistically significant decrease in the HDL cholesterol was observed at Week 4 and this effect was sustained, at approximately the same magnitude, through to the end of the treatment period at Week 8. The lowering of HDLc is reversible following discontinuation of OCA treatment at week 12.

Figure 51: Mean HDLc changes in Trial 747-205



Source: CSR 747-205 page 61-832

Reviewer Comment:

The Applicant stated a difference in the small, medium and large HDL particles however, the clinical significance of the changes of these component are not established in PBC.

LDL Cholesterol Concentration

Figure 52: LDL Cholesterol Concentration (mmol/L) Over Time Following Treatment with OCA 10 mg: ITT Population (N = 26)

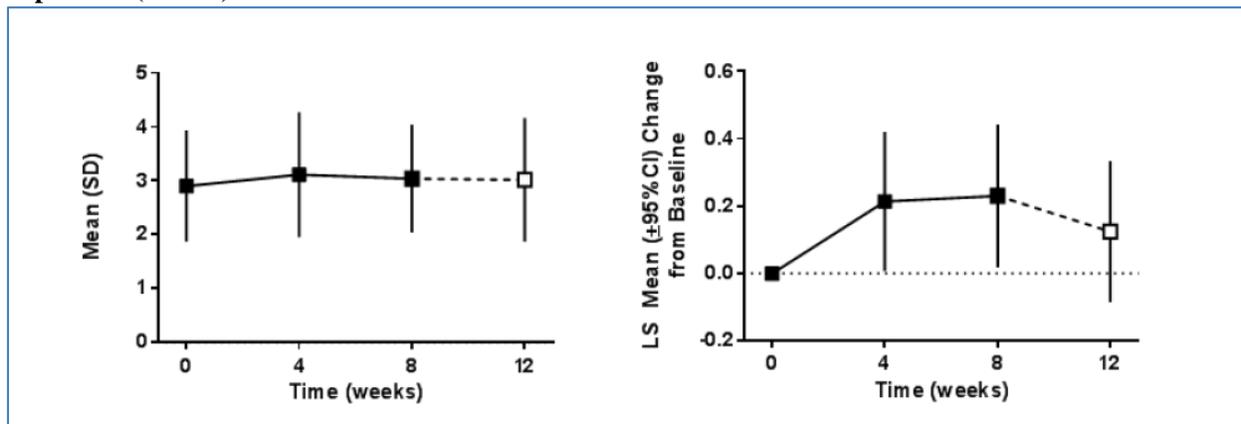


Figure source: CSR 747-205 page 71-832

Reviewer Comment:

Mean LDL cholesterol concentration increased from baseline following treatment with OCA at Week 4 and was sustained at Week 8. Upon discontinuation the increase in LDL changes are reversible. Further the Applicant states the small particle LDLc increased where as IDL and Large LDL particle did not increase. However, the clinical significance of these isolated small particle LDLc needs to be correlated with clinical outcomes.

This trial is very important as this was the only trial in which concomitant medications that alter the lipid metabolism were prohibited, therefore trial 747-205 reflects the true changes in lipid profile in PBC patients.

Table 114: Trial 747-205 Mean LDLc, HDLc, and Total Cholesterol Over Time and Change from Baseline (ITT Population; OCA 10 mg N=26)

	Baseline	Week 8/EOT	Change from Baseline to Week 8/EOT ^b
LDL, Direct (mg/dL)	128.03	125.35	-2.68
HDL Cholesterol (mg/dL)	75.38	57.81	-17.58

Table source: Adapted from the Applicant's submission to the NDA

Baseline is the average of all visit values prior to first dose in double-blind phase (747-301) or primary treatment phase (747-205). If results from only one evaluation are available, the available data from this evaluation is used as the baseline value. EOT = End of Treatment

Trial 747-205 TEAE AEs were mild or moderate for the majority of patients (46% and 23%, respectively). A total of 4 (15%) patients experienced at least 1 severe, related TEAE. Two patients experienced Serious AEs.

Worsening of fatigue and pruritus were the most common AEs seen. Two one due to worsening of pruritus and other due to worsening of fatigue (which did not resolve after discontinuations from trial) were noted. Of the 23 patients who experienced TEAE 15 patients experience TEAE that were considered possible, probably and definitely associated with OCA. Other AEs noted include diarrhea, edema, back pain, constipation, dizziness, headache, nausea, pyrexia, and sinusitis.

Serious adverse event in Trial 747-205:

1. Notably, one patient 149-003 experienced an AE of ascites, jaundice and required hospitalization for management of his SAE. Jaundice occurred on Day 66 of the OCA 10 mg dosing and ascites occurred 78 days after OCA dosing. The patient was symptomatic with rash, icterus, dark urine and pruritus. Of note the patient had cirrhosis seen on liver biopsy done in (b) (6) (patient enrolled in trial in (b) (6)).

Although the patient was treated with Augmentin and moxifloxacin; and Augmentin is known to cause DILI, however, the patient had received Augmentin in the past without any hepatotoxicity incidence. Therefore possibility of OCA causing this event cannot be ruled out.

2. One (4%) patient (Patient 101-003) reported abnormal ECG findings of atrioventricular block first degree and sinus bradycardia at the Week 8 Visit. This is of concern however, this reviewer is not sure if the drug may be a cause for the AE.

Dyslipidemia (HDLc reduction in Trial 747-301)

In the Phase 3 PBC study, HDLc levels at the OCA 10-mg and OCA 5-mg doses were reduced with both OCA doses and this reduction was sustained at month 12. Similar findings were seen in trial 747-205 (mentioned above)

HDLc (mean percent change)	Placebo	OCA titration arm	OCA 10 mg arm
Week 2	1%	9%	20%
Month 12	3%	15%	21%

The LDLc increased by 1% in placebo, 6% in OCA titration and 6% in OCA 10 mg arm seen at week two. Similar findings were seen in trial 747-205 as mentioned above.

8.3.3.1.1 Adverse events in NASH Trials

Safety Data from Studies Conducted in Patients with Other Liver Disease Studies Evaluating OCA Safety data from other completed Intercept:

Safety data from other completed Intercept-Applicant studies in indications other than PBC (747-203 [non-alcoholic fatty liver disease (NAFLD) and Diabetes] and 747-204 [Portal Hypertension in alcoholic cirrhotic]), FLINT trial for NASH; and two ongoing trials at the time for this filing (D8602001 [NASH] and OCABSGS have been reviewed for SAEs (including Deaths) and AEs leading to discontinuations.

Two deaths were reported in the FLINT trial:

Patient 6247, Female, Age 59, OCA 25 mg, FLINT:

One female patient with NASH died due to a suspected cardiac event after 62 weeks of OCA treatment. The patient had a relevant medical history of hypertension, hypercholesterolemia, diet-controlled diabetes, obesity, dyspepsia, and gastric ulcers. The patient sought emergency care for a possible heart attack and died due to a suspected cardiac event approximately 62 weeks after the first dose of OCA. In the absence of a known underlying cardiac disease, the Investigator noted that the death must be considered possibly related to study drug.

Patient 1529, Female, Age 73, OCA 25 mg, FLINT

One female patient died due to anoxic encephalopathy due to stroke. However, the investigator attributed the patient's cause of death to congestive heart failure and respiratory failure in the setting of sepsis, recurrent urinary tract infections, and malnutrition and not related to OCA. The reviewer read the narrative and agrees with Applicant.

Figure 53 Listing of Patients Who Experienced Serious Adverse Events (Study D8602001)

Subject ID	Preferred Term / Verbatim Term	Start Day / Stop Day (Duration) ^a	Severity	Relationship to Study Treatment	Outcome
10303	Cholestasis / Drug-Induced Liver Damage (Cholestatic Type)	40 / 70 (31)	Severe	Probably	Not Recovered/Not Resolved
11010	Radius Fracture / Right Distal Radius Fracture	-13 / 109 (123)	Moderate	Not Related	Recovering/Resolving
	Ascites / Ascites Retention	84 / 109 (26)	Severe	Possibly	Recovered/Resolved
11303	Cholecystitis / Cholecystitis	65 / 75 (11)	Severe	Possibly	Recovered/Resolved

	Cholecystitis / Cholecystitis	313 / 318 (6)	Moderate	Possibly	Recovered/Resolved
11305	Pyrexia / Fever of Unknown Origin	371 / 390 (20)	Moderate	Possibly	Recovered/Resolved
	Interstitial Lung Disease / Interstitial Pneumonia	377 / 390 (14)	Moderate	Possibly	Recovered/Resolved
11805	Ankle Fracture / Lateral Malleolus Bone Fracture of Right Foot Joint	193 / ongoing	Moderate	Not Related	NA
12003	Colonic Polyp / Large Intestine Polyp	34 / 76 (42)	Moderate	Not Related	Recovered/Resolved
13308	Diabetes Mellitus / Worsening of Diabetes Mellitus	71 / ongoing	Severe	Possibly	Not Recovered/Not Resolved
14806	Intervertebral Disc Protrusion / Cervical Disc Herniation	-15 / ongoing	Moderate	Not Related	NA
15403	Drug-Induced Liver Injury / Drug Induced Liver Injury	22 / 56 (35)	Severe	Probably	Not Recovered/Not Resolved
16103	Bile Duct Stone / Cholelithiasis	242 / 273 (32)	Severe	Possibly	Recovered/Resolved
16301	Hepatic Hemorrhage / Liver Bleeding	-52 / -42 (11)	Moderate	Not Related	Recovered/Resolved
19604	Abdominal Pain Upper / Epigastric Pain	182 / 186 (5)	Mild	Possibly	Recovered/Resolved

Source: Copied and electronically reproduced from the Summary of Clinical Safety page 104-162 (NASH trial: AE data)

NA = not available

Note: Data available as of 31 Aug 2014. ^a Days are relative to the first dose of investigational product.

Two patients experienced cholecystitis and/or choledocholithiasis which were moderate to severe AEs. Two patients experienced drug included liver injury was seen in this trial, and the injury was not resolved. All the four patients were discontinued from the trial. Although the reviewer does have narratives to assess if these events were truly a DILI signal or injuries that were suspected as DILI was just biochemical elevations of liver enzymes (i.e., met Hy's Law).

Reviewer Comment:

Cholelithiasis and cholecystitis were seen in normal healthy patients in the clinical pharmacology trial. This signal has been consistently seen across various trials.

The reviewer is not certain if these events were adjudicated by independent liver experts. Of concern are the potential cases of drug induced liver injury seen in NASH trials. It will be difficult to recognize the DILI signal in patients with PBC as they have baseline liver biochemical enzyme abnormalities and worsening of enzymes might mimic clinical disease progression.

8.3.4 Treatment Emergent Adverse Events and Adverse Reactions

As the phase 2 and phase 3 the trials were of different duration a comparison between these trials is not possible. Therefore evaluation of exposure-adjusted rates by PEY was conducted and used to assess the dose-relationship of common TEAEs. Exposure-adjusted incidence in the summary of clinical safety addressed exposures of different duration for a given treatment group. Crude AE incidences are corrected for differences in investigational product exposure by using person-time in the denominator to calculate incidence rates. Adjusted incidence per 100 patient exposure years (PEY) is the number of subjects with an event for whom person-time is available divided by the total PEY for each treatment group and multiplied by 100. Each subject's PEY was calculated as the last dose date minus the first dose date plus 1 divided by 365.25 days/year.

One PEY is the equivalent of one subject exposed to investigational product for one year. Two subjects who are exposed to investigational product for half a year together contribute one PEY. The total PEY of a treatment group is the sum of the person exposure years of each subject in that treatment group.

Table 115: Common ($\geq 5\%$ in Total OCA Group) Treatment-Emergent Adverse Events in Subjects Treated with OCA by Preferred Term- Double-Blind, Placebo-Controlled Studies in Subjects with PBC; Exposure Adjusted Rates (All Treated Subjects, N = 440)

Preferred Term, Events per 100 PEY	Total Placebo (N = 134)/ PEY = 84	OCA Titration ^a (N = 70)/ PEY = 67	OCA 10 mg OCA (N=131)/ PEY = 76	OCA 25 mg (N = 48)/ PEY = 10	OCA 50 mg (N = 57)/ PEY = 9	Total OCA ^b (N=306)/ PEY = 163
All TEAEs	141.4	96.8	157.0	465.9	610.2	176.9
Commonly Reported TEAEs^c						
Pruritus	64.2	58.1	107.3	396.5	523.0	128.3
Fatigue	21.4	16.4	31.4	29.7	65.4	27.0
Headache	26.1	17.9	17.0	49.6	98.1	23.9
Naso-pharyngitis	19.0	25.3	22.2	9.9	10.9	22.1
Nausea	16.6	6.0	15.7	29.7	87.2	16.6
Constipation	8.3	7.4	10.5	39.6	54.5	13.5
Diarrhea	14.3	3.0	14.4	39.6	54.5	13.5
Oropharyngeal pain	3.6	7.4	11.8	39.6	0	11.1
Cough	8.3	6.0	11.8	0	32.7	9.8

Summary of Clinical Safety, page 71-162

PEY = patient exposure years

^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 up-titrate to OCA 10 mg.

^b Total OCA in Pooled Double-Blind Studies includes all doses including titration, 10 mg, 25 mg, and 50 mg OCA

^c Commonly reported TEAEs are based on TEAEs with an incidence of $\geq 5\%$ based on crude incidence of TEAEs that occurred $\geq 5\%$ in the Total OCA column.

A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug.

Reviewer Comment:

There was dose dependent effect for the TEAEs of pruritus, fatigue, headaches, nausea, constipation, diarrhea and cough. The Applicant makes a note that in LTSE most (except pruritus and fatigue) of the AEs were no different than placebo arm. However, in this reviewer's opinion, discontinuation would make this hard to interpret; additionally not information on symptomatic management symptoms was performed.

8.3.5 Laboratory Findings

Please see clinical trial Study Design 6.1.1, 6.2, 6.3 for Laboratory findings AEs for details.

8.3.6 Vital Signs

There were no apparent meaningful differences in the mean (SD) change from Baseline for systolic blood pressure between placebo and OCA treatment arms for each of the time points assessed during the double-blind treatment period. There were no clinically significant or dose-related changes in systolic or diastolic blood pressure, or body temperature at any dose. With the exception of palpitations which were seen more in OCA treatment arm compared to placebo arm (1 patient).

8.3.7 Electrocardiograms (ECGs)

ECG parameters were evaluated using standard 12-lead ECGs in the double-blind studies 747-201, 747-202, and 747-301. Data was recorded using either paper or digital scans, only paper ECG scans were pooled since ECGs collected by different methodologies (paper vs digital) could not be merged. Digital ECGs were only performed in the Phase 3 study (747-301). As a result, assessments for 69 patients, including 22 patients for whom assessments were based on digital scans obtained during Study 747-301 are briefly described.

ECG data was collected at Baseline, Month 1, Month 2, and Month 3/ET in studies 747-201 and 747-202, and at Baseline, Month 6, and Month 12/ET in study 747-301. There were no patients who developed clinically significant abnormalities during treatment with OCA without having clinically significant abnormalities at baseline. Generally changes from baseline in RR, PR, QRS intervals were comparable to those observed in placebo-treated patients in the digital ECG arm.

8.3.8 QT

A Thorough QT (TQT) consult review is summarized below (Review by Huifang Chen, Quianyu Dang, October 21st, 2015)

No significant QTc prolongation effect of obeticholic acid (OCA 100 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between obeticholic acid (OCA 100 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the wo-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 2, indicating that assay sensitivity was established.

In this randomized, blinded, parallel study, 191 healthy patients received OCA 100 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 128

Table 116: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Obeticholic Acid (OCA 100 mg/Day) and the Largest Lower Bound for Moxifloxacin (FDA TQT Team Analysis)

Treatment	Day	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
OCA 100 mg	1	11	2.5	(0.7, 4.4)
OCA 100 mg	3	0	2.3	(0.2, 4.5)
OCA 100 mg	5	3	3.2	(0.4, 5.9)
Moxifloxacin 400 mg*	5	3	9.3	(5.5, 13.0)

* Multiple endpoint adjustment of 4 time points was applied.

Source: TQT reviewers consult

The selected supratherapeutic dose, 100 mg once-daily for 5 days, is reasonable. OCA 100 mg for 5 days is

considered the maximum tolerated dose. On Day 5, the predicted C_{max} ratios of total OCA, OCA, glyco-OCA and tauro-OCA relative to the steady-state exposure after a 10-mg dose are approximately 3.9, 7.2, 5.0 and 2.8.

Conclusions: There are no indication of a relationship between QT interval and OCA concentrations.

Pharmacodynamics

Cardiac Electrophysiology: The effect of Obeticholic acid on the QTc interval was evaluated in a Phase 1 randomized placebo and positive controlled double-blind, parallel thorough QTc study in 191 healthy patients. At the dose 10-fold the therapeutic dose for 5 days, OCA did not prolong QTc to any clinically relevant extent.

8.3.9 Immunogenicity

Not applicable

8.3.10 Long-term Safety Extension

The long terms safety extension, open label trials 747-201 LTSE, 747-202 LTSE and 747-301 LTSE were reviewed and have been summarized below. The discontinuations and SAEs for the DB trial 747-201, 747-202 and 747-301 are described in Section 6.1, 6.2 and 6.3 respectively.

The doses utilized in the LTSE are: OCA 5 mg, OCA 10 mg, OCA 15 mg, OCA 20 mg, OCA 25 mg, OCA 50 mg, OCA 3.3 mg, OCA 2.5 mg. The main AEs seen in LTSE are listed in the Table below.

Extent of Exposure (OCA doses ≤5 mg, 5-10 mg and >10 mg)

A total of 326 patients have been exposed to OCA during LTSE

Of which 79 patients have received OCA for 2 years.

Of the 326 patients 41 (13%) discontinued before trial completion

224 patients still remained enrolled in OCA open-label ongoing trials.

At the relevant doses (i.e., to be approved for use in PBC) the exposure is as follows:

Table 117: Summary of Treatment-Emergent Adverse Events by Phase (Double-Blind versus Long-Term Safety Extension Studies in Patients with PBC)

	Double-Blind, Randomized, Placebo-Controlled in Subjects with PBC ^a				LTSE Phase Data in Subjects with PBC ^b			
					Double-Blind Placebo		Double-Blind OCA	
	Placebo (N = 134)	OCA Titration (N = 70)	OCA 10 mg (N = 131)	OCA (N = 306)	OCA 5 mg (N = 66)	OCA 10 mg (N = 73)	OCA 5 mg (N = 126)	OCA 10 mg (N = 179)
All TEAEs n (%)	119 (89)	65 (93)	120 (92)	288 (94)	52 (79)	57 (78)	91 (72)	109 (61)
Total Number of TEAEs	632	471	637	1527	204	313	293	515
TEAE By Relationship, n (%)								
Not Related	48 (36)	23 (33)	24 (18)	52 (17)	17 (26)	10 (14)	63 (50)	33 (18)
Related	71 (53)	42 (60)	96 (73)	236 (77)	35 (53)	47 (64)	28 (22)	76 (42)
Subjects reporting at Least 1 SAE	5 (4)	11 (16)	8 (6)	25 (8)	5 (8)	4 (5)	9 (7)	6 (3)
Death	0	1 (1)	0	1 (<1)	0	0	0	1 (<1)

Table source: Copied and electronically reproduced from Summary of Clinical Safety, Page 133-162

Note: Subjects can be included in more than one treatment group in the LTSE Phase. A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug.

- ^a 747-201 Double-Blind Phase, 747-202 Double-Blind Phase, and 747-301 Double-Blind Phase. TEAEs that start in the double-blind phase are summarized by the randomized double-blind treatment groups.
- ^b 747-201 LTSE Phase, 747-202 LTSE Phase, 747-301 LTSE Phase. TEAEs that start on or after the first dose of LTSE OCA are summarized using the last dose the subject received (OCA 5 mg OCA, 10 mg) prior to the AE start date within the randomized double-blind treatment group.

Deaths One death occurred during the LTSE phase of Study 747-301; the narrative is described in Section 8.3.1

Patients who completed the full 3 months trial (747-201 and 747-202) were given an option to enroll in the LTSE trial. Depending on tolerability and clinical response, OCA could be titrated every 8 weeks from 10 mg to 25 mg to 50 mg.

The overall incidence of TEAEs in patients treated with OCA was somewhat lower in patients previously treated with OCA during the double-blind phase. Consistent with the double-blind phase, the incidence of TEAE of pruritus continued to remain higher than placebo.

Reviewer Comment:

Comparability of these patients across different LTSE patients is not possible relative to placebo arm because the trials used different durations and OCA exposure. For example patients in trial 747-201 and 747-202 continued to higher doses (i.e. OCA 25 mg and 50 mg), in LTSE phase. However, when the protocol was amended with capping off the dose at OCA 10 mg the placebo patients starting receiving OCA 5 mg for 3 months followed with up-titration of OCA dose to 10 mg.

The overall incidence of TEAEs in patients treated with OCA was somewhat lower for patients previously treated with OCA during the double-blind phase. One OCA-treated patient died (<1%) during the LTSE phase due to sepsis secondary to endocarditis. The death was assessed as not related to OCA (Section 8.4.1).

Table 118: Common (≥5% in Total OCA Group) Treatment-Emergent Adverse Events by Phase (Double-Blind versus Long-Term Safety Extension Studies in Subjects with PBC)

Preferred Term	Double-Blind, Randomized, Placebo-Controlled in Subjects with PBC ^a				LTSE Phase Data in Subjects with PBC ^b			
					Double-Blind Placebo		Double-Blind OCA	
	Placebo (N = 134)	OCA Titration (N = 70)	OCA 10 mg (N = 131)	OCA (N = 306)	OCA 5 mg (N = 66)	OCA 10 mg (N = 73)	OCA 5 mg (N = 126)	OCA 10 mg (N = 179)
All TEAEs	119 (89)	65 (93)	120 (92)	288 (94)	52 (79)	57 (78)	91 (72)	109 (61)
Pruritus	54 (40)	39 (56)	82 (63)	209 (68)	28 (42)	38 (52)	19 (15)	66 (37)
Fatigue	18 (13)	11 (16)	24 (18)	44 (14)	6 (9)	7 (10)	5 (4)	7 (4)
Headache	22 (16)	12 (17)	13 (10)	39 (13)	3 (5)	5 (7)	5 (4)	8 (4)
Nasopharyngitis	16 (12)	17 (24)	17 (13)	36 (12)	3 (5)	2 (3)	9 (7)	11 (6)
Nausea	14 (10)	4 (6)	12 (9)	27 (9)	5 (8)	5 (7)	5 (4)	9 (5)
Constipation	7 (5)	5 (7)	8 (6)	22 (7)	0	3 (4)	4 (3)	2 (1)
Diarrhea	12 (9)	2 (3)	11 (8)	22 (7)	2 (3)	7 (10)	2 (2)	4 (2)
Oropharyngeal pain	3 (2)	5 (7)	9 (7)	18 (6)	1 (2)	3 (4)	3 (2)	1 (<1)
Cough	7 (5)	4 (6)	9 (7)	16 (5)	3 (5)	2 (3)	4 (3)	6 (3)

Table source: Note: Subjects can be included in more than one treatment group in the LTSE Phase. A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug.

Although Study 205 PTP is categorized as a clinical pharmacology study, it is analyzed with the open-label, uncontrolled studies. Common TEAEs were defined based on the common TEAEs in the double-blind, placebo-controlled studies

^a Studies 747-201 Double-Blind Phase, 747-202 Double-Blind Phase, and 747-301 Double-Blind Phase. TEAEs that start in the double-blind phase are summarized by the randomized double-blind treatment groups.

^b Studies 747-201 LTSE Phase, 747-202 LTSE Phase, and 747-301 LTSE Phase. TEAEs that start on or after the first dose of LTSE OCA are summarized using the last dose the subject received (5 mg OCA, 10 mg OCA) prior to the AE start date within the randomized double-blind treatment group.

The exposure adjusted incidence Table is shown below. While it is reasonable to assess patients from exposure adjusted incidence reporting, the patient discontinuations have not been accounted in the stabilization of AE or no worsening of AE. Pruritus seems manageable. Again, not much signal can be identified at this time with exception that there are subset of patients who will tolerate OCA better and not have adverse event of pruritus or fatigue.

Table 119: Common (≥5% in Total OCA Group in Double-Blind Studies) Treatment-Emergent Adverse Events by Phase - Exposure Adjusted Incidence Double-Blind versus Long-Term Safety Extension Studies in Subjects with PBC)

Preferred Term ^a Events per 100 PEY	Double-Blind, Randomized, Placebo-Controlled in Subjects with PBC ^b				LTSE Phase Data in Subjects with PBC ^c			
					Double-Blind Placebo		Double-Blind OCA	
	Placebo (N = 134) PEY = 84	OCA Titration (N = 70) PEY = 67	OCA 10 mg (N = 131) PEY = 76	OCA (N = 306) PEY = 163	OCA 5 mg (N = 66) PEY = 38	OCA 10 mg (N = 73) PEY = 46	OCA 5 mg (N = 126) PEY = 77	OCA 10 mg (N = 179) PEY = 81
All TEAEs	141.4	96.8	157.0	176.9	138.5	124.6	118.5	135.3
Pruritus	64.2	58.1	107.3	128.3	74.6	83.1	24.7	81.9
Fatigue	21.4	16.4	31.4	27.0	16.0	15.3	6.5	8.7
Headache	26.1	17.9	17.0	23.9	8.0	10.9	6.5	9.9
Naso-pharyngitis	19.0	25.3	22.2	22.1	8.0	4.4	11.7	13.7
Nausea	16.6	6.0	15.7	16.6	13.3	10.9	6.5	11.2
Constipation	8.3	7.4	10.5	13.5	0	6.6	5.2	2.5
Diarrhea	14.3	3.0	14.4	13.5	5.3	15.3	2.6	5.0
Oropharyngeal pain	3.6	7.4	11.8	11.1	2.7	6.6	3.9	1.2
Cough	8.3	6.0	11.8	9.8	8.0	4.4	5.2	7.4

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PEY = patient exposure years

Footnote:

Subjects can be included in more than one treatment group in the LTSE Phase. A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug.

Common TEAEs were defined based on the common TEAEs in the double-blind, placebo-controlled studies (ISS SDS 8.2.8)

^a Incidence per 100 PEY. At each level of summation (overall, preferred term), subjects reporting more than one AE are counted only once per dose group.

^b Studies 747-201 Double-Blind Phase, 747-202 Double-Blind Phase, and 747-301 Double-Blind Phase. TEAEs that start in the double-blind phase are summarized by the randomized double-blind treatment groups.

^c Studies 747-201 LTSE Phase, 747-202 LTSE Phase, and 747-301 LTSE Phase. TEAEs that start on or after the first dose of LTSE OCA are summarized using the last dose the subject received (5 mg OCA, 10 mg OCA) prior to the AE start date within the randomized double-blind treatment group.

Long-term safety extension (LTSE) Phase Data in Patients with PBC:

Table 120: Treatment-Emergent Adverse Events of Special Interest by Phase at AESI Onset (Study 747-301 LTSE)

Special Interest Category, n (%)	747-301 LTSE Phase			
	Double-Blind Placebo		Double-Blind OCA	
	5 mg OCA (N=66)	10 mg OCA (N=40)	5 mg OCA (N=126)	10 mg OCA (N=110)
Hepatic Disorders	2 (3)	3 (8)	5 (4)	2 (2)
Pruritus	28 (42)	9 (23)	18 (14)	19 (17)

Table source: Adapted from Applicant's submission of Summary of Clinical safety page 142-162

Note: Subjects reporting more than one AE within a special interest category are counted only once per dose group.

Hepatic adverse event: that occurred during the LTSE phase included: new onset portal hypertension, ascites, esophageal variceal hemorrhage, hepatic encephalopathy, hepatic failure, spider nevus, liver disorder, liver tenderness, liver function test abnormal, hepatic pain, hepatic steatosis, and hyperbilirubinemia. prothrombin time prolonged, varices esophageal.

Pruritus Events included: pruritus and prurigo.

- a TEAEs that start in the double-blind phase are summarized by the randomized double-blind treatment groups.
- b TEAEs that start on or after the first dose of LTSE OCA are summarized using the last dose the subject received (5 mg OCA, 10 mg OCA) prior to the AE start date within the randomized double-blind treatment group.

The patients who experienced a related Adverse Events Leading to Investigational Product Withdrawal or Study Discontinuation the LTSE Program for PBC are as follows:

1. Pruritus: 13 patients experienced pruritus, leading to discontinuation from the trial.
2. Patient 133001 experienced mood swings and this reviewer remains concerned that OCA might be aggravating the underlying depression or increase depression/mood swing. This was noted in double blind 747-301 trial also (one patient had hallucinations, second patient had depression and third patient had worsening of depression of underlying depression)

Six patients experienced SAE in LTSE trials. After reading narrative reviewer considers these AE may be probably or possibly related to OCA treatment. The OCA treatment patients were discontinued in these patients:

1. Choledocholithiasis and Jaundice in Patient 012001 on OCA 25 mg (although at higher dose it is relevant as this AE has been seen across trials of different indications)
2. Patient 109004, Trial 747-301 LTSE: on OCA 10 mg arm experienced esophageal variceal bleed and hyponatremia
3. OCA dose 5 mg: Cholelithiasis
4. Patient 119008 (747-301 LTSE, on OCA 5 mg): Hepatic encephalopathy
5. Trial 747-202 LTSE on OCA 10 mg: Patient 012007: Hyperbilirubinemia
6. Trial 747-201 LTSE Patient 021004 on OCA 10 mg: Worsening of hepatic decompensation noted as onset of cirrhosis and hepatic encephalopathy.

Reviewer Comment:

Other SAEs that were seen in LTSE in different patients has been summarized these were noted to be not related to OCA use: small bowel obstruction, bradycardia, atrial flutter, worsening tricuspid regurgitation, ankle fracture, clavicular fracture, hip fracture, lung neoplasm, transient ischemic attack, endocarditis and sepsis with renal failure in one patient, parotitis, splenic artery aneurysms, Spondylolisthesis, digital ischemia, pneumonia, uterine fibroids, uterine prolapse, vaginal prolapse atelectasis, rib fracture, appendicitis, pyelonephritis, renal oncocytoma and one

patient had four SAEs including: aortic valve stenosis, renal failure and cardiac failure, are moderate to severe but likely not related to OCA treatment.

8.4 Review of PBC Study Group Data by the FDA

Since most patients are currently diagnosed and treated at an early stage of PBC, traditional clinical benefit points, such as the occurrence of death or liver transplantation will take years to assess. There have been multiple communications between the Applicant and the FDA for accepting surrogate endpoint for OCA approval since 2004. The data presented by the PBC Study group was supportive for the FDA's acceptance of use of the "Composite Surrogate Endpoint of ALP and TB" for accelerated approval and a confirmatory trial to show clinical benefit. The problem was identified when the NDA data were analyzed and found that majority patient's in the trial had "early stage disease" i.e., had normal TB. Therefore the endpoint on which the approval of OCA hinges on is "ALP" alone.

Overall, the design of the 747-301 pivotal study was deemed adequate from a statistical perspective, and the applicant's corresponding SAP was deemed appropriate. There were no statistical review issues identified for this pivotal trial that would preclude product approval. Although the design, statistical analyses and results of this trial appeared to be convincing and robust, the fundamental issue of this trial, and the NDA overall, was that the patients enrolled in this phase 3 study were not adequately comparable to the broad spectrum of PBC disease patients studied by the Global PBC Group. This rendered, as questionable, the overall adequacy/applicability of the pivotal trial's primary composite endpoint, which was to be used by the applicant as a basis for accelerated approval of this NDA. In particular, the primary composite endpoint was constructed based on the overall Global PBC study results and accordingly incorporated 12 month changes/reductions in both ALP and TB levels assuming elevated levels for each parameter. However, the enrolled trial patients primarily represented the early stage PBC disease population (whose patients only exhibit elevated ALP levels as specified by the Rotterdam PBC disease staging criteria) who were also concomitantly using UDCA.

Dr. Min, an independent statistical reviewer, who was purposefully requested not to study any 747-301 trial data in order to maintain a blinded analysis, conducted her review using the submitted patient-level Global PBC Study data to adequately match a clinically meaningful subset of Global PBC Study registry patients with the aforementioned majority of enrolled patients in study 747-301, while subsequently assessing whether a 12-month reduction in ALP levels alone could be reasonably likely to predict clinical outcome (i.e., death or liver transplant) in this PBC disease subpopulation. She ultimately confirmed the reasonable predictability of ALP, and the statistical team proposed a stratified cut-point to further confirm OCA's efficacy in the treatment of PBC trial patients. Please see Dr. Min's review for further details as well as analyses in DARRTs.

Exploratory Analysis of ALP response based on Stratified Endpoint Derived from Analysis of the Global PBC Study Group Data:

Several different cut points for ALP were applied retrospectively to patients in the 747-301 trial. Some of these cut points were selected because they could be linked to transplant-free survival within a 909 patient subset of the Global PBC Study that matched the characteristics of early stage disease of 181 patients enrolled trial 747-301. The relevant demographics and baseline characteristics comparing these non-concurrent cohorts (181 patients from study 747-301 and the 909 subjects from the Global PBC Study) are presented below in Table 133

Table 121: Demographic and Baseline Characteristics of the Comparable Cohorts from Study 747-301 and the Global PBC Study

	Study 747-301 (N = 181)	Global PBC Study (N = 909)
Age at Screening (years)		
N	181	909
Mean (SD)	55.5 (9.82)	54.4 (11.16)
Median	54.0	54.0
Min, Max	29, 81	24, 86
Age Category – n (%)		
< 65 years old	151 (83.4%)	730 (80.3%)
≥ 65 years old	30 (16.6%)	179 (19.7%)
PBC Diagnosis Age (years)		
N	181	909
Mean (SD)	47.1 (10.03)	52.9 (11.24)
Median	47.0	53.0
Min, Max	25, 78	23, 86
PBC Diagnosis Age Category – n (%)		
< 45 years old	72 (39.8%)	209 (23.0%)
≥ 45 years old	109 (60.2%)	700 (77.0%)
Diagnosis Year Category – n (%)		
< 1990	2 (1.1%)	244 (26.8%)
≥ 1990	179 (98.9%)	665 (73.2%)
Duration of PBC (years)		
N	181	909
Mean (SD)	8.5 (5.63)*	2.2 (3.79)*
Median	7.8	0.27
Min, Max	0.4, 32	0, 36
Duration of PBC Category – n (%)		
< 7.5 years	87 (48.1%)	821 (90.3%)
≥ 7.5 years	94 (51.9%)	88 (9.7%)
Gender – n (%)		
Female	165 (91.2%)	842 (92.6%)
Male	16 (8.8%)	67 (7.4%)
Race – n (%)		
Asian	2 (1.1%)	Race
Black or African American	2 (1.1%)	Not
Other	6 (3.3%)	Available
White	171 (94.5%)	

Source: Reviewer's Table generated from the 747-301 ADSL and 747-301 ADLIVER datasets along with the GPBC_FDA and GPBClab_FDA datasets.
 Note: Denominators for percentages are N. ** signifies available Total Daily UDCA Dose data for 687 subjects. There was unavailable Total Daily UDCA Dose data for 202 subjects.

Table 122: Demographic and Baseline Characteristics of the Comparable Cohorts from Study 747-301 and the Global PBC Study

	Study 747-301 (N = 181)	Global PBC Study (N = 909)
Geographical Region – n (%)		
Australia	9 (5.0%)	0
Europe	118 (65.2%)	639 (70.3%)
North America	54 (29.8%)	270 (29.7%)
Total Daily UDCA Dose (mg)		
N	181	687*
Mean (SD)	1091.2 (312.66)	809.5 (233.66)
Median	1000.0	750.0
Min, Max	300, 2700	250, 1500
ALP Concentration (U/L)		
N	181	909
Mean (SD)	311.3 (95.54)	478.7 (390.77)
Median	281.5	388.0
Min, Max	200, 746	2, 2545
ALP Concentration (×ULN)		
N	181	909
Mean (SD)	2.621 (0.8101)	3.365 (1.770)
Median	2.380	2.722
Min, Max	1.68, 6.31	1.67, 15.30
TB Concentration (µmol/L)		
N	181	909
Mean (SD)	9.6 (4.37)	7.0 (5.65)
Median	8.3	8.0
Min, Max	2, 25	0.2, 22
TB Concentration (×ULN)		
N	181	909
Mean (SD)	0.480 (0.2077)	0.579 (0.2043)
Median	0.425	0.571
Min, Max	0.08, 0.99	0.12, 1.00

Source: Reviewer's Table generated from the 747-301 ADSL and 747-301 ADLIVER datasets along with the GPBC_FDA and GPBClab_FDA datasets.

Note: Denominators for percentages are N. ** signifies available Total Daily UDCA Dose data for 687 subjects. There was unavailable Total Daily UDCA Dose data for 202 subjects.

Table 129 above shows there were areas of imbalance; however, given the non-concurrent nature of these cohorts, the data were reasonably balanced. Notably there is a difference in disease duration between the two groups with the duration of disease from the Global PBC Study group being shorter. This may be secondary to the way the data were collected and recorded in the Global PBC Study, or may represent a real difference. As presented previously in Section 4, many different cut point criteria that utilized ALP reduction alone after 12 months of observation in predicting transplant-free survival were explored and assessed within the 909 patient subset of the Global PBC Study. All of the explored/assessed ALP cut points at 12 months were applied to the comparable 181 ITT patients from study 747-301 by treatment group for re-analysis purposes. The responder analysis results from the most relevant cut points explored are presented in Table 135 below. Note that this group is 181 because the patients with elevated TB at baseline are excluded as well as the patients on monotherapy.

Table 123: Proportion of Patients who Achieved Response at Month 12 by Relevant Explored ALP Cut Point Criteria (Comparable ITT)

Explored Cut Points	10 mg OCA (N = 60)	OCA Titration (N = 60)	Placebo (N = 61)
ALP < 1.0×ULN at Month 12 – n (%)	5 (8.3%)	1 (1.7%)	0
ALP < 1.67×ULN at Month 12 – n (%)	37 (61.7%)	29 (48.3%)	11 (18.0%)
ALP < 2.0×ULN at Month 12 – n (%)	47 (78.3%)	41 (68.3%)	20 (32.8%)
Decrease in ALP ≥ 40% at Month 12 – n (%)	19 (31.7%)	18 (30.0%)	1 (1.6%)
Decrease in ALP ≥ 15% at Month 12 – n (%)	48 (80.0%)	46 (76.7%)	19 (31.2%)
ALP < 1.67×ULN and Decrease ≥ 40% at Month 12 – n (%)	17 (28.3%)	12 (20.0%)	0
ALP < 1.67×ULN and Decrease ≥ 15% at Month 12 – n (%)	35 (58.3%)	28 (46.7%)	7 (11.5%)
ALP < 2.0×ULN and Decrease ≥ 40% at Month 12 – n (%)	18 (30.0%)	15 (25.0%)	1 (1.6%)
ALP < 2.0×ULN and Decrease ≥ 15% at Month 12 – n (%)	43 (71.7%)	36 (60.0%)	10 (16.4%)
Stratified Cut Point at Month 12 – n (%)	26 (43.3%)	23 (38.3%)	3 (4.9%)

Source: Reviewer's Table generated from ADLIVER dataset.
 Note: Denominators for percentages are N.

It can be seen that applying all of these explored ALP cut points at 12 months resulted in consistent relative differences in response rates between the treatment groups. It should be noted that responder analysis results from ALP cut points assessed that were not presented within Table 135 above were also consistent (i.e., similar relative differences in response rates between the treatment groups).

The stratified ALP cut point at Month 12 was defined as follows:

If baseline ALP was $\geq 2.0 \times \text{ULN}$, then a patient would be designated as a responder if both of the following conditions were met:

- 12-Month value of ALP < $2.0 \times \text{ULN}$
- ALP reduction from baseline at Month 12 $\geq 40\%$;

Else if baseline ALP was $\geq 1.67 \times \text{ULN}$ but < $2.0 \times \text{ULN}$, then a patient would be designated as a responder if both of the following conditions were met:

- 12-Month value of ALP < $1.67 \times \text{ULN}$ **AND**
 - ALP reduction from baseline at Month 12 $\geq 15\%$.

This stratified ALP cut point at Month 12 was relatively the best performing cut point according to the analyses presented above in Section 4. Table 135 above was reproduced and expanded by applying this stratified ALP cut point to the 181 comparable ITT patients for re-analysis purposes.

Table 124: Proportion of Patients who Achieved Response at Month 12 using Stratified Cut Point (Comparable ITT)

Statistics	10 mg OCA (N = 60)	OCA Titration (N = 60)	Placebo (N = 61)
Response at Month 6 – n (%) [1]	25 (41.7%)	21 (35.0%)	1 (1.6%)
Corresponding 95% Wald CI	29.2%, 54.1%	22.9%, 47.1%	0.0%, 4.8%
<u>Baseline ALP $\geq 2.0 \times \text{ULN}$ – n (%)</u>	42 (70.0%)	47 (78.3%)	46 (75.4%)
ALP $< 2.0 \times \text{ULN}$ at Month 6 – n (%) [2]	30 (71.4%)	24 (51.1%)	8 (17.4%)
Decrease in ALP $\geq 40\%$ at Month 6 – n (%) [2]	10 (23.8%)	13 (27.7%)	0
ALP $< 2.0 \times \text{ULN}$ and Decrease $\geq 40\%$ at Month 6 – n (%) [2]	9 (21.4%)	11 (23.4%)	0
<u>Baseline ALP $\geq 1.67 \times \text{ULN}$ but $< 2.0 \times \text{ULN}$ – n (%)</u>	18 (30.0%)	13 (21.7%)	15 (24.6%)
ALP $< 1.67 \times \text{ULN}$ at Month 6 – n (%) [3]	17 (94.4%)	10 (76.9%)	3 (20.0%)
Decrease in ALP $\geq 15\%$ at Month 6 – n (%) [3]	16 (88.9%)	11 (84.6%)	1 (6.7%)
ALP $< 1.67 \times \text{ULN}$ and Decrease $\geq 15\%$ at Month 6 – n (%) [3]	16 (88.9%)	10 (76.9%)	1 (6.7%)
Response at Month 12 – n (%) [1]	26 (43.3%)	23 (38.3%)	3 (4.9%)
Corresponding 95% Wald CI	30.8%, 55.9%	26.0%, 50.6%	0.0%, 10.3%
<u>Baseline ALP $\geq 2.0 \times \text{ULN}$ – n (%)</u>	42 (70.0%)	47 (78.3%)	46 (75.4%)
ALP $< 2.0 \times \text{ULN}$ at Month 12 – n (%) [2]	29 (69.1%)	28 (59.6%)	9 (19.6%)
Decrease in ALP $\geq 40\%$ at Month 12 – n (%) [2]	13 (31.0%)	16 (34.0%)	1 (2.2%)
ALP $< 2.0 \times \text{ULN}$ and Decrease $\geq 40\%$ at Month 12 – n (%) [2]	12 (28.6%)	13 (27.7%)	1 (2.2%)
<u>Baseline ALP $\geq 1.67 \times \text{ULN}$ but $< 2.0 \times \text{ULN}$ – n (%)</u>	18 (30.0%)	13 (21.7%)	15 (24.6%)
ALP $< 1.67 \times \text{ULN}$ at Month 12 – n (%) [3]	16 (88.9%)	11 (84.6%)	6 (40.0%)
Decrease in ALP $\geq 15\%$ at Month 12 – n (%) [3]	14 (77.8%)	10 (76.9%)	2 (13.3%)
ALP $< 1.67 \times \text{ULN}$ and Decrease $\geq 15\%$ at Month 12 – n (%) [3]	14 (77.8%)	10 (76.9%)	2 (13.3%)

Source: Reviewer's Table generated from ADLIVER dataset.

Note: Denominators for percentages are N.

[1]: Response is defined by the Stratified ALP Cut Point.

[2]: The denominator for this calculation is the number of patients with Baseline ALP $\geq 2.0 \times \text{ULN}$.

[3]: The denominator for this calculation is the number of patients with Baseline ALP $\geq 1.67 \times \text{ULN}$ but $< 2.0 \times \text{ULN}$.

Table 131 shows that both OCA treatment groups demonstrated a difference in the proportion/percentage of patients achieving response at Month 12 when individually compared to placebo. This analysis was repeated utilizing the Completer and EE analysis sets and the conclusions were consistent. The ultra-worse-case imputation strategy, implemented by the FDA statistical reviewer as described above, did not impact the results. All of the previously presented analyses were re-conducted utilizing a baseline value that was the median of all pre-first dose measurements, and, separately, a traditional baseline definition (both approaches as described above); there was no impact on the results with either approach.

8.5 Analysis of Submission-Specific Safety Issues

A consult for assessment of fractures was done. No signal of increase in risk of fractures or bone density was detected. At this time, there are no concerns OCA increases the risk of fractures.

A COA team was consulted to assess VAS, 5-D -itch score.

Comorbidities in Patients with OCA Based on the medical history of patients with PBC, an analysis of comorbidities that occurred $\geq 20\%$ of patients was conducted. In this population, the following comorbidities were: hyperglycemia, osteoporosis, dyslipidemia, and sicca syndrome. These were well balanced across each treatment group.

8.5.1 Consults

1. Clinical Outcome Assessment Consult Summary:

DGIEP requested COA Staff to review three patient reported outcome (PRO) instruments that were used to assess pruritus severity and impact; to review these instruments as safety assessments.

The PRO safety assessments include:

- a. Itch domain of the PBC 40, which assesses impact of itching
- b. 5-D Pruritus Scale, total score assesses severity and impact of itching
- c. Pruritus Visual Analog Scale (VAS)

These instruments were not intended to support efficacy or comparative safety claims in labeling. Therefore, the review criteria were not the same as would be required for an efficacy claim. The COA reviewer (Dr. Daniels) focused on whether the instruments were fit-for-purpose in the context of this particular drug development program to assess worsening of itch as a safety assessment in the clinical trial.

Reviewer Comment: Scoring algorithms for PBC-40 and 5-D Pruritus Scale were documented in the references that the applicant provided.

The 5-D Pruritus total score is not the optimal measure to assess the severity of pruritus as it includes multiple dimensions, or subscales, (i.e., duration, degree, direction, disability, and distribution) that measure different aspects of the patient experience. There is a possibility that one dimension (subscale) may be driving the total score.

The development of the PBC-40 is described in published literature. It appears that the questionnaire was developed in an appropriate PBC population; however, it was developed only in a UK population. No documentation has been provided on cross-cultural equivalence. There are some concerns about the structure and format of the items in PBC-40, particularly combining symptoms and non-symptoms in the same domain. The questionnaire also consists of distal attributes that may not be impacted by treatment. Additional details will be needed to determine if content validity has been established in this scale.

Conclusion: The COA reviewer states these instruments appear fit-for purpose for this drug development program. However, it is unclear what threshold of change represents clinically meaningful deterioration on each of these scales. The COA Staff deferred to the Clinical team to review the overall safety profile of this drug development program.

2. A Division of Pediatric and Maternal Health consult was requested. Summary is noted in Section 8.7.2.
3. A summary of TQT consult can be found in Section 8.3.9
4. A consult was placed for the Division of Bone, Reproductive and Urologic Products (DBRUP) for recommendation on assessment of fractures. A summary of the consult can be found in Section 6.3.12. The reviewer noted that OCA is unlikely to cause these fractures. In the clinical settings, the standard medical care should be appropriate to assess bone monitoring, so specific post-marketing bone monitoring is warranted with OCA use. The following is the summary in which this reviewer has additional comments embedded. For details, the reader is referred the clinical consult review memo placed in DARRTs by clinical reviewer from DBRUP (Dr. John T. Stinson).

Demographic Based Risk of Adverse Events:

Age at PBC Diagnosis

Patients diagnosed at a younger age (females <30 years of age) have been shown to have a higher rate of adverse outcomes. There were only 4 patients who were <30 years enrolled in this trial precluding any definitive conclusions on differences in AE's.

Age

82% of patients enrolled in the trial were <65 years in age. The incidence of treatment emergent SAEs was similar overall in OCA-treated patients within both age sub-groups (<65 years and ≥65 years of age). The small number of ≥65 year old patients preclude definitive conclusions.

A comparison of the incidence of TEAEs in patients who were diagnosed <50 years old versus those that were diagnosed later in life (≥50 years old) was performed and the difference in AEs are as follows:

- Incidence of pruritus was similar across all age groups but higher was in OCA treated patients than placebo treated patients.
- Patients treated with OCA also had a higher incidence of fatigue compared to placebo arm treated patients. There was no clear meaningful interpretation in the incidence of fatigue in OCA-treated patients by age at diagnosis.
- An increase in hepatic disorders was observed in younger patients treated with OCA 50 mg compared with those who were older (11% and 5%, respectively).

Reviewer Comment: The sample size is too small to make any meaningful interpretation.

The duration of treatment in all 3 double-blind placebo controlled studies is considered too short and the number of patients exposed too small to derive meaningful conclusions regarding the incidence of cardiovascular events.

BMI

The incidence of TEAEs by BMI subgroup could not be assessed given the disparity in patient numbers that prohibits definitive conclusions (of the 306 patients treated with OCA, 242 had a BMI <30 kg/m² while 63 patients had a BMI of ≥30 kg/m²).

Sex

In the double-blind period, 306 patients with PBC were treated with OCA, of which 27 (9%) were male, similar to the 10 (7%) of the 134 placebo patients. A similar proportion of male and female patients experienced TEAEs, 96% of males and 94% of females.

Three male OCA-treated patients experienced 5 SAEs; 3 of these events were cardiovascular in nature, 1 SAE resulted in death and the other 2 SAEs were clavicle fracture and angioedema (allergic reaction to a food product). Applicant states, none of the SAEs were considered to be related to investigational product. No OCA-treated female patients experienced a cardiac disorder SAE, while one female patient treated with placebo had an SAE of sick sinus syndrome. *Numerically, there were higher SAEs in males; few SAEs were unrelated to OCA use (death, clavicle fracture, angioedema).*

Race The majority of patients who participated in the double-blind studies were white patients versus non-white patients (296 patients versus 10 patients); 95% and 80% of patients, respectively, experienced a TEAE. *Again, the small sample size precludes any meaningful interpretation.*

Reviewer Comment: In the pivotal trial, the majority of patients enrolled in Europe and the primary efficacy endpoint for the trial was seen in patients enrolled at European sites. American sites did not show a statistically significant difference, but numerically higher number of patients achieved the primary efficacy endpoint. It is important to note that no single site influenced or drove the overall study results.

Hepatic Impairment

The Applicant did not conduct a study in PBC patients who have had hepatic decompensation events.

(b) (4)

Reviewer Comment:

1. *Patients treated with higher doses of OCA (25 mg and 50 mg) experienced higher liver related AEs, including serious reactions i.e., hepatic decompensations.*
2. *FDA proposed recommendations for dose adjustment which the Applicant accepted. Since the confirmatory trials also exclude patients with hepatic decompensation events, a PMR is required to assess the safety of use in these patients.*

Disease Severity:

Elevated total bilirubin in PBC is associated with worse clinical prognosis (Lammers 2014). Of 306 patients treated with OCA, 284 patients had baseline total bilirubin \leq ULN and 22 patients had baseline total bilirubin $>$ ULN. Of 134 patients treated with placebo, 124 had baseline total bilirubin \leq ULN and 10 had baseline total bilirubin $>$ ULN. Again, the sample size is too small to make a safety conclusion in these 2 groups.

Renal impairment:

No specific clinical studies have been conducted in patients with renal impairment. The radiolabelled studies in healthy volunteers indicate $<$ 3% OCA is eliminated in the urine, suggesting minimal renal elimination.

Safety as Monotherapy: To assess OCA as monotherapy Applicant conducted a phase 2 trial, for 85 days (747-201).

Reviewer Comments: The reviewer notes, there were no serious adverse events reported even at higher doses (OCA 50 mg) when OCA was used a monotherapy. The reason for this is not clear but as seen in trial 747-202, patients experienced more AEs and SAEs at higher doses (OCA 25 mg and OCA 50 mg). A PMR has been requested to assess OCA as monotherapy in order to better understand this apparent low incidence of SAEs.

UDCA Use and Treatment-Emergent Adverse Events - Double-Blind, Placebo-Controlled Studies in Patients with PBC:

In Trial 747-202, all patients were on UDCA and in trial 747-301 a total of 93% patients were on UDCA. No conclusions can be made for safety on the basis of sample size. However, when the data was pooled for trials 747-201 and 747-301, there is adequate data to support accelerated approval but additional safety and clinical efficacy data are needed post-marketing.

Concomitant Medication Use During the Trial:

Bile acid sequestrants were commonly used to manage treatment emergent pruritus. A total of 104 OCA-treated patients received BAS compared with 17 placebo-treated patients. A similar incidence in overall discontinuations was observed in OCA-treated patients who received BAS and those who did not receive BAS (14% and 16%, respectively). The incidence of pruritus leading to study discontinuations was similar in patients who received BAS versus those who did not (13% and 10%, respectively)

8.6 Specific Safety Studies/Clinical Trials

Please see Section 6: Review of Relevant Individual Trials Used to Support Efficacy for discussion of safety and adverse events noted during the trials.

8.7 Additional Safety Explorations

Not applicable.

8.7.1 Human Carcinogenicity or Tumor Development

There were two patients who developed tumors during the PBC drug development program, one patient developed lung adenoma and other patient developed colon adenoma. This must be kept in mind while assessing the confirmatory trial.

In a 2-year oral carcinogenicity study in Crl:CD1 mice, there were no drug-related neoplastic findings at OCA doses up to 25 mg/kg/day. In an oral carcinogenicity study in Crl:CD(SD) rats of up to 2 years in duration, 20 mg/kg/day OCA caused an increase in the incidence of benign granulosa cell tumors in the ovaries and benign granular cell tumors in the cervix and vagina of female rats. There were no drug-related neoplastic findings in male rats at OCA doses up to 20 mg/kg/day.

8.7.2 Human Reproduction and Pregnancy

The limited available human data on the use of obeticholic acid during pregnancy is not sufficient to inform a drug-associated risk. In animal reproduction studies, no developmental abnormalities or fetal harm was observed when pregnant rats or rabbits were administered obeticholic acid during the period of organogenesis at exposures approximately 13 times and 6 times, respectively, at the maximum recommended human dose (MRHD) of 10 mg.

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

There is no information on the presence of obeticholic acid in human milk, the effects on the breast-fed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for obeticholic acid and any potential adverse effects on the breastfed infant from obeticholic acid or from the underlying maternal condition.

Division of Pediatric and Maternal Health Review: The DPMH recommends a postmarketing pregnancy monitoring study or substudy within a patient registry to monitor the outcomes of pregnant women and infants exposed to Ocaliva. This study should include both prospective and retrospective data collection, if possible, for better follow up of pregnancy and infant outcomes.

8.7.3 Pediatrics and Assessment of Effects on Growth

PBC has been reported extremely rarely in pediatric patients. Therefore, no clinical studies were conducted in pediatric PBC patients by the Applicant.

(b) (4)

8.7.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There have been no reports of overdose during the development program. In the event of an overdose OCA administration should be interrupted. Due to enterohepatic recirculation, the effective half-life of OCA is approximately 4 days. Therefore, stopping OCA treatment will not immediately result in decreased plasma levels. The Applicant states that it is anticipated that hepatic levels will decrease in conjunction with decreasing plasma levels. Although it appears reasonable that treatment with BAS is appropriate in an overdose situation, there is no evidence to support such treatment. Clinical signs and symptoms should be monitored with particular attention to signs and symptoms of liver toxicity.

Based on the mechanism of action of OCA, there is no pharmacologic evidence suggestive of abuse potential for OCA. In nonclinical studies, OCA did not appear to pass the blood-brain barrier and no specific animal or human studies have been conducted to evaluate the abuse potential of OCA.

Data on liver enzymes following controlled withdrawal of OCA (during the follow-up period of Phase 2 studies), indicate that there was no evidence of rebound following withdrawal or discontinuation of investigational product. For example, there did not appear to be a worsening beyond baseline levels or biochemistries including bilirubin or ALP, immediately after cessation of OCA.

8.8 Safety in the Postmarket Setting

8.8.1 Safety Concerns Identified Through Postmarket Experience

There is no post-marketing experience because this drug has not yet been approved.

8.8.2 Expectations on Safety in the Postmarket Setting

PMRs have been issued to assess safety of use in populations that were not enrolled in the phase 2 and phase 3 trials (advanced stage disease and the PBC patients with hepatic decompensations).

8.9 Additional Safety Issues From Other Disciplines

None

8.10 Integrated Assessment of Safety

Please see Section 6.1 for assessment of safety for trial 747-301.

9 Trial 747-302 (Phase 3b/4 Trial)

9.1 Trial Description:

Study Design:

Study 747-302 is a Phase 3b, double-blind, randomized, placebo-controlled, multicenter, multinational (in approximately 170 investigational sites) study evaluating the effect of OCA on clinical outcomes in patients with PBC.

The primary objective of this study is to assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in patients with PBC as measured by time to first occurrence of any of the following adjudicated clinical events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥ 15 (this indicates the need for liver transplantation)
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
 - Variceal bleed
 - Encephalopathy (as defined by a West Haven score of ≥ 2)
 - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (i.e., diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities.

The above composite event endpoint is the pre-specified primary endpoint of this study, and every previously specified/listed clinical event for participating patients will be adjudicated by an independent committee (see below for more details regarding this adjudication).

The key secondary objectives of this study are to assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary composite event endpoint as listed above and to also include liver-related death. Note that the formally pre-specified key secondary endpoints are listed in the order that follows:

- Time to first occurrence of MELD score ≥ 15
- Time to Liver Transplant or Death (all cause)
- Change from Baseline in TB at end of study (EOS)
- Change from Baseline in ALP at EOS

An additional secondary study objective is instituted, for supportive analysis purposes, to provide further comparative evaluation of the clinical benefit of OCA. The effect of OCA will be compared to historical controls (separately and in combination) on liver-related clinical outcomes (i.e., death or liver transplant). These historical controls will be made available from the historical PBC observational databases of the United Kingdom (UK)-PBC and Global PBC Study Groups. Each database includes approximately 5000 patients with long-term follow-up.

After a patient provides informed consent, each patient will undergo screening assessments to determine study eligibility. Note that screening will be conducted over a 1 to 8 week period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and TB values. The two most significant inclusion criteria for determining study eligibility pertain to the aforementioned pre-treatment assessed ALP and TB values along with allowing concomitant usage of UDCA while participating in this study. Specifically, these two inclusion criteria, respectively, are as follows:

- Have at least one (i.e., “and/or”) of the following qualifying biochemistry values (representing the mean of all available screening values)
 - ALP $> 5 \times \text{ULN}$ and/or,
 - TB $> \text{ULN}$ but $\leq 3.0 \times \text{ULN}$

Taking UDCA for at least 12 months (with a stable dose for at least 3 months) prior to study start, or unable to tolerate UDCA (i.e., no UDCA usage for at least 3 months) prior to study start.

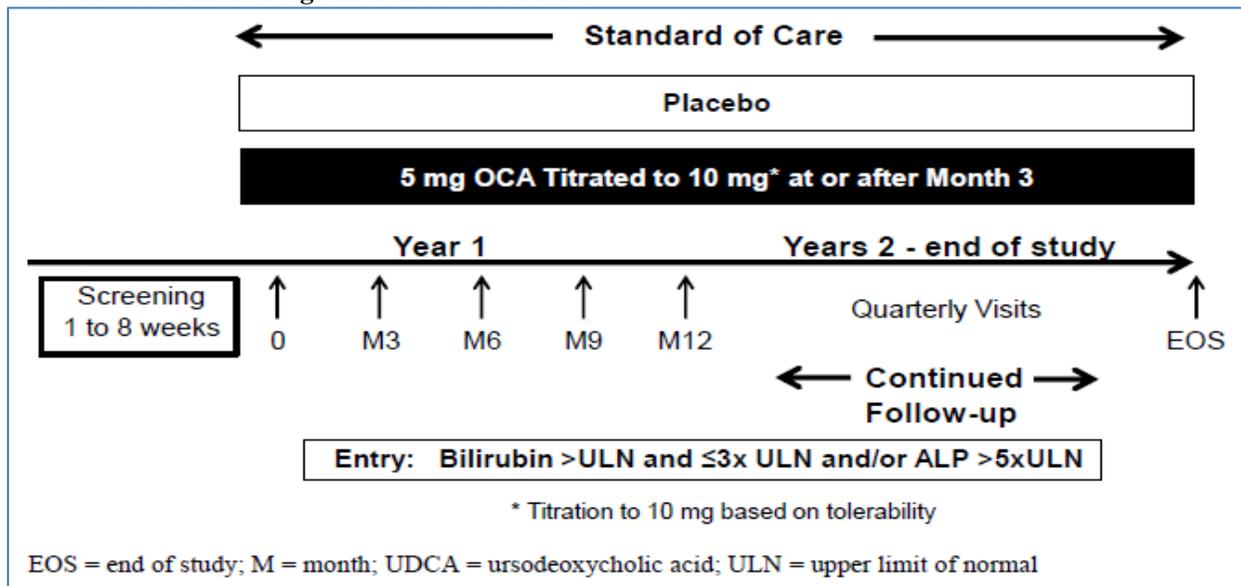
The most significant exclusion criteria for determining study eligibility are the presence of clinical complications of PBC or clinically significant hepatic decompensation, including:

- History of liver transplant, current placement on a liver transplant list, or current MELD score > 12 . Patients who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria
- Cirrhosis with complications, including history (within the past 12 months) or presence of:
 - Variceal bleed
 - Uncontrolled ascites
 - Encephalopathy
 - Spontaneous bacterial peritonitis
- Known or suspected hepatocellular carcinoma
- Prior transjugular intrahepatic portosystemic shunt procedure
- Hepatorenal syndrome (type I or II) or screening (visit 1 or 2) serum creatinine $> 2 \text{ mg/dL}$ ($178 \text{ } \mu\text{mol/L}$).

Investigational product will be initiated at 5 mg OCA or matched placebo, and after 3 months of treatment the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the 3-month visit or any subsequent study visit based on tolerability. For those patients that increased their dose to 10 mg, they may decrease their dose to 5 mg at any time during the study as considered appropriate (e.g., tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the investigator as soon as possible with the goal that all patients remain on the 10 mg dose if tolerated. Patients will be seen at quarterly visits for the duration of the study, and it is estimated that individual patients will be followed up for a minimum of 6 years. The study is event driven and the total duration of treatment will be determined by the time to accrue 121 total primary endpoint events. Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 121 events (from both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on the time to clinical outcomes. In addition, based on the remaining assumptions stated above, it is estimated that approximately 350 patients (i.e., 175 per treatment arm) will be enrolled to attain 121 events. A minimum of 6 years patient participation; and total trial duration of 8 years is anticipated (based upon number of clinical events).

Throughout the execution of this protocol, an independent data and safety monitoring committee (DSMC) will operate according to a DSMC Charter. It will provide an ongoing, independent, and expert review of the safety data in order to provide risk management during the conduct of the study. Note that there are no formally planned interim analyses for this study.

Table 125: Schematic Diagram of the 747-302 Trial



Source: Figure 1 from page 28 of the 747-302 protocol (Amendment 1: April 29, 2015)

Reviewer Comments:

ALP is not on the causal pathway of PBC (i.e., ALP is not on the immune-pathogenesis pathway of the disease); therefore, a confirmatory trial is being conducted to prove the clinical benefit of OCA use in patients. However, ALP is elevated, secondary to bile duct injury and ductopenia/ductular reaction, and is a surrogate of disease progression.

1. The enrollment criteria includes ALP > 5 × ULN and/or, TB > ULN but ≤ 3.0 × ULN; adequate number of patients with elevated TB must be enrolled to provide adequate power for analyzing the results.
2. Patients with ALP > 5 × ULN represent high risk patients and such patients are likely to progress to a clinical endpoint sooner than patients with lower levels of ALP, but there are no published literature to support this threshold qualifies patients for advanced disease stage.
3. The phase 3 trial population (early stage disease patients), in whom the clinical benefit must also be proven, is currently not included in the confirmatory trial and this should be discussed with the Applicant.
4. Patients with hepatic decompensations events are excluded from the trial, therefore a PMR has been requested to assess safety and efficacy of OCA in this population.
5. One component of the composite primary endpoint, "Time to first occurrence of MELD score ≥ 15" must be revised to assure an increase in MELD score is truly a clinically meaningful increase. In trial 747-301, there were increases in MELD scores that were not clinically meaningful, and were interpreted by the Applicant as relevant increases in MELD scores (please see Section 6 for details). The Applicant must repeat the laboratory parameters (i.e., Serum creatinine, INR and total bilirubin) and confirm that the MELD score is truly increased and that this rise is not related to cofounders such as use of anti-coagulants, disease-related vitamin K deficiency due to use of antibiotics, one time isolated increase in INR, laboratory errors etc..
6. If a patient does not achieve a biochemical response with OCA using an adequate dose and duration, the patient must be considered a non-responder for possible discontinuation from the trial.
7. The protocol should address how dyslipidemia (low HDLc) will be managed in patients and also how long will that patient be observed prior to discontinuation from therapy.

8. *The Applicant stated that since the trial is multi-center and includes clinical sites in countries where the Applicant has not yet sought marketing approval, patient retention should be less challenging in these countries. Additionally, the Applicant thinks they will also be able to retain patients in the trial in the countries in which it is approved by utilizing reduced cost incentives.*

The Statistical analysis plan for this trial has been reviewed by Benjamin Vali, statistical reviewer, for details the reader is referred to his review in DARRTs.

10 Advisory Committee Meeting and Other External Consultations

Questions to the Committee:

1. **DISCUSSION:** Discuss whether the evidence from the Global PBC Study Group data presented today on the reduction in alkaline phosphatase (ALP) supports the use of alkaline phosphatase as a surrogate endpoint reasonably likely to predict clinical benefit in the treatment of early stage Primary Biliary Cirrhosis (PBC). Comment on the strength of evidence that supports the stratified responder criteria that were developed by the FDA statistical team's review of the Global PBC Study Group data.

Committee Discussion: There was a general consensus that the evidence from the Global PBC Study Group data presented on the reduction in alkaline phosphatase (ALP) supports the use of alkaline phosphatase as a surrogate endpoint reasonably likely to predict clinical benefit in the treatment of early stage Primary Biliary Cirrhosis (PBC). Some members commented that while ALP is the only surrogate endpoint in early stage of the disease, bilirubin should also be considered. A committee member commented that the evidence is persuasive in using stratified responder analysis from a statistical standpoint, but that the decision on accepting ALP as a surrogate reasonably likely to predict clinical benefit is both a clinical determination and a statistical determination. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss the appropriateness of the Applicant's proposed dosage schema, i.e., a starting dose of 5 mg of obeticholic acid (OCA) with up titration to 10 mg after 3 months. Include in your discussion and dosing recommendation the safety and tolerability of obeticholic acid in addition to the biochemical response (alkaline phosphatase reduction).

Committee Discussion: The majority of the committee agreed that the starting dose of 5 mg with titration to 10 mg after 3 months is reasonable given the data presented. Members commented that the increased incidence of hepatic adverse events at the 10 mg dose is concerning, but may be acceptable given the benefit provided by OCA, and that phase 4 trials should attempt to better characterize hepatic adverse events, as well as monitor HDL cholesterol levels. Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Discuss the adequacy of the data to support the use of OCA as monotherapy for patients intolerant to ursodeoxycholic acid (UDCA). Include in your discussion whether the applicant should be required to further study the use of OCA as monotherapy.

Committee Discussion: Committee members commented that the data supporting the use of OCA as monotherapy appear sufficient, but further study in patients who are non-responders to UDCA or intolerant of UDCA is warranted. Please see the transcript for details of the committee discussion.

4. **DISCUSSION:** Discuss the adequacy of the data to support the use of OCA in moderately advanced and advanced stages of PBC. Include in your discussion whether the applicant should be required to further study the use of OCA in moderately advanced and advanced stages of PBC.

Committee Discussion: *The majority of the committee agreed that the data are limited on the use of OCA in moderately advanced stage PBC patients, and absent in advanced stage PBC patients, to support the use of OCA in moderately advanced and advanced stages of PBC, while some members supported the use of OCA in moderately advanced PBC patients, but not advanced stage PBC patients. Please see the transcript for details of the committee discussion.*

5. **DISCUSSION:** Discuss whether the available evidence (i.e., PK modeling, dose response) supports the FDA's proposed dosing of OCA in PBC patients with moderately advanced (Child-Pugh B) and advanced (Child-Pugh C) cirrhosis.

Committee Discussion: *The majority of the committee commented on the insufficient data to support dosing of OCA in PBC patients with moderately advanced (Child-Pugh B) and advanced (Child-Pugh C) cirrhosis and called for additional studies. However, there were panel members who commented that there are sufficient data to justify treatment of patients with moderately advanced cirrhosis, but insufficient data to support treatment of patients with advanced cirrhosis. Please see the transcript for details of the committee discussion.*

6. **DISCUSSION:** Discuss the pros and cons of continuing OCA treatment in patients who do not demonstrate reduction in alkaline phosphatase after 6 months of treatment on a maximally tolerated dose. Take into consideration the risk of alterations in lipid profile vs. the potential for benefit.

Committee Discussion: *The majority of the committee agreed that it may be premature to discontinue therapy at 6 months despite no reduction in ALP. One member opined that therapy should be continued to 12 months, and if there is still no reduction in ALP, then treatment should be discontinued. Please see the transcript for details of the committee discussion.*

7. **VOTE:** Taking into account the risks and benefit of OCA in the population studied, is there substantial evidence to support accelerated approval of OCA for the proposed indication, based on its effect on alkaline phosphatase?

YES: 17 NO: 0 ABSTAIN: 0

Committee Discussion: *The committee unanimously agreed that there is substantial evidence to support accelerated approval of OCA for the proposed indication, based on its effect on alkaline phosphatase. Members commented on the efficacy of the drug when compared to placebo, favorable benefit to risk ratio, and the ability of the drug to address an unmet need. Please see the transcript for details of the committee discussion.*

8. **DISCUSSION:** Discuss what if any changes in the enrollment criteria or design of the postmarketing confirmatory trial would be necessary to obtain any additional information that you think is necessary for full/regular approval of OCA for the treatment of PBC.

Alternatively, discuss what additional post-marketing studies you think would be necessary to obtain any data or information that has not been provided.

Committee Discussion: *The committee members suggested obtaining additional data including, but not limited to, use of OCA as monotherapy in patients who do not respond to or are intolerant of UDCA, pharmacokinetic profile of OCA in advanced stage PBC patients, long term cardiovascular/lipid profile effects of OCA, a broader spectrum of patients with PBC (i.e., patients with abnormal bilirubin levels, not just abnormal ALP levels) and safety and efficacy of OCA in compensated cirrhotic patients. Committee members also commented on the difficulty of getting patients to participate in a post-marketing placebo-controlled trial given that the drug will be commercially available. Some members also expressed concerns regarding the possible use of an historical control in the confirmatory trial. Please see the transcript for complete details of the committee discussion.*

11 Labeling Recommendations

11.1 Prescribing Information

The labeling negotiations were ongoing at the time of this review. For final labeling agreements, see the approved label for OCA.

11.2 Patient Labeling

The labeling negotiations were ongoing at the time of this review. For final labeling agreements, see the approved label for OCA.

11.3 Nonprescription Labeling

Not applicable.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable

13 Postmarketing Requirements and Commitments

PMR 3057-1

A randomized, placebo-controlled clinical trial to evaluate the safety, efficacy and steady-state pharmacokinetics of obeticholic acid in patients with primary biliary cholangitis/cirrhosis (PBC) with Child-Pugh Classes B and C hepatic impairment, including Child-Pugh Class C patients with varying levels of MELD scores. You may conduct this as a stand-alone trial, or in a subset of patients in your confirmatory trial (PMR#3057-3).

The Applicant chose to address this PMR in a subset of patients in their ongoing confirmatory trial 747-302. The timeline proposed are as follows:

(b) (4)

Final Protocol Submission: **12/01/2016**

Study/Trial Completion: **12/01/2022**

Final Report Submission: **04/01/2023**

PMR 3057-2

A randomized, placebo-controlled trial to evaluate the safety and efficacy of OCALIVA used as monotherapy in patients with primary biliary cholangitis/cirrhosis (PBC) who are intolerant of or non-responsive to ursodeoxycholic acid (UDCA). Enroll patients across all stages of PBC, by the Rotterdam criteria. You may conduct this as a stand-alone trial or in a sub-set of patients in your confirmatory trial (PMR # 3057-3).

Applicant chose to address PMR 3057-2 in a subset of patients in the confirmatory trial 747-302.

The proposed timelines are as follows:

(b) (4)

Final Protocol Submission: **12/01/2016**

Study/Trial Completion: **12/01/2022**

Final Report Submission: **04/01/2023**

PMR 3057-3

A randomized, double-blind, placebo-controlled trial to verify and describe that OCALIVA-induced reductions in alkaline phosphatase and/or total bilirubin are associated with improvements in the composite clinical endpoint of

progression to cirrhosis, death, transplant, decompensation events and hepatocellular cancer. Your ongoing trial (747-302) should be revised to include patients across the spectrum of stages of primary biliary cholangitis/cirrhosis (PBC), including patients with early, moderately advanced and advanced PBC by the Rotterdam criteria, and should be adequately powered to demonstrate benefit in each stage.

Draft Amended Protocol Submission: 09/01/2016

Final Protocol Submission: 12/01/2016

Study/Trial Completion: 12/01/2022

Final Report Submission: 04/01/2023

Applicant agrees to will revise the ongoing confirmatory trial 747-302 to address PMR 3057 1-3 including patients across the spectrum of stages of primary biliary cholangitis/cirrhosis (PBC), evaluations of safety/efficacy in patients PBC with Child-Pugh Classes B and C hepatic impairment and safety/efficacy of OCALIVA monotherapy in patients with PBC.

This ongoing study is intended to support a conditional approval in the EU as well as accelerated approval in the US. The Applicant wishes to have agreement across both regions before finalizing the protocol. The Applicant anticipates submitting the draft amended protocol to FDA and EMA in concert with the response to d180 questions (anticipated Q32016) with a final protocol by end of the year.

PMR 3057-4

Develop a formulation that would allow once daily dosing for patients with hepatic impairment. Conduct a (b) (4) study in healthy patients to characterize the relative bioavailability of the new formulation. Submit your (b) (4) study protocol once you have a new formulation.

Final Protocol Submission: 11/01/2017

Study/Trial Completion: 04/01/2019

Final Report Submission: 08/01/2019

Applicant intends to develop and characterize the relative bioavailability of formulation(s) to allow for once daily dosing for patient with hepatic impairment. Applicant states, the formulation development (including biopharmaceutics considerations, e.g., dissolution) will take ~18 months and will serve as a prerequisite for the finalization of the (b) (4) study protocol. The proposed timelines currently assume enrollment of a significant number of patients with hepatic impairment to enable adequate measurement of plasma concentrations of OCA and its conjugates.

14 Appendices

14.1 Financial Disclosures

The statements on financial disclosures (Form FDA 3454) were reviewed. A total of 107 investigators who participated in the phase 2 and 3 trials (747-201, 747-202, and 747-301) certified that they had no financial arrangements as defined in 21 CFR 54.2. All investigators and sub investigators who participated in these trials responded to the Applicant's request to complete the Form FDA 3454.

Although, unrelated to the PBC patient population, Intercept Pharmaceuticals conducted a trial in a different patient population and has submitted the following disclosure:

Disclosure: Financial Interests and Arrangements of Clinical Investigators, FDA Form 3455 – (b) (6)

He served as an investigator in Protocol 747-203, An Exploratory Study of INT-747 in Patients with Type 2 Diabetes and Presumed Nonalcoholic Fatty Liver Disease. (b) (6) received \$ 40,425 (\$ 38,925 for the trial and \$ 1,500 as consultation fees) for payment and consultation. However, to minimize potential bias, the Intercept Pharmaceuticals staff was blinded to the treatment assignments of patients and the SAP was finalized prior to database lock.

Covered Clinical Study (Name and/or Number): 747-201

Table 126: Financial Disclosures

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>18 Investigators</u>		
Number of investigators who are Applicant employees (including both full-time and part-time employees): <u>No</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>None</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>No</u> Significant payments of other sorts: <u>No</u> Proprietary interest in the product tested held by investigator: <u>No</u> Significant equity interest held by investigator in S Applicant of covered study: <u>No</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 747-202

Table Continued: Financial Disclosures

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>30 Investigators</u>		
Number of investigators who are Applicant employees (including both full-time and part-time employees): <u>No</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>No</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>No</u> Significant payments of other sorts: <u>No</u>		

Proprietary interest in the product tested held by investigator: <u>No</u>		
Significant equity interest held by investigator in S		
Applicant of covered study: <u>No</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 747-301

Table Continued: Financial Disclosures

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>59 investigators</u>		
Number of investigators who are Applicant employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>None</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>No</u>		
Significant payments of other sorts: <u>No</u>		
Proprietary interest in the product tested held by investigator: <u>No</u>		
Significant equity interest held by investigator in S		
Applicant of covered study: <u>No</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

14.2 Detailed Events of Pre-Submission Regulatory History

IND 63,307 was submitted on 27 January 2006, received Orphan drug designation on 9th April 2008, fast track designation in the treatment of PBC on May 27, 2014, and rolling review was granted on 18 November 2014. Presubmission regulatory activities related to this submission included approximately 5 formal face-to-face meetings between the Applicant and FDA. In addition, there were a number of teleconferences and written correspondences exchanged during the development program. The Phase 3 protocol was developed in communication with the FDA and is consistent with the PBC Study Group analyses of data, including the general study

design, patient population, and primary efficacy endpoint. In order to support global registration, the Applicant included an evaluation of efficacy at month 12 (FDA recommendation) with a confirmatory trial which is underway. Details of the Pre-Submission regulatory history are below.

Details of the Pre-Submission Regulatory History

18 November 2004: Type B, Pre-IND meeting, with written responses only, the Applicant asked questions pertaining to non-clinical, CMC and clinical issues for further development of INT-747 for liver fibrosis from different indications. The Division requested further nonclinical studies prior to submitting an IND.

27 January 2006: IND-63,307 Obeticholic acid (OCA) for treatment of primary biliary cirrhosis new IND was submitted and deemed safe to proceed.

1 February 2007: Type B, End of Phase (EOP) 1, face to face meeting, purpose was to discuss the study design and phase 2 endpoints for the development of INT-747 for the treatment of primary biliary cirrhosis and nonalcoholic steatohepatitis.

PBC questions:

1. Applicant proposed the use of alkaline phosphatase as a surrogate primary endpoint for Phase 2 and 3 trials. The Division remains concerned about using ALP as a primary endpoint. However, the Division recommended the Applicant to conduct a phase 2 trial using ALP as endpoint, and then have further discussion with the Division after the results of this trial were available. The Division also stated, from regulatory perspective, if ALP was used as surrogate, then application would qualify for Subpart H submission.
2. The Division encouraged the Applicant to collect data on: for non-invasive serum biomarkers for liver fibrosis and noninvasive monitoring for liver stiffness, and to also perform pre- and post-liver biopsy on a subset of patients
3. Quality of life measures for fatigue and pruritus as primary endpoint in phase 3 were proposed by Applicant. FDA recommended using adequate and well-constructed patient reported outcomes (PRO) to assess fatigue and pruritus prior to embarking on phase III trial, and stated the PBC-40 instrument may be acceptable, if the recall time was shorter.
4. A single 6 month Phase 3 trial to demonstrate efficacy for the required surrogate endpoint was proposed by the Applicant. The Division stated Phase 3 trial would require clear, robust demonstration of statistically meaningful effect from a large multicenter trial in a diverse population. A single trial results should be consistent across study subgroups, centers, and show evidence of effect on multiple study endpoints with highly significant results, with extremely low p-values. The Division further clarified, even if approved under accelerated approval pathway with short term exposure (i.e. 1 to 2 years), the Applicant must demonstrate proof of clinical benefit with a commitment to acquire long term safety and efficacy data (i.e. 5 years) in a post-marketing trial.

5. [REDACTED] (b) (4) The Division stated for safety profile total number of patients included in trial, incidence of serious adverse events, and the length of exposure are all important variables, and directed the Applicant to ICH-E1A guidelines for recommendations.

9 April 2008: Orphan Designation

Primary biliary cirrhosis is a rare disease, with only one approved medical treatment option, i.e. ursodeoxycholic acid (UDCA) with which ~40% patients do not respond. In patients who do not respond to UDCA, the disease progresses leading to either a liver transplantation or death. Given, the unmet medical need OCA (6 α -ethyl-chenodeoxycholic acid) as the active moiety was granted orphan drug designation (#07-2532) on 09 April 2008 for the treatment of primary biliary cirrhosis. Therefore submission of a pediatric assessment or a waiver is not required for this New Drug Application.

6 October 2009: Type C meeting, teleconference, the purpose of the meeting was to discuss the statistical analysis plan (SAP) for the soon to be completed dose-ranging study (Protocol 747-202). The questions asked by Applicant were related to the choice of the primary study endpoint, use of absolute or percent change in ALP. The Division recommended that the Applicant perform both analyses. The Division also recommended that the analysis be performed on the intent-to-treat (ITT) population. Other details of the SAP were also discussed.

5 August 2010: Type B, EOP 2, face-to-face meeting; the purpose of the meeting was to discuss the clinical development plan. The Applicant proposed using ALP as a primary surrogate endpoint for clinical outcomes in PBC patients in a phase 3 trial. The Division did not agree that ALP alone would be considered an appropriate endpoint to demonstrate efficacy and that it was an applicant's responsibility to show that the proposed surrogate endpoint is reasonably associated with clinical benefit when requesting approval under the Subpart H program. The Division encouraged Intercept to maintain a dialog for their clinical program as they work to find a viable surrogate endpoint.

Further the Division remained concerned as most of the data and justification for proposed surrogate (i.e., ALP) were related to the prognosis in patients with PBC who were taking UDCA. Division stated PBC is slowly progressive disease, and in patients with early disease clinical benefit may not be demonstrable with short duration trials. The Division recommended that Intercept enroll patients with moderate and severe disease so that clinical outcome may be measured during the trials. The adverse event of pruritus as seen in Phase 1 and Phase 2 trials was concerning and additional information on safety would be necessary.

The Applicant proposed stratification of patients for enrollment as follows:

1. Prior response with UDCA: ALP > 3 x upper limit of normal (ULN) or aspartate aminotransferase (AST) > 2 x ULN or bilirubin > 1.0 mg/dL (17 μ mol/L) 1 year post UDCA (Paris Criteria) OR,
2. OCA monotherapy, patients who are not on UDCA.

FDA recommended that stratification of PBC patients will be important due to small trial which additionally has several confounders. To provide balanced representation stratification should be done at enrollment and patients with features of overlap syndrome and autoimmune hepatitis must be excluded.

Additionally, the Division recommended a liver biopsy be performed in a subset of patients for evaluating the improvement, deterioration, or no deterioration in selected markers of liver injury on histology. The patient subset should include an adequate number of patients from each category: with or without biochemical, and clinical improvement. The Applicant proposed and the Division encouraged the use of transient elastography and enhanced liver fibrosis blood markers as exploratory endpoints. The Division encouraged Intercept to consider longer duration of treatment so that interpretable data can be generated from the trial(s). The Division also communicated that OCA was intended for long term treatment of PBC. Therefore it is the responsibility of the Applicant to show adequate safety during the clinical drug development program based on the occurrence and detection of adverse events (AE profile).

Since the bile acids are excreted mainly via the fecal route and <0.25% of the drug is excreted via urine (mainly as glycine conjugate).

The Applicant proposed not perform a study in renally impaired patients. The FDA agreed to this during this meeting. The Division informed the Applicant, TQT study is a requirement that the Applicant must fulfil. The Division stated in addition to UDCA and OCA plasma levels, the in vitro CYP450 studies with OCA (bile salt analogue) studies; the interaction between OCA and bile salt export pump activity (i.e. drug bile interaction) in-vitro studies be conducted. CMC questions pertaining to bioavailability and bioequivalence; proposed concurrent validation plan and qualified impurities were clarified by CMC.

Accelerated approval with a post-marketing commitment to conduct a placebo controlled confirmatory trial was proposed by the Applicant and the Division provided guidance on a path forward.

The pharmacology and toxicology studies submission timelines were discussed.

2 February 2011: Type A, face to face meeting (stalled development) with the Applicant. The purpose of the meeting was to discuss the acceptability of an alkaline phosphatase-based endpoint to support marketing approval. Data to support the use of ALP was provided by the Applicant prior to the meeting. Expert hepatologists attended the meeting, some via teleconference, and others were present during the face-to-face meeting. No agreement for using ALP as a primary endpoint could be reached during this meeting. The Applicant stated that reliance on clinical outcome endpoints in a clinical development plan in this setting will be prohibitive because the progression of the disease is slow. The Applicant proposed the composite endpoint (consistent with Toronto III and Mayo II criteria) as a primary endpoint for phase 3 trial

Entry: ALP $\geq 1.67 \times$ ULN or bilirubin > normal

Endpoint: ALP < $1.67 \times$ ULN and > 15% fall and bilirubin \leq normal

FDA stated $1.67 \times$ elevation of alkaline phosphatase (ALP) as responder criteria and the survival curves of these exploratory analyses indicate group difference for patients managed with concomitant UDCA. Additionally, correlation between the responder definition and survival presented in the dataset only indicates an association relationship between alkaline phosphatase and death; it may not be able to fully address the influences of the disease on death (the primary endpoint). The Division stated that the data does not definitively establish the proposed endpoint as an adequate surrogate reasonably likely to predict clinical benefit. The Division remained concerned the outcome trial may not be completed successfully post-approval of a short term efficacy trial as part of subpart H approval requirements.

FDA continued to have concerns about the appropriate patient population that had the potential to be the best responders to the effects of OCA treatment. (b) (4)

The numbers of patients exposed to OCA required for Phase 3 trial and marketing approval were again discussed. The Division reiterated because PBC is chronic disease requiring a lifelong treatment, it will be important to have safety data to review on patients that have received therapy for at least one year.

4 October 2011: Type A, teleconference meeting to discuss the trial design for Phase 3 program.

FDA expressed concern due to considerable variability in performance of biomarkers (ALP and bilirubin) in predicting the long term outcomes of the patients with PBC. The Division planned to review this with the senior management during a regulatory briefing within the agency to gain guidance about an appropriate path forward. To facilitate this conversation, the Division requested Intercept to obtain data from the Toronto PBC database for review.

The Division expressed concerns that a placebo-controlled confirmatory trial may not be feasible, especially if the drug is approved under Subpart H prior to the initiation of a confirmatory trial. The Division noted that patients enrolled in a placebo-controlled trial who have changes in biomarkers would likely withdraw from the study to receive open-label treatment.

FDA stated the population to be studied was not clearly defined. FDA was concerned population in either extreme (mild or severe) of the disease spectrum may lead to uninterpretable results. And this is exactly what happened with this trial. Majority patients enrolled in pivotal trial were early stage disease patient.

FDA recommended Intercept to re-evaluate the natural history data for PBC to obtain information to guide the study design including specific population (length of disease, baseline biochemical characteristics, response to previous treatments), event rates for each clinical endpoint based on the population to be studied which can be used to guide the length of study required (b) (4)

FDA recommended Intercept conduct additional dose ranging trial for OCA to evaluate lowest effective dose.

FDA recommended Intercept to identify the metabolic pathway and food effect of OCA for understanding the overall clinical pharmacology.

11 October 2011: An informal teleconference meeting was held to discuss Phase 3 program for INT-747 for the treatment of PBC. The Division agreed with Intercept's plan to form a collaborative group and evaluate the data from multiple studies to understand better the relationship between biochemical markers and clinical outcomes in PBC. The Division requested a representative of the Division participate in the review of this PBC data along with the Collaborative Study group.

The Division reiterated that the acceptability of the use of a surrogate endpoint under 21CFR 314.50 Subpart H will depend on the outcomes reported by the review and analyses of the data by the collaborative group. The Division agreed to work with Intercept Pharmaceuticals to help develop potential confirmatory study designs if they choose to pursue Subpart H approval.

August 30th, 2013: Written response sent by the Division to the Applicant answering the questions pertaining the statistical analysis plan (SAP), and the answers to the clinical questions about collecting data for analyses by the collaborative group.

Applicant proposed validation of the surrogate based on the retrospective analyses conducted by the collaborative PBC Study group.

FDA stated that validation of a biomarker that is a surrogate for clinical benefit would require analyses based upon the data from a randomized, controlled trial in which a treatment effect has been established. The current retrospective data collection and planned analyses may provide support for use of a surrogate that is reasonably likely to predict clinical benefit under 21CFR314.50 Subpart H. The Division facilitated and encouraged Intercept to bring the collaborative Study group together (Global PSC Group) for promoting the scientific understanding the disease, its progression and pertinent biochemical changes and for collection of natural history data for PBC globally. The FDA stated the deficiencies in the case report form that failed to collect information on many aspects of PBC including:

1. Identification and characterization of clinical differences between patients who are not taking UDCA versus the patients who are

taking UDCA. Characterization of patients whether they failed to tolerate UDCA or never received the UDCA, and if so an explanation of why the patients are not receiving this standard of care for adequate interpretation of the data.

2. Concomitant medications use such as statins, cholestyramine that may be helpful in interpretation of the analyses
3. To include the data on absence or presence of pruritus and fatigue in analyses planned to identify populations that can be predicted to achieve measurable clinical outcomes in specific time intervals.
4. The Division stated that the liver biopsy staging must be clarified. What histological classification system will be used? Finally, the key components must be captured for biopsy interpretation such as interface hepatitis, ductopenia, cholestasis, fibrosis, bile stasis location etc. The Division also encouraged the Applicant to collect genetic polymorphism, serum markers of fibrogenesis when known.

Additionally, the Division also stated because of heterogeneity of the disease severity, stratification of analyses by disease severity will be helpful for this retrospective data collection. A potential surrogate must be correlated with endpoints and clinical outcomes such as transplant free survival. The Division suggested subgroup analysis:

1. Analyze by stage of PBC (asymptomatic, symptomatic or pre-terminal), presence of autoimmune overlap, AMA status, presence of cirrhosis (compensated or decompensated), and by Child-Pugh Score and MELD score in patients with cirrhosis.
2. Analyze by response to UDCA at 1 year (propose definitions of UDCA response).
3. Pathological evidence of poor prognosis such as interface hepatitis, and degree of fibrosis, when known.
4. In addition, assess the influence of UDCA dose on outcomes relative to the Alkaline Phosphatase (ALP) and Bilirubin categories surmised to predict clinical outcome (i.e. $ALP < 1.67 \times ULN$ or $ALP > 1.67 \times ULN$; Normal Bilirubin or Abnormal Bilirubin).
5. Additional analyses will impact the interpretability of the data and may facilitate identification of a population of patients which will most likely benefit from treatment (i.e. an "enrichment population") and/or achieve a clinical outcome in a shorter period on study.
6. Finally, as an additional sensitivity analysis for the secondary outcome (i.e. liver related transplant or death), assume that the cause of death is not liver-related if the patient died and the cause of death was not available on the CRF.

14 November 2013: Type C teleconference meeting, the purpose of the meeting was to gain concurrence regarding proposed CMC registration plans for Obeticholic acid.

January 29, 2014: Type C, face to face meeting; the purpose of the meeting was to discuss the confirmatory trial design for Obeticholic acid (OCA) in the treatment of primary biliary cirrhosis.

The Division remained concerned that with accelerated approval under CFR 314 subpart H of OCA there may be difficulty with recruitment and retention of patients in the confirmatory placebo-controlled long-term trial. Additional concerns include problems with interpreting the natural historical control data and relying on historical control as a comparator. The Division stated in order to make meaningful treatment comparisons with OCA utilizing historical control the Applicant must show the diagnosis; patient characteristics and disease progression are consistent between Global PBC study patients and the patients participating in the placebo controlled trial. The Division recommended considering the use of Hepatic Venous Pressure Gradient (HVPG) in a subset of patients to provide critical supportive data to support the efficacy of OCA at an earlier time point.

The Division agreed with the proposed high risk patient population ($APL > 5 \times ULN$ and/or bilirubin $> ULN$ to $\leq 3 \times ULN$) in the confirmatory trial, based on PBC study group data assuming that the analysis is accurate.

The Division asked Intercept to clearly define each component of the composite clinical endpoints such as ascites, hepatic encephalopathy ("HE") (e.g., new onset of episode of "HE" with a West Haven score of 2 or greater, new onset of ascites requiring diuretics and/or paracentesis). The definition of the components of the endpoint must be precise and interpretable across centers. For example clarify "hospitalization for" is necessary to define a decompensation event, and clearly establish the criteria such as length of stay to define hospitalization (b) (4)

The Division stated Intercept should demonstrate the comparability between the historical control subjects and the placebo group patients in the double-blinded randomized trial, with respect to both patient characteristics and disease progression. The Division also stated that it will be a review issue whether these two groups of patients can be combined for efficacy analysis purposes. The Division asked Intercept to consider the feasibility and appropriateness of a head-to-head trial with ursodeoxycholic acid (URSO) as a confirmatory trial. Although this trial design maybe very complex and potentially lengthy.

10 February 2014

Type C meeting: the purpose of the meeting was to discuss the sufficiency of the pharmacology (nonclinical and clinical) and toxicology registration package for obeticholic acid (OCA) for the treatment of patients with PBC.

The Division agreed to the drug interaction studies, and in addition, recommended that Intercept evaluate the impact of renal impairment on the exposure of OCA and its conjugates in patients with End Stage Renal Disease (ESRD) not yet on dialysis post NDA approval.

27 February 2014: Type C meeting with written response only; the purpose of the meeting was to discuss Statistical analysis plan and clinical endpoints for safety analyses to adequately describe safety profile of OCA.

The primary efficacy endpoint and the secondary efficacy endpoint analyses were discussed. The Division also advised on handling dropouts and missing data.

In addition, the Division clarified the proposed safety analyses may not be sufficient in case of biliary obstruction. A relationship between bilirubin and transaminases increase (greater than 2 time baseline) after receiving OCA, or patients who drop out as a result of abnormal transaminases and or bilirubin must be analyzed. These patients must be followed until elevated enzymes return to baseline or a competing etiology is found. The resolution of these enzyme elevations post OCA discontinuation must be reported as an adverse reaction.

May 27, 2014: The Division concluded INT-747 (Obeticholic acid) met the required criteria for Fast Track Designation.

24 June 2014: Type C, teleconference meeting; the purpose of the meeting was to discuss and reach a consensus with the Division regarding the biocomparability of OCA, including the final design of the open-label, two-way cross-over trial to demonstrate biocomparability between the clinical and commercial formulations of OCA.

22 July 2014: Type C, teleconference meeting, the purpose of the meeting was to discuss the design of the confirmatory trial to support accelerated approval for Obeticholic acid (OCA) in the treatment of primary biliary cirrhosis. The discussion was focused on statistical analysis plan for confirmatory trial.

18 November 2014: Type B, face to face meeting, the purpose of the meeting was to discuss the content and format of the planned

Clinical Review
Ruby Mehta
NDA 207999
OCALIVA [Obeticholic acid (OCA)]

NDA submission for INT-747 (Obeticholic acid) for the treatment of primary biliary cirrhosis (PBC) for patients with inadequate response to or unable to tolerate ursodeoxycholic acid.

A rolling submission and review of portions of the planned NDA for INT-747 was granted

(b) (4)



14.3 Severity of Pruritus

Pruritus assessment tools in PBC Trials, these tools have been shown below:

Adverse event reporting

Itch domain of the PBC 40, which assesses impact of itching

5-D Pruritus Scale, total score assesses severity and impact of itching

Pruritus Visual Analog Scale (VAS)

Figure 54: Severity of Pruritus

Pruritus Grade	Clinical Description of Severity for Pruritus	Titration Eligibility Guideline
1 = Mild	Generally localized; causing no limitation of usual activities or minimal sleep disturbance; the subject may have experienced slight discomfort. Medicinal intervention was not indicated.	Yes
2 = Moderate	Intense or widespread; causing some limitation of usual activities or sleep disturbance; the subject may have experienced annoying discomfort. Medicinal intervention may have been indicated.	Yes; use clinical judgment
3 = Severe	Intense or widespread and interfering with activities of daily living, ie, causing inability to carry out usual activities, or severe sleep disturbance; the subject may have experienced intolerable discomfort. Medicinal intervention was typically indicated.	No

Figure 55: Pruritus VAS

Intercept pharmaceuticals		PRURITUS VAS QUESTIONNAIRE		<input type="checkbox"/> Day 0
PROTOCOL NO. 747-301		SITE NUMBER <input style="width: 30px; height: 20px;" type="text"/>	SUBJECT IDENTIFIER <input style="width: 30px; height: 20px;" type="text"/>	<input type="checkbox"/> Week 2
		Screening Number <input style="width: 30px; height: 20px;" type="text"/>	SUBJECT INITIALS <input style="width: 30px; height: 20px;" type="text"/>	<input type="checkbox"/> DB Month: _____
		first middle last		<input type="checkbox"/> DB Month 12/LTSE Day 1
				<input type="checkbox"/> LTSE Month: _____

PRURITUS VISUAL ANALOG SCALE (Page 1 of 1) — To be completed by the patient

Severity: Draw a line anywhere on the scale that best represents the severity of your itching:
 (See example below):

No itching Worst possible itching

0 2 4 6 8 10

Example:

No itching Worst possible itching

0 2 4 6 8 10

Patient, please initial and date: _____

day			month			year					

Figure 56: PBC-40

Intercept 747-301		Intercept 747-301 eCRF		Day 0
PBC 40 Questionnaire				
0	Was PBC-40 questionnaire completed by the subject?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<i>To be completed by the patient. For each statement, please circle the response that comes closest to how you feel.</i>				
Can you say how often the following statements about digestion and diet applied to you IN THE LAST FOUR WEEKS?				
1	I was able to eat what I liked	<input type="checkbox"/> Never	<input type="checkbox"/> Rarely	
		<input type="checkbox"/> Sometimes	<input type="checkbox"/> Most of the time	
		<input type="checkbox"/> Always		
2	I ate or drank only a small amount, and still felt bloated	<input type="checkbox"/> Never	<input type="checkbox"/> Rarely	
		<input type="checkbox"/> Sometimes	<input type="checkbox"/> Most of the time	
		<input type="checkbox"/> Always		
3	I felt unwell when I drank alcohol	<input type="checkbox"/> Never	<input type="checkbox"/> Rarely	
		<input type="checkbox"/> Sometimes	<input type="checkbox"/> Most of the time	
		<input type="checkbox"/> Always	<input type="checkbox"/> Did not apply/ never drink alcohol	
And IN THE LAST FOUR WEEKS, how often did you experience any of the following?				
4	I had discomfort in my right side	<input type="checkbox"/> Never	<input type="checkbox"/> Rarely	
		<input type="checkbox"/> Sometimes	<input type="checkbox"/> Most of the time	
		<input type="checkbox"/> Always		
5	I had dry eyes	<input type="checkbox"/> Never	<input type="checkbox"/> Rarely	
		<input type="checkbox"/> Sometimes	<input type="checkbox"/> Most of the time	
		<input type="checkbox"/> Always		
6	My mouth was very dry	<input type="checkbox"/> Never	<input type="checkbox"/> Rarely	
		<input type="checkbox"/> Sometimes	<input type="checkbox"/> Most of the time	
		<input type="checkbox"/> Always		
7	I had aches in the long bones of my arms and legs	<input type="checkbox"/> Never	<input type="checkbox"/> Rarely	
		<input type="checkbox"/> Sometimes	<input type="checkbox"/> Most of the time	
		<input type="checkbox"/> Always		
Some people with PBC experience itching. How often did you experience itching IN THE LAST FOUR WEEKS? If you did not itch, please circle Did not apply.				
8	Itching disturbed my sleep	<input type="checkbox"/> Never	<input type="checkbox"/> Rarely	
		<input type="checkbox"/> Sometimes	<input type="checkbox"/> Most of the time	
		<input type="checkbox"/> Always	<input type="checkbox"/> Did not apply/ no itch	
9	I scratched so much I made my skin raw	<input type="checkbox"/> Never	<input type="checkbox"/> Rarely	
		<input type="checkbox"/> Sometimes	<input type="checkbox"/> Most of the time	
		<input type="checkbox"/> Always	<input type="checkbox"/> Did not apply/ no itch	
10	I felt embarrassed because of the itching	<input type="checkbox"/> Never	<input type="checkbox"/> Rarely	
		<input type="checkbox"/> Sometimes	<input type="checkbox"/> Most of the time	
		<input type="checkbox"/> Always	<input type="checkbox"/> Did not apply/ no itch	
Fatigue can also be a problem for many people with PBC. How often did the following statements apply to you IN THE LAST FOUR WEEKS?				
11	I had to force myself to get out of bed	<input type="checkbox"/> Never	<input type="checkbox"/> Rarely	
		<input type="checkbox"/> Sometimes	<input type="checkbox"/> Most of the time	

PBC 40: Figure (continued)

Intercept 747-301		Intercept 747-301 eCRF	Day 0
			<input type="checkbox"/> Always
25	Because of PBC, I had difficulty keeping up with conversations		<input type="checkbox"/> Never <input type="checkbox"/> Rarely <input type="checkbox"/> Sometimes <input type="checkbox"/> Most of the time <input type="checkbox"/> Always
26	Because of PBC, I found it difficult to concentrate on anything		<input type="checkbox"/> Never <input type="checkbox"/> Rarely <input type="checkbox"/> Sometimes <input type="checkbox"/> Most of the time <input type="checkbox"/> Always
27	Because of PBC, I found it difficult to remember what I wanted to do		<input type="checkbox"/> Never <input type="checkbox"/> Rarely <input type="checkbox"/> Sometimes <input type="checkbox"/> Most of the time <input type="checkbox"/> Always
Now some more general statements about how PBC may be affecting you as a person. How much do the following statements apply to you?			
28	Because of PBC, I get more stressed about things than I used to		<input type="checkbox"/> Not at all <input type="checkbox"/> A little <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much
29	My sex life has been affected because of PBC		<input type="checkbox"/> Not at all <input type="checkbox"/> A little <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much <input type="checkbox"/> Does not apply
30	Having PBC gets me down		<input type="checkbox"/> Not at all <input type="checkbox"/> A little <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much
31	I feel I neglect my family because of having PBC		<input type="checkbox"/> Not at all <input type="checkbox"/> A little <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much <input type="checkbox"/> Does not apply
32	I feel guilty that I can't do what I used to do because of having PBC		<input type="checkbox"/> Not at all <input type="checkbox"/> A little <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much
33	I worry about how my PBC will be in the future		<input type="checkbox"/> Not at all <input type="checkbox"/> A little <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much
These statements relate to the possible effects of PBC on your social life. Thinking of your own situation, how much do you agree or disagree with them?			
34	I sometimes feel frustrated that I can't go out and enjoy myself		<input type="checkbox"/> Strongly agree <input type="checkbox"/> Agree <input type="checkbox"/> Neither agree nor disagree <input type="checkbox"/> Disagree <input type="checkbox"/> Strongly disagree
35	I tend to keep the fact that I have PBC to myself		<input type="checkbox"/> Strongly agree <input type="checkbox"/> Agree <input type="checkbox"/> Neither agree nor disagree <input type="checkbox"/> Disagree <input type="checkbox"/> Strongly disagree
36	I can't plan holidays because of having PBC		<input type="checkbox"/> Strongly agree <input type="checkbox"/> Agree <input type="checkbox"/> Neither agree nor disagree <input type="checkbox"/> Disagree <input type="checkbox"/> Strongly disagree
37	My social life has almost stopped		

PBC-40 Figure (Continued)

Intercept 747-301		Intercept 747-301 eCRF	Day 0
		<input type="checkbox"/> Strongly agree <input type="checkbox"/> Agree <input type="checkbox"/> Neither agree nor disagree <input type="checkbox"/> Disagree <input type="checkbox"/> Strongly disagree	
The next section is about the impact that PBC may be having on your life overall. How much do you agree or disagree with them?			
38	Everything in my life is affected by PBC	<input type="checkbox"/> Strongly agree <input type="checkbox"/> Agree <input type="checkbox"/> Neither agree nor disagree <input type="checkbox"/> Disagree <input type="checkbox"/> Strongly disagree	
39	PBC has reduced the quality of my life	<input type="checkbox"/> Strongly agree <input type="checkbox"/> Agree <input type="checkbox"/> Neither agree nor disagree <input type="checkbox"/> Disagree <input type="checkbox"/> Strongly disagree	
40	I can still lead a normal life, despite having PBC	<input type="checkbox"/> Strongly agree <input type="checkbox"/> Agree <input type="checkbox"/> Neither agree nor disagree <input type="checkbox"/> Disagree <input type="checkbox"/> Strongly disagree	
41	Date PBC 40 Questionnaire Completed	<input type="text"/> / <input type="text"/> / <input type="text"/> month day year	
Optional Comments			

Figure 57: 5-D Pruritus Scale

Intercept 747-301		Intercept 747-301 eCRF		Day 0
5-D Descriptive Pruritus Scale				
0	Was 5-D Descriptive Pruritus Scale completed by the subject?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
1. Duration:				
1	During the last 2 weeks, how many hours a day have you been itching?	<input type="checkbox"/> Less than 6 hrs/day <input type="checkbox"/> 6-12 hrs/day <input type="checkbox"/> 12-18 hrs/day <input type="checkbox"/> 18-23 hrs/day <input type="checkbox"/> All day		
2. Degree:				
2	Please rate the intensity of your itching over the past 2 weeks	<input type="checkbox"/> Not present <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe <input type="checkbox"/> Unbearable		
3. Direction:				
3	Over the past 2 weeks has your itching gotten better or worse compared to the previous month?	<input type="checkbox"/> Completely resolved <input type="checkbox"/> Much better, but still present <input type="checkbox"/> Little bit better, but still present <input type="checkbox"/> Unchanged <input type="checkbox"/> Getting worse		
4. Disability: Rate the impact of your itching on the following activities over the last 2 weeks				
4	Sleep	<input type="checkbox"/> Never affects sleep <input type="checkbox"/> Occasionally delays falling asleep <input type="checkbox"/> Frequently delays falling asleep <input type="checkbox"/> Delays falling asleep and occasionally wakes me up at night <input type="checkbox"/> Delays falling asleep and frequently wakes me up at night		
5	Leisure/ Social	<input type="checkbox"/> Never affects this activity or N/A <input type="checkbox"/> Rarely affects this activity <input type="checkbox"/> Occasionally affects this activity <input type="checkbox"/> Frequently affects this activity <input type="checkbox"/> Always affects this activity		
6	Housework/ Errands	<input type="checkbox"/> Never affects this activity or N/A <input type="checkbox"/> Rarely affects this activity <input type="checkbox"/> Occasionally affects this activity <input type="checkbox"/> Frequently affects this activity <input type="checkbox"/> Always affects this activity		
7	Work/School	<input type="checkbox"/> Never affects this activity or N/A <input type="checkbox"/> Rarely affects this activity <input type="checkbox"/> Occasionally affects this activity <input type="checkbox"/> Frequently affects this activity <input type="checkbox"/> Always affects this activity		
5. Distribution:				
<i>Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.</i>				
8	Head/Scalp	<input type="checkbox"/>		
9	Face	<input type="checkbox"/>		
10	Chest	<input type="checkbox"/>		
11	Abdomen	<input type="checkbox"/>		
12	Back	<input type="checkbox"/>		
13	Buttocks	<input type="checkbox"/>		
14	Thighs	<input type="checkbox"/>		
15	Lower Legs	<input type="checkbox"/>		
16	Tops of Feet/Toes	<input type="checkbox"/>		
17	Soles	<input type="checkbox"/>		
18	Palms	<input type="checkbox"/>		
19	Tops of Hands/Fingers	<input type="checkbox"/>		
20	Forearms	<input type="checkbox"/>		

Figure: (Continue) 5-D Pruritus

Intercept 747-301		Intercept 747-301 eCRF		Day 0
21	Upper Arms	[]		
22	Points of Contact with Clothing: Waistband	[]		
23	Points of Contact with Clothing: Undergarment	[]		
24	Points of Contact with Clothing: Other	[]		
25	Other Point of contact, specify	[_____]		
26	Groin	[]		
27	Date 5-D Questionnaire Completed	[][][][][][]		
		month	day	year
Optional Comments				

Table 127: Diagnosis of PBC Based on PBC Diagnostic Criteria from PBC Disease

14.4 References

- Abbas G, Jorgensen RA, Lindor KD. Fatigue in primary biliary cirrhosis. *Nature reviews Gastroenterology & hepatology*. 2010 Jun;7(6):313-9.
- Angulo P, Batts KP, Thorneau TM, Jorgensen RA, Dickson ER, Lindor KD. Long-term ursodeoxycholic acid delays histological progression in primary biliary cirrhosis. *Hepatology*. Mar 1999;29(3):644-647
- Angulo P, Lindor KD, Thorneau TM, et al. Utilization of the Mayo risk score in patients with primary biliary cirrhosis receiving ursodeoxycholic acid. *Liver*. 1999 Apr;19(2):115-21.
- Beuers U. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. *Nat Clin Pract Gastroenterol Hepatol*. 2006 Jun;3(6):318-28.
- Beuers U, Kremer AE, Bolier R, et al. Pruritus in Cholestasis: Facts and Fiction. *Hepatology*. 2014 July;60(1):399-407.
- Boonstra, K., Beuers, U., & Ponsioen, C. Y. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol* 2012; 56(5): 1181-1188.
- Carbone M, Mells G, Pells G, et al. Sex and Age Are Determinants of the Clinical Phenotype of Primary Biliary Cirrhosis and Response to Ursodeoxycholic Acid. *Gastroenterology*. 2013 Mar;144(3):560-9.
- Corpechot C. Comparison of Paris I, Paris II and Toronto-Mayo criteria of biochemical response to UDCA in PBC. *J Hepatology*. 2011 55:1361-7.
- Corpechot C, Carrat F, Bonnand AM, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. *Hepatology*. Dec 2000;32(6):1196-1199.
- Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology*. 2008 Sep;48(3):871-7.
- Corpechot C, Chazouilleres O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. *Journal of hepatology*. 2011 Dec;55(6):1361-7.
- Crippin JS, Lindor KD, Jorgensen R, et al. Hypercholesterolemia and atherosclerosis in primary biliary cirrhosis: what is the risk? *Hepatology*. 1992 May;15(5):858-62.
- EASL. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. *Journal of hepatology*. 2009;51(2):237-67.
- Elman S, Hynan LS, Gabriel V, et al. The 5-D itch scale: a new measure of pruritus. *Br J Dermatol*. 2010 Mar;162(3):587-93.
- Gross RG, Odin JA. Recent advances in the epidemiology of primary biliary cirrhosis. *Clin Liver Dis*. 2008 May;12(2):289-303; viii.
- http://www.aasld.org/sites/default/files/guideline_documents/PrimaryBiliaryCirrhosis2009.pdf
- Hansen B. Results of the effect of Alkaline Phosphatase at 1 yr and 2 yr follow-up on death and liver transplantation in the Dutch PBC cohort study. 2011a May 12.
- Hansen B, Kuiper EM, Janssen HL, et al. Alkaline phosphatase as predictor for survival free of liver transplantation in patients with primary biliary cirrhosis treated with UDCA. The Dutch PBC cohort study. *Hepatology*. 2011b;54(4 (SUPPL)):1203A.
- Hirschfield GM, Gershwin ME. The immunobiology and pathophysiology of primary biliary cirrhosis. *Annu Rev Pathol*. 2013 Jan 24;8:303-30.

- Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. *Gut*. 2005 Nov;54(11):1622-9.
- Jones EA, Bergasa NV. The pruritus of cholestasis. *Hepatology*. 1999 Apr;29(4):1003-6.
- Kamath PS, Kim WR. The model for end-stage liver disease (MELD). *Hepatology*. 2007 Mar;45(3):797-805.
- Kim WR, Lindor KD, Locke GR, 3rd, et al. Epidemiology and natural history of primary biliary cirrhosis in a US community. *Gastroenterology*. 2000 Dec;119(6):1631-6.
- Kuiper EM, Hansen BE, Adang RP, et al. Relatively high risk for hepatocellular carcinoma in patients with primary biliary cirrhosis not responding to ursodeoxycholic acid. *European journal of gastroenterology & hepatology*. 2010 Dec;22(12):1495-502.
- Kuiper EM, Hansen BE, de Vries RA, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. *Gastroenterology*. 2009 Apr;136(4):1281-7.
- Kumagi T, Guindi M, Fischer SE, et al. Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. *American Journal of Gastroenterology*. 2010a;105(10):2186-94.
- Kumagi T, Guindi M, Fischer SE, et al. Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. *The American journal of gastroenterology*. 2010b Oct;105(10):2186-94.
- Lammers WJ, van Buuren HR, Hirschfield G, et al. Alkaline phosphatase values are a surrogate marker in prediction of transplant free survival in patients with primary biliary cirrhosis- An international, collaborative analysis. *Journal of hepatology*. 2013
- Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of Alkaline Phosphatase and Bilirubin Are Surrogate End Points of Outcomes of Patients With Primary Biliary Cirrhosis: An International Follow-up Study. *Gastroenterology*. 2014 Aug 23;147(6):1338-49.
- Longo M, Crosignani A, Battezzati PM, Squarcia Giussani C, Invernizzi ZuinM, et al. Hyperlipidaemic state and cardiovascular risk in primary biliary cirrhosis. *Gut* 2002;51:265-269
- Allocca M, Crosignani A, Gritti A, Ghilardi G, Gobatti D, Caruso D, et al., Hypercholesterolaemia is not associated with early atherosclerotic lesions in primary biliary cirrhosis. *Gut* 2006;55:1795-1800.
- Meaney C, Kumagi T, Al-Harthy N, et al. Developing End Points for Clinical Trials in PBC: Alkaline Phosphatase as a predictor of Outcome. *Journal of hepatology*. 2011
- Mells G, Pells G, Newton JL, et al. The impact of primary biliary cirrhosis on perceived quality of life: The UK-PBC national study. *Hepatology*. 2013 Mar 7;58(1):273-83.
- Momah N, Silveira MG, Jorgensen R, et al. Optimizing biochemical markers as endpoints for clinical trials in primary biliary cirrhosis. *Liver international : official journal of the International Association for the Study of the Liver*. 2012 May;32(5):790-5.
- Mounach A, Ouzzif Z, Wariaghli G, et al. Primary biliary cirrhosis and osteoporosis: a case- control study. *J Bone Miner Metab*. 2008;26(4):379-84.
- Newton JL. Fatigue in primary biliary cirrhosis. *Clin Liver Dis*. 2008 May;12(2):367-83; ix.
- Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. *Gastroenterology*. 2006 Mar;130(3):715-20.
- Pares A, Guanabens N. Osteoporosis in primary biliary cirrhosis: pathogenesis and treatment. *Clin Liver Dis*. 2008 May;12(2):407-24; x.
- Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *The Journal of clinical investigation*. 2003 Jun;111(12):1805-12.
- Prince MI, James OF. The epidemiology of primary biliary cirrhosis. *Clin Liver Dis*. 2003 Nov;7(4):795-819.
- [Poupon R](#), Liver alkaline phosphatase: a missing link between cholestasis and biliary inflammation. [Hepatology](#). 2015 Jun;61(6):2080-90.

Poupon RE, Lindor KD, Pares A, Chazouilleres O, Poupon R, Heathcote EJ. Combined analysis of the effect of treatment with ursodeoxycholic acid on histologic progression in primary biliary cirrhosis. *J Hepatol*. Jul 2003;39(1):12-16.

Roll J, Boyer JL, Barry D, et al. The prognostic importance of clinical and histologic features in asymptomatic and symptomatic primary biliary cirrhosis. *The New England journal of medicine*. 1983 Jan 6;308(1):1-7.

Shapiro JM, Smith H, Schaffner F. Serum bilirubin: a prognostic factor in primary biliary cirrhosis. *Gut*. 1979 Feb;20(2):137-40.

Silveira MG, Brunt EM, Heathcote J, et al. American Association for the Study of Liver Diseases endpoints conference: design and endpoints for clinical trials in primary biliary cirrhosis. *Hepatology*. 2010 Jul;52(1):349-59.

ter Borg PC, Schalm SW, Hansen BE, van Buuren HR, Dutch PBCSG. Prognosis of ursodeoxycholic Acid-treated patients with primary biliary cirrhosis. Results of a 10-yr cohort study involving 297 patients. *Am J Gastroenterol*. Sep 2006;101(9):2044-2050.

Trevisani F, Merli M, Savelli F, et al. QT interval in patients with non-cirrhotic portal hypertension and in cirrhotic patients treated with transjugular intrahepatic portosystemic shunt. *Journal of hepatology*. 2003;38(4):461-7.

UK-PBC. Validation of surrogate endpoints in primary biliary cirrhosis using the UK-PBC research cohort. Applicant's submission with this NDA. 2015.

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- ¹ Kuiper EM, Hansen BE, de Vries RA, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. *Gastroenterology* 2009 Apr; 136(4):1281-7
Dec; 22(12):1495-502
- ² Kuiper EM, Hansen BE, Adang RP, et al. Relatively high risk for hepatocellular carcinoma in patients with primary biliary cirrhosis not responding to ursodeoxycholic acid. *European journal of gastroenterology & hepatology* 2010
- ³ Boonstra, K., Beuers, U., & Ponsioen, C. Y. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol* 2012; 56(5): 1181-1188
- ⁴ Carbone M, Mells G, Pells G, et al. Sex and Age Are Determinants of the Clinical Phenotype of Primary Biliary Cirrhosis and Response to Ursodeoxycholic Acid. *Gastroenterology* 2013 Mar;144(3):560-9
- ⁵ http://www.aasld.org/sites/default/files/guideline_documents/PrimaryBiliaryCirrhosis2009.pdf
- ⁶ Longo M, Crosignani A, Battezzati PM, Squarcia Giusani C, Invernizzi P. Zinc Metal Hyperlipidaemic state and cardiovascular risk in primary biliary cirrhosis. *Gut* 2002;51:265-269
- ⁷ Allocca M, Crosignani A, Gnitti A, Ghilardi G, Gobatti D, Caruso D, et al. Hypercholesterolaemia is not associated with early atherosclerotic lesions in primary biliary cirrhosis. *Gut* 2006;55:1795-1800
- ⁸ Shapiro JM, Smith H, Schaffner F. Serum bilirubin: a prognostic factor in primary biliary cirrhosis. *Gut* 1979 Feb;20(2):137-40
- ¹⁰ Angulo P, Batts KP, Therneau TM, Jorgensen RA, Dickson ER, Lindor KD. Long-term ursodeoxycholic acid delays histological progression in primary biliary cirrhosis. *Hepatology* Mar 1999;29(3):644-647
- ¹¹ Corpechot C, Carrat F, Bonnard AM, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. *Hepatology* Dec 2000;32(6):1196-1199
- ¹² Poupon RE, Lindor KD, Pares A, Chazouilleres O, Poupon R, Heathcote EJ. Combined analysis of the effect of treatment with ursodeoxycholic acid on histologic progression in primary biliary cirrhosis. *J Hepatol* Jul 2003;39(1):12-16
- ¹³ Corpechot C, Carrat F, Bahr A, Chretien Y, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. *Gastroenterology* Feb 2005;128(2):297-303
- ¹⁴ ter Borg PC, Schalm SW, Hansen BE, van Buuren HR, Dutch PBCSG. Prognosis of ursodeoxycholic Acid-treated patients with primary biliary cirrhosis. Results of a 10-yr cohort study involving 297 patients. *Am J Gastroenterol* Sep 2006;101(9):2044-2050
- ¹⁵ Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical
- ¹⁶ Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of Alkaline Phosphatase and Bilirubin Are Surrogate End Points of Outcomes of Patients with Primary Biliary Cirrhosis: An International Follow-up Study. *Gastroenterology* 2014 Aug 23;147(6):1338-49

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/s/

RUBY MEHTA
05/27/2016

LARA DIMICK-SANTOS
05/27/2016

CLINICAL OUTCOME ASSESSMENTS CONSULT REVIEW

Template version: June 24, 2015

COA TRACKING NUMBER	2015-157
IND/NDA/BLA NUMBER	NDA 207999
LETTER DATE/SUBMISSION NUMBER	2
PDUFA GOAL DATE	
DATE OF CONSULT REQUEST	10 September 2015
REVIEW DIVISION	Division of Gastroenterology and Inborn Errors Products (DGIEP)
MEDICAL REVIEWER	Ruby Mehta, M.D.
REVIEW DIVISION PM	Anissa Davis-Williams
CLINICAL OUTCOME ASSESSMENT (COA) REVIEWER(S)	Selena Daniels, Pharm.D, MS
ASSOCIATE DIRECTOR, COA (ACTING)	Elektra Papadopoulos, M.D., MPH
REVIEW COMPLETION DATE	16 March 2016
ESTABLISHED NAME	Obeticholic Acid
TRADE NAME	INT-747
APPLICANT	Intercept Pharmaceuticals, Inc.
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported Outcome
ENDPOINT(S) CONCEPT(S)	Pruritus severity and impact
MEASURE(S)	Primary Biliary Cirrhosis-40 (PBC-40); 5-D Pruritus Scale; Pruritus Visual Analog Scale (VAS)
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
INTENDED POPULATION(S)	Adults with PBC with inadequate response or intolerability to UDCA
NOTE	This NDA review examined completed analysis results for PRO endpoints in Study 747-301 (LTSE) rather than a dossier submission.

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Gastroenterology and Inborn Errors Products (DGIEP) regarding NDA 207999: obeticholic acid (OCA) for the treatment of adult patients with primary biliary cirrhosis (PBC).

DGIEP requested COA Staff to review three patient reported outcome (PRO) instruments that were used to assess pruritus severity and impact. The applicant does not seek labeling claims. However, DGIEP asks COA Staff to review these instruments as safety assessments.

The PRO safety assessments include:

- Itch domain of the PBC 40, which assesses impact of itching
- 5-D Pruritus Scale, total score assesses severity and impact of itching
- Pruritus Visual Analog Scale (VAS)

These instruments were not intended to support efficacy or comparative safety claims in labeling. Therefore, the review criteria were not the same as would be required for an efficacy claim. Instead, the review focused on whether the instruments were fit-for-purpose in the context of this particular drug development program to assess worsening of itch as a safety assessment in the clinical trial. This review concludes that these instruments appear fit-for purpose for this drug development program. However, it is unclear what threshold of change represents clinically meaningful deterioration on each of these scales. The COA Staff defers to the Clinical team to review the overall safety profile of this drug development program.

B. BACKGROUND INFORMATION

Regulatory history:

- Studies 747-201, 202, and 205 have already been reviewed during previous NDA cycles; therefore, the assessments used in Study 747-301 are the primary focus of this review.
- Sensitivity analyses to further evaluate the patient-reported outcome (PRO) safety data were requested on 28 October 2015.

Materials reviewed:

- Common Technical Document Summaries (2.5; 2.7.3; 2.7.4)
- Clinical Study Report 747-301

1 CONTEXT OF USE (COU)

1.1 Target Study Population and Clinical Setting

The target study population for the Phase 3 study included adult patients with an inadequate response to UDCA or who are unable to tolerate UDCA. The inclusion and exclusion criteria of the patient population are listed in the protocol synopses (pages 39-40 in Clinical Study Report 747-301).

1.2 Clinical Trial Design, Protocol, and Analysis Plan

Double-Blind Phase

Study 747-301, a randomized, multi-dose, parallel group, double-blind, placebo-controlled, Phase 3, 12-month study, was designed to assess longer-term efficacy, safety, and tolerability of Obeticholic Acid (OCA) in subjects with PBC to support a second line indication for OCA for the treatment of subjects with PBC (subjects were either on a stable dose of UDCA or unable to tolerate UDCA).

OCA doses evaluated in this study were either:

- 10 mg for the entire 12-month period
- Titration: All subjects received 5 mg for the initial 6-months treatment period. At Month 6, subjects either:
 - Remained at 5 mg if the primary endpoint was achieved and/or the subject had tolerability issues or

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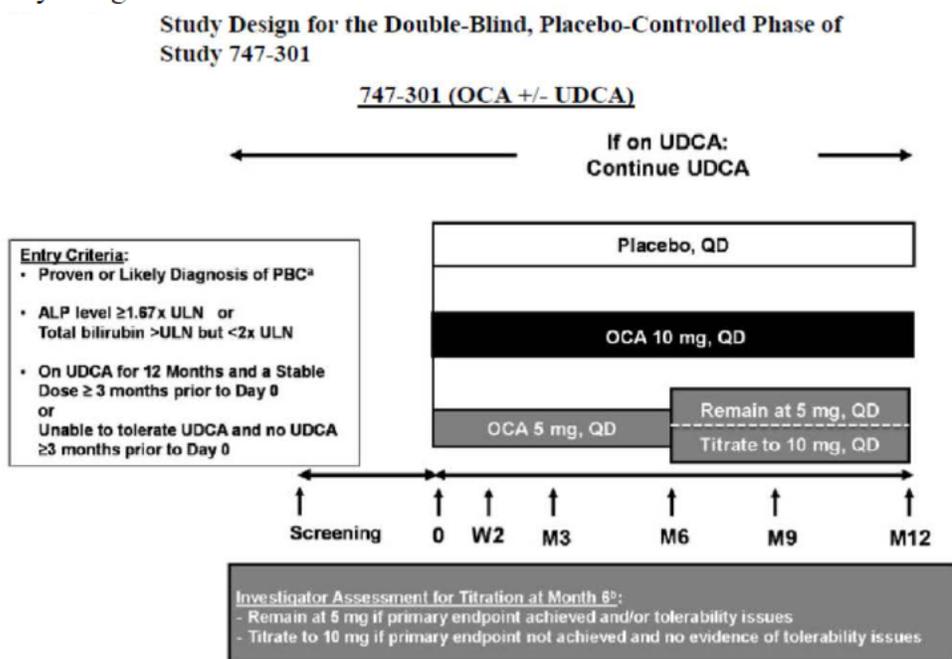
Obeticholic Acid

PBC-40; 5-D Pruritus Scale; Pruritus VAS

- Uptitrated to 10 mg for the remainder of the 12-month period if the subject did not achieve the primary composite endpoint and was able to tolerate OCA.

Subjects received either OCA in combination with UDCA or OCA monotherapy. Subjects who entered the study on an UDCA regimen continued their prestudy, stable dose of UDCA throughout the study. Subjects who were unable to tolerate UDCA and had not received UDCA for at least 3 months prior to Screening received investigational product as a monotherapy. Subjects taking other medications with potential effects on PBC were excluded from the study to ensure that the study provided the clearest comparison of the effects of OCA versus placebo on the background of standard of care (ie, UDCA) or as a monotherapy.

The study design is illustrated below.



^a Definite or probable diagnosis of PBC was defined as having at least 2 of the following 3 diagnostic factors:

- History of elevated ALP levels for at least 6 months;
- Positive AMA titer or if AMA negative or low titer ($< 1:80$), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex);
- Liver biopsy consistent with PBC

^b Primary Composite Endpoint: ALP $< 1.67 \times$ ULN, total bilirubin \leq ULN, and a $\geq 15\%$ reduction in ALP.

Source: 747-301 Double-Blind Phase

Long-term Safety Extension Phase

Subjects who completed the double-blind phase were eligible to enroll in a long-term (up to 5-year) open-label, long-term safety extension (LTSE). This extension provided all subjects with OCA and extended regular medical supervision of their disease for a substantial period. Subjects

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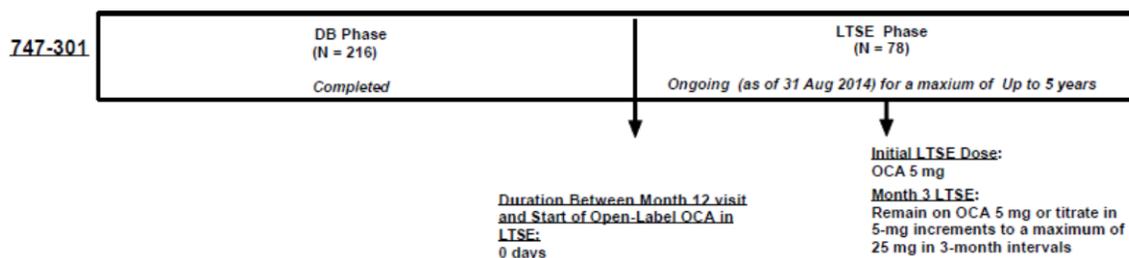
PBC-40; 5-D Pruritus Scale; Pruritus VAS

entered the LTSE after all study procedures for the double-blind phase of the study were completed at the study termination visit (double-blind Month 12). The subject treatment allocation in the double-blind phase was not made available until the entire study was unblinded.

Accordingly, all subjects were initially started on OCA 5 mg for the LTSE phase regardless of the randomized treatment in the double-blind phase (ie, placebo, 5 mg, or 10 mg). Using this approach, overall study blinding was maintained and data on the effects of down-titrating from 10 mg to 5 mg were also obtained in the LSTE portion of the study. All subjects continued at a 5 mg dose for a minimum of 3 months. Subsequent to the LTSE Month 3 visit, OCA doses could be titrated (incrementally from 5 mg to 10 mg to 15 mg, up to 25 mg OCA at a frequency of no more than one up-titration every 3 months) provided that subjects met the following criteria:

- ALP $\geq 1.67x$ ULN, and/or
- Total bilirubin $>ULN$, or
- $<15\%$ ALP reduction versus the mean double-blind pretreatment value(s), and
- AEs (eg, severe pruritus) did not limit the administration of a higher dose

The transition from double-blind phase to long-term safety extension (LTSE) phase is as follows:



Schedule of Assessments

The schedule of assessment tables are provided below.

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Schedule of Assessments: Double-Blind Phase of 747-301

Double-Blind Phase Visits	Screening	Day 0	Wk 2	Safety Contact ^a	M3	M6 (Visit A) ^b	M6 (Visit B) ^b	M9	M12 (LTSE D1)	EOT	Follow - Up (4 wks)
Visit Windows (±)	≤1 to 8 wks		±7 d	±7 d	±2 wk	≤7 d vs M6 (Visit B)	±2 wk	±2 wk	±2 wk		±7 d
STUDY PROCEDURES											
Informed Consent	X										
Medical and Disease History	X										
Inclusion/Exclusion Criteria	X	X									
Physical Exam (Height at Screening only)	X						X		X	X	
Vital Signs	X	X	X		X		X	X	X	X	X
12-Lead Electrocardiogram	X						X		X	X	
Subject Questionnaires ^d		X	X		X		X	X	X ^e	X ^e	X
TE ^e		X							X	X ^e	
Liver Biopsy ^f	X				X	X			X		
DEXA Scan ^g		X							X	X ^e	
Adverse Events		X	X	X	X		X	X	X	X	X
MRS / MELD	X										
Prior and Concomitant Medications	X	X	X	X	X		X	X	X	X	X
Randomization/Treatment Assigned		X							X		
Dose Titration (if applicable)							X				
Dispense Investigational Product		X	X		X		X	X	X		
Investigational Product Accountability/Compliance			X	X ^a	X		X	X	X	X	
On-site Investigational Product Administration			X		X		X	X	X		

Schedule of Assessments: Double-Blind Phase of 747-301 (Continued)

Double-Blind Phase Visits	Screening	Day 0	Wk 2	Safety Contact ^a	M3	M6 (Visit A) ^b	M6 (Visit B) ^b	M9	M12 (LTSE D1)	EOT	Follow - Up (4 wks)
Visit Windows (±)	≤1 to 8 wks		±7 d	±7 d	±2 wk	≤7 d vs M6 (Visit B)	±2 wk	±2 wk	±2 wk		±7 d
CLINICAL LABORATORY EVALUATIONS											
Serum Chemistry/Hematology	X ^h	X	X		X	X		X	X	X	X
Serum Bile Acids		X				X			X	X	
Lipoprotein Analysis		X				X			X	X	
ELF/Other Analytes		X				X			X	X ^c	
Genetics Study ^d		X							X		
Urinalysis (dipstick)	X	X				X			X	X	
Urine-based β-hCG Pregnancy Test ^e	X	X	X		X	X		X	X	X	

AE = adverse event; ALP = alkaline phosphatase; DB = double-blind; d = day; DEXA = dual-emission X-ray absorptiometry; ECG = electrocardiogram;

ELF = enhanced liver fibrosis; EOT = end of treatment; β-hcg = beta human chorionic gonadotropin; LTSE = long term safety extension;

MRS = Mayo Risk Score; MELD = Model for End Stage Liver Disease; M = months; TE = transient elastography; PBC = primary biliary cirrhosis;

ULN = upper limit of normal; VAS = Visual Analog Scale; wk = week

^a Subjects were contacted by telephone on a monthly basis (±7 days) between at-clinic study visits starting at Month 1 and continuing through the double-blind phase to assess for AEs and verify that they were dosing as directed.

^b The Month 6 study assessment occurred across 2 separate at-clinic visits and a remote telephone Safety Contact approximately 2 weeks after Month 6 for subjects who met the titration criteria (ie, were presumably titrated).

^c If a subject completed the following assessments within 3 months of terminating early, AND so long as safety issues did not warrant repeated tests, the 12-lead ECG, ELF/Other Analytes, and DEXA scan could have been omitted. Similarly, so long as a TE assessment had been done within 6 months, it could be omitted.

^d Subject Questionnaires included PBC-40, 5-D Pruritus Scale, and Pruritus VAS; a Subject Research Questionnaire was administered at double-blind M12, or double-blind EOT if early termination, only.

^e TE was conducted at selected study sites where the Fibroscan® TE device was available. If a TE was performed within 3 months of Day 0 and a report/adequate data were available, a pretreatment TE at Day 0 was not required.

^f Subjects could have a pretreatment liver biopsy conducted or could provide access to pretreatment liver biopsy samples, if within 1 year of Day 0; both actions were optional.

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^g The DEXA bone density scan was done at selected study sites only. Subjects that had a recent DEXA scan within 6 months prior to Day 0 and for which a report of the results was available for use in this study, did not need to repeat the Baseline DEXA scan. Otherwise, a window of ± 2 weeks for the scan was acceptable.

^h Subjects whose Screening ALP value was $< 2 \times$ ULN OR whose Screening bilirubin was $> 1 \times$ ULN, returned at least 2 weeks later for a second Screening ALP OR bilirubin assessment. For these subjects, the mean of both Screening values (ALP and/or bilirubin) was used to confirm eligibility.

ⁱ A genetics study was conducted for subjects and at study sites willing to provide samples. Willing subjects had to specifically consent to participate in this evaluation.

^j Urine-based β -hCG pregnancy tests were performed in females of childbearing potential. If positive, a confirmatory blood test was performed at the site. If the blood test was also positive, the subject was not enrolled or was discontinued from the study.

1.3 Endpoint Positioning

Intercept defined the primary composite endpoint for Study 747-301 as follows:

The proportion of patients reaching specific biochemical criteria for ALP and bilirubin after 1 year of treatment (ALP $< 1.67 \times$ ULN [with a $\geq 15\%$ reduction] and bilirubin \leq ULN)

Primary Endpoint

- Percentage of subjects (OCA 10mg vs placebo) achieving composite endpoint at Month 12

Other Secondary Endpoint (PRO):

- Absolute and percent change from Baseline at all timepoints on PBC-40 domains (including Itch domain)

Safety Endpoints (PRO):

- Change from baseline to Days 29, 57, and 85 on 5D-Pruritus scale domains and total score:
- Change from baseline to Week 2, Month 3, Month 6B, Month 9 and Month 12 on Pruritus VAS

2 CONCEPT OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interests for the clinical outcome assessments are listed below:

- PBC-40: Health-related Quality of Life (HRQoL)
- 5-D Pruritus Scale: Pruritus severity/intensity
- Pruritus VAS: Pruritus severity/intensity

Please refer to Appendices B and C for the conceptual frameworks for PBC-40 and 5-D Pruritus Scale, respectively.

[Reviewer's comment: The 5-D Pruritus Scale and Pruritus VAS are being used as safety assessments in this study.]

3 CLINICAL OUTCOME ASSESSMENT (COA) INSTRUMENTS

- Instrument

PBC-40

The PBC-40 is a profile measure, covering six PBC specific quality of life domains (cognitive, social, emotional function, fatigue, itch, and other symptoms). Each item is scored on a scale of 1 to 5 (where 1= least impact, 5= greatest impact). A score for each domain was provided (but a total score was not calculated).

5-D Pruritus Scale

The 5-D Pruritus Scale is a multidimensional measure that quantifies pruritus. The scale consists of five domains: duration (1 item), degree (1 item), direction (1 item), disability (4 items), and distribution (16 locations of itch). All items of the first four domains were measured on a five-point Likert scale.

Pruritus VAS

A 0-10cm VAS was used, where “0” indicates “no itching” and “10” indicates “worst possible itching.”

- Prior versions
No documentation has been provided on any prior versions of the proposed measures.
- User manual
No documentation has been provided on a user manual for any of the proposed measures.
- Timing, data collection method and mode of administration
The schedule of assessment table is provided in Section 1.2 of this review. The scales were administered at Baseline (Day 0); Week 2; Months 3, 6, 9, and 12; End of Treatment (EOT); and Follow-up (FU).
- Scoring algorithm (method of creating a single score from multiple items)

PBC-40

For each domain, scoring involved summing individual question response scores; with higher scores indicating poorer health-related quality of life.

5-D Pruritus Scale

The scores of each of the five domains are achieved separately and then summed together to obtain a total 5-D score. 5-D scores can potentially range between 5 (no pruritus) and 25 (most severe pruritus). Single-item domain scores (duration, degree, and direction)

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Obeticholic Acid

PBC-40; 5-D Pruritus Scale; Pruritus VAS

are equal to the value indicated below the response choice (range 1-5). For the distribution domain, the number of affected body parts is tallied (potential sum 0-16) and the sum is sorted into five scoring bins: sum of 0-2 = score of 1, sum of 3-5 = score of 2, sum of 6-10 = score of 3, sum of 11-13 = score of 4, and sum of 14-16 = score of 5.

Pruritus VAS

The VAS is set between 0 and 10cm, higher values represent a worse outcome.

[Reviewer's comment: Scoring algorithms for PBC-40 and 5-D Pruritus Scale were documented in the references that the applicant provided. The 5-D Pruritus total score is not the optimal measure to assess the severity of pruritus as it includes multiple dimensions, or subscales, (i.e., duration, degree, direction, disability, and distribution) that measure different aspects of the patient experience. There is a possibility that one dimension (subscale) may be driving the total score.]

- Training method/materials (patient, investigator and other study site personnel, as appropriate)
No documentation has been provided on training materials for any of the scales.

4 CONTENT VALIDITY

PBC-40

PBC-40 was developed in three phases:

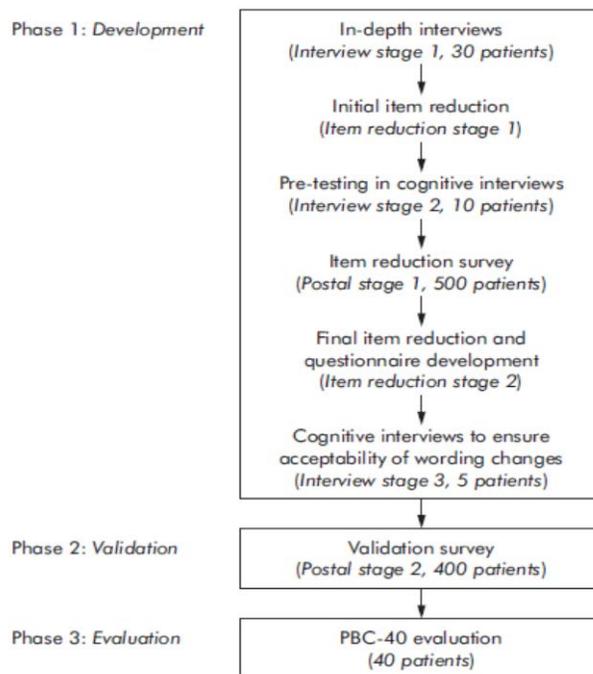
Phase 1: In-depth interviews with patients were used to derive an initial measure, which was then reduced in size and refined following completion by a large patient cohort.

Phase 2: The resulting measure (PBC-40) was refined and validated in a further large patient survey.

Phase 3: The PBC-40 was evaluated in PBC patients in comparison with previously used health-related quality of life measures.

Below is a flow diagram of the development of the PBC-40:

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[Reviewer's comment: The development of the PBC-40 is described in published literature. It appears that the questionnaire was developed in an appropriate PBC population, however, it was developed only in a UK population. No documentation has been provided on cross-cultural equivalence. There are some concerns about the structure and format of the items in PBC-40, particularly combining symptoms and non-symptoms in the same domain. The questionnaire also consists of distal attributes that may not be impacted by treatment. Additional details will be needed to determine if content validity has been established in this scale.]

5-D Pruritus Scale

Preliminary items for the 5-D Pruritus Scale were derived from (1) modification of the Total Neuropathy Scale to be relevant to pruritus rather than neuropathy, (2) clinical experience by the authors and expert consultants with chronic pruritus under conditions of patient care and clinical trials, and (3) review of the pruritus literature. The preliminary version included both open-ended questions and specific response questions regarding the patient's perception of pruritus. This preliminary version was administered to 21 patients participating in a trial of sertraline for a treatment of cholestatic pruritus. Ambiguous items or response choices were revised and response choices selected less than 5% of the time were removed.

[Reviewer's comment: The development of the 5-D Pruritus Scale is vaguely described in published literature. There is insufficient evidence to support the content validity of this scale.]

Pruritus VAS

No documentation has been provided on the development of this scale, therefore it cannot be determined if content validity has been established.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

As content validity cannot be determined for any of these measures without additional supportive information, the other measurement properties of these instruments cannot be reviewed.

6 INTERPRETATION OF SCORES

The interpretation of meaningful changes in these measures is unknown.

The following information was requested for Study 747-301:

- Provide cumulative distribution function (CDF) curves, one curve for each study arm (placebo, Obeticholic acid [OCA] 5 mg titration arm and OCA 10 mg arm) for the following PRO assessments: PBC-40 Itching and Fatigue subscales, PBC-40 Question 14, 5D- Pruritus Scale, and Pruritus VAS.

[Reviewer's comment: The results of the sensitivity analyses were received 20 November 2015; however, the data provided was plotted only at baseline. Clarification was provided to the applicant to provide analyses showing change score from baseline to primary time points (Months 6 and 12) on 18 December 2015. The updated results were received 24 December 2015. However, CDF plots were not received for the PBC-40 as the Division had excluded the request for this scale as they wanted the focus on pruritus severity scales (5-D Pruritus Scale and Pruritus VAS). COA staff discussed with Clinical about the CDF plots and determined that that no information from the applicant was needed.]

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

No documentation has been provided on translation and cultural adaptation of these measures.

[Reviewer's comment: The PBC-40 was developed in an UK population. No documentation has been provided on cross-cultural equivalence. If the applicant will be using this measure outside the UK, it is recommended to translate and culturally adapt this measure per best practices. This recommendation is for the other measures as well.]

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable.

9 REVIEW USER MANUAL

No documentation has been provided on a user manuals for the proposed measures.

10 KEY REFERENCES FOR MEASURES

Elman S, Hynan LS, Gabriel V, and Mayo MJ. The 5-D itch scale: a new measure of pruritus. *British Journal of Dermatology*. 2010; 162(3): 587-593.

Jacoby A, Rannard A, Buck D, Bhala N, Newton JL, James O, and Jones D. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. *Gut*. 2005; 54: 1622-1629.

C. APPENDICES

APPENDIX A: PBC-40

Intercept 747-301	Intercept 747-301 eCRF	Day 0
PBC 40 Questionnaire		
0	Was PBC-40 questionnaire completed by the subject?	() Yes () No
<i>To be completed by the patient. For each statement, please circle the response that comes closest to how you feel.</i>		
<i>Can you say how often the following statements about digestion and diet applied to you IN THE LAST FOUR WEEKS?</i>		
1	I was able to eat what I liked	() Never () Rarely () Sometimes () Most of the time () Always
2	I ate or drank only a small amount, and still felt bloated	() Never () Rarely () Sometimes () Most of the time () Always
3	I felt unwell when I drank alcohol	() Never () Rarely () Sometimes () Most of the time () Always () Did not apply/ never drink alcohol
<i>And IN THE LAST FOUR WEEKS, how often did you experience any of the following?</i>		
4	I had discomfort in my right side	() Never () Rarely () Sometimes () Most of the time () Always
5	I had dry eyes	() Never () Rarely () Sometimes () Most of the time () Always
6	My mouth was very dry	() Never () Rarely () Sometimes () Most of the time () Always
7	I had aches in the long bones of my arms and legs	() Never () Rarely () Sometimes () Most of the time () Always
<i>Some people with PBC experience itching. How often did you experience itching IN THE LAST FOUR WEEKS? If you did not itch, please circle Did not apply.</i>		
8	Itching disturbed my sleep	() Never () Rarely () Sometimes () Most of the time () Always () Did not apply/ no itch
9	I scratched so much I made my skin raw	() Never () Rarely () Sometimes () Most of the time () Always () Did not apply/ no itch
10	I felt embarrassed because of the itching	() Never () Rarely () Sometimes () Most of the time () Always () Did not apply/ no itch
<i>Fatigue can also be a problem for many people with PBC. How often did the following statements apply to you IN THE LAST FOUR WEEKS?</i>		
11	I had to force myself to get out of bed	() Never () Rarely () Sometimes () Most of the time

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Intercept 747-301	Intercept 747-301 eCRF	Day 0
		<input type="radio"/> Always
12	I had to have a sleep during the day	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
13	Fatigue interfered with my daily routine	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
14	I felt worn out	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
15	I felt so tired, I had to force myself to do the things I needed to do	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
16	I felt so tired, I had to go to bed early	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
17	Fatigue just suddenly hit me	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
18	PBC drained every ounce of energy out of me	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
<i>The next section is about the effort and planning that can be involved in living with PBC. Thinking about THE LAST FOUR WEEKS, how often did the following apply to you?</i>		
19	Some days it took me a long time to do anything	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
20	If I was busy one day I needed at least another day to recover	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
21	I had to pace myself for day-to-day things	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
<i>The following statements are about the effects that PBC may have on things like memory and concentration. Thinking about THE LAST FOUR WEEKS, how often did the following statements apply to you?</i>		
22	Because of PBC I had to make a lot of effort to remember things	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
23	Because of PBC I had difficulty remembering things from one day to the next	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always
24	My concentration span was short because of PBC	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time

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Intercept 747-301		Intercept 747-301 eCRF	Day 0
		<input type="radio"/> Always	
25	Because of PBC, I had difficulty keeping up with conversations	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always	
26	Because of PBC, I found it difficult to concentrate on anything	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always	
27	Because of PBC, I found it difficult to remember what I wanted to do	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Sometimes <input type="radio"/> Most of the time <input type="radio"/> Always	
Now some more general statements about how PBC may be affecting you as a person. How much do the following statements apply to you?			
28	Because of PBC, I get more stressed about things than I used to	<input type="radio"/> Not at all <input type="radio"/> A little <input type="radio"/> Somewhat <input type="radio"/> Quite a bit <input type="radio"/> Very much	
29	My sex life has been affected because of PBC	<input type="radio"/> Not at all <input type="radio"/> A little <input type="radio"/> Somewhat <input type="radio"/> Quite a bit <input type="radio"/> Very much <input type="radio"/> Does not apply	
30	Having PBC gets me down	<input type="radio"/> Not at all <input type="radio"/> A little <input type="radio"/> Somewhat <input type="radio"/> Quite a bit <input type="radio"/> Very much	
31	I feel I neglect my family because of having PBC	<input type="radio"/> Not at all <input type="radio"/> A little <input type="radio"/> Somewhat <input type="radio"/> Quite a bit <input type="radio"/> Very much <input type="radio"/> Does not apply	
32	I feel guilty that I can't do what I used to do because of having PBC	<input type="radio"/> Not at all <input type="radio"/> A little <input type="radio"/> Somewhat <input type="radio"/> Quite a bit <input type="radio"/> Very much	
33	I worry about how my PBC will be in the future	<input type="radio"/> Not at all <input type="radio"/> A little <input type="radio"/> Somewhat <input type="radio"/> Quite a bit <input type="radio"/> Very much	
These statements relate to the possible effects of PBC on your social life. Thinking of your own situation, how much do you agree or disagree with them?			
34	I sometimes feel frustrated that I can't go out and enjoy myself	<input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Neither agree nor disagree <input type="radio"/> Disagree <input type="radio"/> Strongly disagree	
35	I tend to keep the fact that I have PBC to myself	<input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Neither agree nor disagree <input type="radio"/> Disagree <input type="radio"/> Strongly disagree	
36	I can't plan holidays because of having PBC	<input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Neither agree nor disagree <input type="radio"/> Disagree <input type="radio"/> Strongly disagree	
37	My social life has almost stopped		

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Intercept 747-301		Intercept 747-301 eCRF	Day 0
		<input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Neither agree nor disagree <input type="radio"/> Disagree <input type="radio"/> Strongly disagree	
<i>The next section is about the impact that PBC may be having on your life overall. How much do you agree or disagree with them?</i>			
38	Everything in my life is affected by PBC	<input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Neither agree nor disagree <input type="radio"/> Disagree <input type="radio"/> Strongly disagree	
39	PBC has reduced the quality of my life	<input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Neither agree nor disagree <input type="radio"/> Disagree <input type="radio"/> Strongly disagree	
40	I can still lead a normal life, despite having PBC	<input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Neither agree nor disagree <input type="radio"/> Disagree <input type="radio"/> Strongly disagree	
41	Date PBC 40 Questionnaire Completed	___/___/____ month day year	
<i>Optional Comments</i>			

APPENDIX B: PBC-40 FRAMEWORK

Domain	Question	Response options*
Symptoms	<i>In the last 4 weeks:</i> I was able to eat what I liked I ate or drank only a small amount, and still felt bloated I felt unwell when I drank alcohol I had discomfort in my right side I had dry eyes My mouth was very dry I had aches in the long bones of my arms and legs	Never, rarely, sometimes, most of the time, always
Itch	<i>In the last 4 weeks:</i> Itching disturbed my sleep I scratched so much I made my skin raw I felt embarrassed because of the itching	Never, rarely, sometimes, most of the time, always
Fatigue	<i>In the last 4 weeks:</i> I had to force myself to get out of bed I had to have a sleep during the day Fatigue interfered with my daily routine I felt worn out I felt so tired, I had to force myself to do the things I needed to do I felt so tired, I had to go to bed earlier than usual Fatigue just suddenly hit me PBC drained every ounce of energy out of me Some days it took me a long time to do anything If I was busy one day I needed at least another day to recover I had to pace myself for day-to-day things	Never, rarely, sometimes, most of the time, always
Cognition	<i>In the last 4 weeks:</i> I had to make a lot of effort to remember things I had difficulty remembering things from one day to the next My concentration span was short because of PBC I had difficulty keeping up with conversations I found it difficult to concentrate on anything I found it difficult to remember what I wanted to do	Never, rarely, sometimes, most of the time, always
Social	My sex life has been affected by having PBC I feel I neglect my family because of having PBC I feel guilty that I can't do what I used to do because of having PBC I sometimes feel frustrated that I can't go out and enjoy myself I tend to keep the fact that I have PBC to myself I can't plan holidays because of having PBC My social life has almost stopped Everything in my life is affected by PBC PBC has reduced the quality of my life I can still lead a normal life, despite having PBC	Not at all, a little, somewhat, quite a bit, very much
Emotional	Because of PBC, I get more stressed about things than I used to Having PBC gets me down I worry about how my PBC will be in the future	Not at all, a little, somewhat, quite a bit, very much

*Items are scored from 1 to 5 and the individual item scores are summed to give a total domain score. Maximum and minimum domain scores are shown in table 5. The direction of scoring of some items is reversed for calculation of domain scores so that in all cases, high scores represent high impact and low scores low impact of PBC on quality of life.
 †Copies of the questionnaire and full scoring instructions are obtainable from the authors.

APPENDIX C: 5-D Pruritus Scale

Intercept 747-301	Intercept 747-301 eCRF	Day 0
5-D Descriptive Pruritus Scale		
0	Was 5-D Descriptive Pruritus Scale completed by the subject?	() Yes () No
1. Duration:		
1	During the last 2 weeks, how many hours a day have you been itching?	<input type="radio"/> Less than 6 hrs/day <input type="radio"/> 6-12 hrs/day <input type="radio"/> 12-18 hrs/day <input type="radio"/> 18-23 hrs/day <input type="radio"/> All day
2. Degree:		
2	Please rate the intensity of your itching over the past 2 weeks	<input type="radio"/> Not present <input type="radio"/> Mild <input type="radio"/> Moderate <input type="radio"/> Severe <input type="radio"/> Unbearable
3. Direction:		
3	Over the past 2 weeks has your itching gotten better or worse compared to the previous month?	<input type="radio"/> Completely resolved <input type="radio"/> Much better, but still present <input type="radio"/> Little bit better, but still present <input type="radio"/> Unchanged <input type="radio"/> Getting worse
4. Disability: Rate the impact of your itching on the following activities over the last 2 weeks		
4	Sleep	<input type="radio"/> Never affects sleep <input type="radio"/> Occasionally delays falling asleep <input type="radio"/> Frequently delays falling asleep <input type="radio"/> Delays falling asleep and occasionally wakes me up at night <input type="radio"/> Delays falling asleep and frequently wakes me up at night
5	Leisure/ Social	<input type="radio"/> Never affects this activity or N/A <input type="radio"/> Rarely affects this activity <input type="radio"/> Occasionally affects this activity <input type="radio"/> Frequently affects this activity <input type="radio"/> Always affects this activity
6	Housework/ Errands	<input type="radio"/> Never affects this activity or N/A <input type="radio"/> Rarely affects this activity <input type="radio"/> Occasionally affects this activity <input type="radio"/> Frequently affects this activity <input type="radio"/> Always affects this activity
7	Work/School	<input type="radio"/> Never affects this activity or N/A <input type="radio"/> Rarely affects this activity <input type="radio"/> Occasionally affects this activity <input type="radio"/> Frequently affects this activity <input type="radio"/> Always affects this activity
5. Distribution:		
<i>Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.</i>		
8	Head/Scalp	[]
9	Face	[]
10	Chest	[]
11	Abdomen	[]
12	Back	[]
13	Buttocks	[]
14	Thighs	[]
15	Lower Legs	[]
16	Tops of Feet/Toes	[]
17	Soles	[]
18	Palms	[]
19	Tops of Hands/Fingers	[]
20	Forearms	[]

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Intercept 747-301		Intercept 747-301 eCRF	Day 0
21	Upper Arms	[]	
22	Points of Contact with Clothing: Waistband	[]	
23	Points of Contact with Clothing: Undergarment	[]	
24	Points of Contact with Clothing: Other	[]	
25	Other Point of contact, specify	_____	
26	Groin	[]	
27	Date 5-D Questionnaire Completed	____/____/____ month day year	
<i>Optional Comments</i>			

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Intercept 747-301		Intercept 747-301 eCRF		Day 0
Pruritus Visual Analog Scale				
1	Was a VAS form completed by the subject?	<input type="checkbox"/> Yes <input type="checkbox"/> No		
2	Date VAS form completed	_ _ / _ _ / _ _ _ _ month day year		
3	Result value	_ _ mm		
4	Is the patient currently experiencing pruritus?	<input type="checkbox"/> Yes <input type="checkbox"/> No		
5	Severity of pruritus	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe		
6	Treatment	<input type="checkbox"/> None <input type="checkbox"/> Non-drug Treatment <input type="checkbox"/> Medication <input type="checkbox"/> Other, specify		
	If other treatment, please specify			
<i>Optional Comments</i>				

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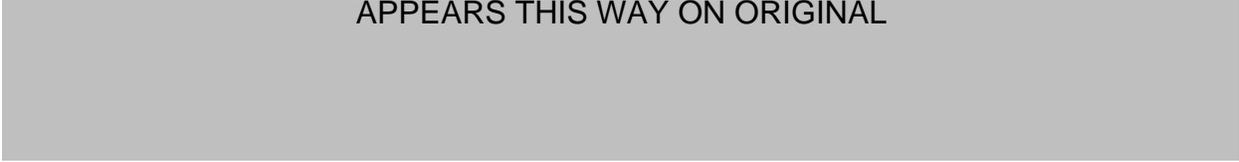
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APPEARS THIS WAY ON ORIGINAL



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/s/

SELENA R DANIELS
04/21/2016

ELEKTRA J PAPADOPOULOS
04/23/2016

Memorandum of Consultation

From: John T. Stinson, M.D. Medical Officer, Division of Bone, Reproductive and Urologic Products (DBRUP)

Through: Theresa Kehoe, M.D. Clinical Team Leader, DBRUP
Hylton Joffe, M.D., M.M.Sc Division Director, DBRUP

To: Ruby Mehta, M.D., Medical Officer, Division of Gastroenterology and Inborn Errors Products (DGIEP)
CDR Anissa Davis-Williams, Regulatory Project Manager, DGIEP

RE: Obeticholic Acid (OCA) Tablets

NDA: 207999

Indication: Treatment of primary biliary cirrhosis

Sponsor: Intercept Pharmaceuticals, Inc.

Consult Date: November 6, 2015

Consult Tracking Number: 150

Consult Request:

During a Phase 3 trial conducted over a period of 12 months with Obeticholic acid in 216 patients with primary biliary cirrhosis (1:1:1 randomization to receive placebo versus OCA 5 mg versus OCA 10 mg); 3 patients experienced adverse event (AE) of fracture in OCA arm 5 mg; 3 patients experienced AE of fracture in OCA 10 mg, and 3 patients had AE of fracture in the placebo arm. Primary biliary cirrhosis patients are at risk population for fractures, due to underlying osteomalacia and osteopenia, secondary to the cholestatic liver disease. The DEXA scans were done in 122 patients at baseline; patients were generally normal to osteopenic and generally remained within the same range at 12 months in all treatment groups. We request your opinion and expertise to answer the following questions:

- 1. Evaluating DEXA scan results,*
- 2. If the fracture is a potential AE signal,*
- 3. Recommendations for further investigations and evaluations for follow up if fractures seem to be a potential AE signal.*

Background

NDA 207999 was submitted on June 27, 2015 in support of marketing approval for Obeticholic acid for the treatment of primary biliary cirrhosis (PBC). PBC is a serious, life-threatening, cholestatic liver disease that, if left untreated, progresses to hepatic fibrosis, cirrhosis, hepatic decompensation, and the need for liver transplantation. PBC is a global rare disease that disproportionately affects women versus men (approximately 10:1). PBC is typically diagnosed in patients between 40 years to 60 years of age and is fatal without liver transplantation. While the cause of PBC is unclear, genetic predispositions have been described. 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.

PBC is characterized by cholestasis with progressive impairment of bile flow in the liver that results in increased hepatocellular bile acid concentrations. Bile acids are natural detergents, and abnormally elevated hepatocellular concentrations can be toxic to the liver. Such hepatocellular injury results in a local inflammatory response and is signaled early on by the secretion of alkaline phosphatase. 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. Patients with advanced disease are also predisposed to hepatocellular carcinoma.

Biochemically, PBC is characterized by increases in alkaline phosphatase and gamma-glutamyl transferase enzymes with or without elevations of hepatocellular transaminases and bilirubin. The presence of anti-mitochondrial antibodies (AMA) is a specific immunological hallmark of PBC and is diagnostic of the disease. In contrast to anti-mitochondrial antibodies, alkaline phosphatase and gamma-glutamyl transferase levels have been shown to correlate with disease progression, and alkaline phosphatase, assessed over the first year, with and without treatment, is highly predictive of long-term clinical outcomes, eg, transplant-free survival.

Both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines base the diagnosis of PBC on 3 diagnostic criteria:

- Biochemical evidence of cholestasis based on ALP elevation
- Presence of AMA titer or
- In the absence of AMA antibodies, liver biopsy consistent with PBC

Bile acids have long been known to facilitate digestion and absorption of lipids and to control cholesterol homeostasis. Endogenous bile acids, as chenodeoxycholic (CDCA), are potent signaling molecules through activation of the nuclear farnesoid X receptor (FXR).

Obeticholic Acid (OCA, NDA 207999) is a modified bile acid and FXR agonist currently under FDA review for the treatment of PBC. OCA is also being developed for the treatment of other chronic liver diseases. OCA is derived from the primary human bile acid chenodeoxycholic acid, as is ursodeoxycholic acid, the only drug therapy currently approved for PBC (Urso®, NDA 20675). Chenodeoxycholic acid is the natural human FXR ligand. Unlike OCA, ursodeoxycholic acid has no significant FXR agonist properties. The primary mechanism of action is based on FXR-mediated activation resulting in release of FGF-19 from the intestine and downregulation of bile acid synthesis in the liver.

FXR activation suppresses cholesterol 7 alpha-hydroxylase, the rate-limiting enzyme in bile acid synthesis from cholesterol. In this way a negative feedback pathway is established in which synthesis of bile acids is inhibited when cellular levels are already high. FXR can be considered as a bile acid sensor that has evolved to maintain the enterohepatic circulation of bile acids and to protect hepatocytes from the toxicity of cellular bile acid overload. Besides the liver, FXR is expressed in the intestine, kidney and adipose tissue. Activation of FXR impacts a considerable number of genes and FXR ligands also are currently under investigation for treatment of dyslipidemias and insulin resistance.

FXR is a modulator of osteoblastic and osteoclastic activity, and FXR activation stimulates osteoblastic differentiation of bone marrow stromal cells (Boufker 2011). In mice, *in vivo* deletion of FXR results in a significant decrease in bone mass through decreased bone formation. FXR knockout mice also showed increased bone resorption parameters that included the osteoclast number and fractional surface (Cho 2013). Metabolic bone disease is recognized as a complication of chronic liver disease, and the term 'hepatic osteodystrophy' was first introduced in 1960. Hepatic osteodystrophy comprises two types of change in the bone, a secondary osteoporosis and osteomalacia related to vitamin D deficiency and malnutrition. In advanced stages of PBC, both these conditions may overlap. The relative importance of osteoporosis and osteomalacia as factors leading to hepatic osteodystrophy is unclear (Goel 2010).

Secondary osteoporosis is common in patients with PBC. Also, PBC occurs mainly in middle-aged women who are the highest risk group in primary osteoporosis. Most studies indicate that the development of osteoporosis in PBC is more associated with decreased bone formation. Bone biopsy and histomorphometry investigations demonstrate a decreased mineral appositional rate, decreased mean osteoid seam width and prolonged mineralization lag time were suggestive of a defect in matrix synthesis and potential a mineralization defect (Stellon 1987). Total resorption surfaces and fasting urinary calcium/creatinine ratios were increased, suggesting that increased resorption may also contribute to bone loss in primary biliary cirrhosis. The impaired function of osteoblasts may be the effect of cirrhosis-related (i.e. not solely PBC-related) reduction in the production of certain growth factors (especially IGF-1), increased synthesis of oncofetal fibronectin, or the direct toxic effect of unconjugated bilirubin and lithocholic acid on precursors and osteoblasts (Guanabens 2011).

In patients with PBC, the dysfunction in enterohepatic circulation of bile acids is associated with the impaired absorption of fats and fat soluble vitamins (Shibata 2015). Vitamin D and K deficiency leads to secondary osteoporosis and osteomalacia, resulting in an increased risk of bone fracture. Reduced hepatic synthesis of vitamin D binding proteins, reduced activity of 25-hydroxylase activity and reduced concentrations of the vitamin D receptor, inducing peripheral resistance to the hormone, may cause secondary hyperparathyroidism, which increases bone resorption and deepens the deficit of calcium ions. In turn, vitamin K deficiency, frequently observed in cholestasis, impairs osteoclast maturation and function.

The incidence of osteoporosis in PBC ranges from 20% to 44% and increases with the progression of the disease (Guanabens 2005, Mounach 2008). The reported prevalence of osteoporosis varies considerably across studies, and in the larger studies the incidence is approximately 30%. Bone densitometry, conducted using dual X-ray absorptiometry (DXA) scans, is recommended at the time of diagnosis of PBC. DXA is recommended to be conducted at 1 to 5 year intervals in the EASL cholestatic liver disease clinical practice guidelines (EASL 2009).

As anticipated by the high prevalence of osteoporosis in PBC, the incidence of bone fractures is high (10-20%) in this group of patients (Raszeja 2014). The fracture incidence increases with advanced liver disease (Pares 2008).

Protocol 747-301 Summary

Protocol 747-301 was 12 month Phase 3, double-blind, randomized, placebo-controlled parallel-group trial of OCA in patients with PBC, followed by an open-label extension study. Fifty-nine Investigators from 13 countries participated in this study. The study period from the first subject enrolled until the last subject completing the double-blind phase was March 2012 to December 2013. This review focuses on the 12 month double-blind phase of this protocol and the results germane to bone health.

Title: A Phase 3, Double Blind, Placebo Controlled Trial and Long Term Safety Extension of Obeticholic Acid in Patients with Primary Biliary Cirrhosis

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

- Serum alkaline phosphatase (ALP) and total bilirubin, together as a composite endpoint
- Safety (Including DXA and Adverse Event analysis for fracture)

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 noninvasive assessments of liver fibrosis
- Bile acids
- Other exploratory evaluations

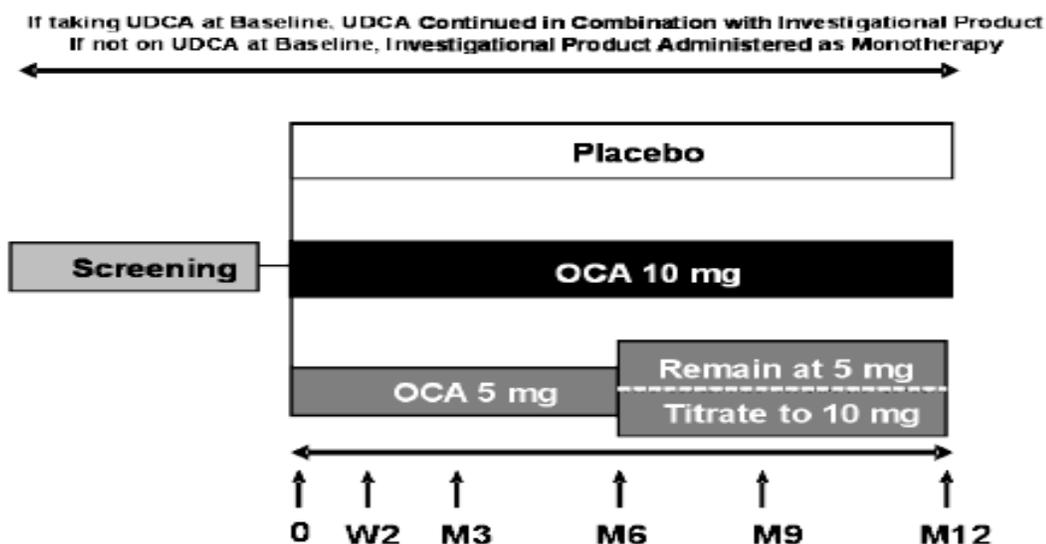
Study design: This study evaluated OCA in subjects with PBC who were either taking: 1) ursodeoxycholic acid (UDCA), the current standard of care for PBC, for at least 12 months (stable dose for ≥ 3 months) or 2) subjects who were unable to tolerate UDCA and did not receive UDCA for ≥ 3 months prior to Day 0. A total of 217 subjects were randomized into 3 groups in the study: (a) placebo (n = 73), (b) OCA 10 mg (n = 73), and (c) OCA titration (n = 71). The randomization was stratified using biochemical response criteria and tolerance to UDCA treatment as follows:

1. Pretreatment ALP $>3x$ upper limit of normal (ULN) and/or aspartate aminotransferase (AST) $>2x$ ULN and/or total bilirubin $> ULN$, intolerant to UDCA
2. Pretreatment ALP $\leq 3x$ ULN and/or AST $\leq 2x$ ULN and/or total bilirubin $\leq ULN$, intolerant to UDCA
3. Pretreatment ALP $>3x$ ULN and/or AST $>2x$ ULN and/or total bilirubin $>ULN$, currently taking UDCA

Subjects began taking investigational product on Day 1. All doses of investigational product were to be administered orally once daily. Subjects randomized to the OCA 10 mg treatment group received 10 mg throughout the entire 12-month duration. Subjects randomized to the OCA titration group received OCA 5 mg for the initial 6-month period. At Month 6, subjects in the OCA titration group who did not yet meet the criteria for the composite endpoint and did not have evidence of tolerability issues were titrated from OCA 5 mg to OCA 10 mg for the final 6 months of the double-blind phase.

During the double-blind phase, subjects who were taking UDCA before Screening continued UDCA treatment, a permitted concomitant medication. Unlike OCA, UDCA has no significant FXR agonist properties, which permits comparison of OCA treatment effect across treatment groups. The majority (93%) of the population was on UDCA at Baseline. The few (7%) subjects who were unable to tolerate UDCA before Screening received investigational product as a monotherapy. Figure 1 is a schematic of the 12 month double-blind phase study design:

Figure 1: Protocol 747-301 Study Design



Main inclusion criteria:

- Age ≥ 18 years
- A definite or probable diagnosis of PBC (consistent with American Association for the Study of Liver Diseases and European Association for the Study of the Liver Practice Guidelines, defined as having at least 2 of the following 3 diagnostic factors:
 - History of elevated ALP levels for at least 6 months
 - Positive anti-mitochondrial antibody (AMA) titer or if AMA negative or low titer ($<1:80$), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
 - Liver biopsy consistent with PBC
- At least 1 of the following qualifying biochemistry values:
 - ALP level $\geq 1.67x$ ULN
 - Total bilirubin $>ULN$ but $<2x$ ULN
- 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

Study populations:

1. Intent-to-Treat Population: All randomized subjects who received at least 1 dose of investigational product (N = 216). Treatment assignment was randomized.
2. 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.

3. Efficacy Evaluable 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.
4. Safety Population: All subjects who received at least 1 dose of investigational product (N = 216). Treatment assignment based on the treatment actually received.

Endpoints evaluated:

The assessment for composite efficacy endpoint was defined as follows: The percentage of subjects reaching an ALP <1.67x ULN and a ≥15% reduction in ALP from Baseline and a total bilirubin ≤ULN.

- Primary endpoint: Percentage of subjects (OCA 10 mg vs placebo) achieving composite endpoint at Month 12
- Key Secondary Endpoint: Percentage of subjects (OCA titration vs placebo) achieving composite endpoint at Month 12

Safety assessments:

Safety was assessed in the Safety Population by treatment-emergent adverse events, vital sign measurements, weight, BMI, 12-lead electrocardiograms, physical examinations, clinical laboratory results, dual-emission x-ray absorptiometry (DXA) scans, Mayo Risk Score, and Model for End Stage Liver Disease (MELD) scores. Pruritus was considered an adverse event (AE) of special interest. The study also employed patient questionnaires (5-dimensional pruritus, and pruritus visual analog scale)

Schedule of Assessments

The bone-related schedule of assessments for the double-blind phase of Protocol 747-301 is shown in Table 1:

Table 1: Schedule of bone-related assessments: double-blind Phase of 747-301

Visits	Screening	Day 0	Wk2	M3	M6 ^a	M9	M12	EOT ^b
Study Procedures								
DXA		X					X	X
AEs		X	X	X		X	X	X
Serum chemistry, hematology	X	X	X	X		X	X	X

a. The Month 6 assessment was for subjects who met the titration criteria

b. If a subject was withdrawn from the study early (regardless of the cause), all of the end-of-treatment (EOT) evaluations were performed at the time of withdrawal, to the extent possible.

Results

Demographic and Baseline Characteristics:

The mean (SD) age for all enrolled subjects was 56 (11) years, with a range from 29 to 86 years. A total of 81% of subjects were <65 years of age. As expected with PBC, the study population was predominantly female (91%) and white (94%). The majority of the population was European (67%), followed by North American (29%), and Australian (4%). Overall, the mean (SD) age at time of diagnosis was 47 (11) years. Out of 140 subjects enrolled with baseline DXA data, 10 were under the age of 40, and 27 were aged 40 to 50. The mean age of the 140 subjects undergoing DXA analysis was 57. The mean (SD) duration of PBC at time of entry was 9 (6) years. There appeared to be a comparable percentage of subjects with a duration of PBC of ≤7.5 years versus >7.5 years. The sponsor reports that baseline biochemical characteristics were well balanced across treatment groups.

Exposure:

A total of 216 subjects received at least 1 dose of investigational product: 73 subjects received placebo and 73 subjects received OCA 10 mg for the duration of the study. In the OCA titration group, 70 subjects received at least 1 dose of OCA 5 mg from Day 0 to Month 6. Table 2 shows exposure for subjects in the DXA substudy:

Table 2: Exposure in DXA Substudy Protocol 747-301

	Baseline (n=140)	Month 12 (n=124)
10 mg OCA:	44	38
5 mg titration to 10 mg OCA	47	44
Placebo	49	42

Bone Health- Protocol 747-301

Bone health was assessed in a subset of the Safety population, which included all subjects who received at least one dose of investigational product (N=216). Given that osteoporosis occurs frequently in patients with PBC (20% to 30%) and the fracture incidence increases with advanced liver disease, bone density using DXA scans were evaluated as an additional safety measure to evaluate if there was any worsening of osteoporosis or bone density (consistent with EASL guidelines) in each individual patient.

Bone Mineral Density

DXA scans were used to assess femoral neck and lumbar spine bone mineral density at Baseline and Month 12 in approximately 55% of subjects from the ITT population (n = 138 at Baseline and n = 122 at Month 12). DXA scans of the lumbar spine and femoral neck were conducted at a subset of study sites with the capabilities to perform this assessment. At those selected centers, all subjects were to undergo the assessment. A total of 40/59 (68%) of study sites indicated they had the capability of performing DXA scans. Thirty-seven of the 40 sites with DXA capabilities actually performed DXA scans. Of these 37 sites, 144 subjects were enrolled and the majority (96%) of these subjects underwent DXA assessment. No explanation was

provided for why the 6 subjects (4%) did not have DXA scans performed. Of these 6 subjects, 2 were in the placebo arm, 3 were on OCA 10 mg, and 1 was on OCA titration 5-10 mg.

For Protocol 747-301 DXA scans could be scheduled ± 2 weeks from each appropriate visit. Subjects who had a recent DXA scan with an available report within 6 months prior to Day 0 did not need to repeat the Baseline DXA scan. There were no specifications on the type of DXA device to be used. The protocol did require that the same two bone locations be scanned (i.e., femoral neck and lumbar spine) and that scans be performed with central rather than peripheral devices. Study site personnel recorded the bone location scanned, and for femoral neck scans, the side of the body for the femoral neck scan (left or right) was recorded. Bone density data were read locally from the device and entered directly by the study site into the eCRF. There was no systematic harmonization of DEXA data across sites, nor documentation of quality control measures at each site. That subjects be rescanned on the same machine at followup was not specified.

Results of the DXA scan were reported as bone mineral density (g/cm^2), T-score and Z-score for each subject. The DXA scan results of the femoral neck and lumbar spine (using T-score, Z-score, and bone mineral density) were summarized by treatment group using descriptive statistics at baseline and Month 12. Changes from baseline at Month 12 were analyzed using an ANCOVA model with baseline values as a covariate. T-scores were used to compare each subject's results with that of a healthy 30 year old same-sex adult while Z-scores were used to compare the subject to a same-sex, age-matched adult with the same ethnicity.

Reviewer Comments: The age-matched reading, known as the Z-score, compares a person's bone density to what is expected in someone of equivalent age, sex, and size. However, among older and elderly adults, low bone mineral density is common, so that comparison with age-matched norms can be misleading. The Z-score is useful in premenopausal women, men under the age of 50, and in children.

T-score changes may correlate inaccurately with bone mineral density changes, as varying baseline standards for peak bone mass are used. Important racial, geographic and gender differences exist in average peak bone mass values, often explained by differences in body size. The only bone DXA-derived endpoint acceptable to FDA is bone mineral density expressed in units of g/cm^2 .

Summarized DXA data from dataset ADMEAS are shown in Table 2:

Table 2: Summary DXA Data, Protocol 747-301 Subset of Safety Population (N = 140)

	Placebo			OCA Titration			OCA 10 mg		
	Baseline N=47	Month 12 N=44	Mean Actual Change	Baseline N=49	Month 12 N=42	Mean Actual Change	Baseline N=44	Month 12 N=38	Mean Actual Change
Lumbar (L2-L4) BMD									
g/cm ²	0.97	0.97	0	1.02	1.01	-0.01	1.03	1.00	-0.03
T-Score	-1.16	-1.42	-0.26	-1.10	-1.10	0	-0.82	-1.02	-0.09
Femoral Neck BMD									
g/cm ²	0.79	0.76	-0.03	0.80	0.81	0.01	0.87	0.81	-0.06
T-Score	-1.15	-1.48	-0.33	-1.29	-1.28	-0.01	-0.89	-1.06	-0.17

Source: Compiled by reviewer from dataset ADMEAS.

The World Health Organization diagnostic criteria for osteoporosis define osteoporosis in terms of a T-score below -2.5 and osteopenia (low bone mass) when T-score is between -2.5 and -1, inclusive. T-scores above -1 are considered normal. By these criteria, at Baseline subjects generally had normal to low bone mass and most remained within the same range at 12 months in all treatment groups.

One subject (USUBJID 129002, OCA 10 mg group) had a decrease in hip bone density of 8%, dropping from 0.846 to 0.781 g/cm². The event was reported by the Investigator as moderate severity TEAE and possibly related to investigational product. No TEAEs of fractures were reported in this subject. However, placebo subject 105002 also had an 8% decrease in femoral neck bone density over 12 months and sustained a fractured tibia.

Reviewer Comments: Mean changes in lumbar and femoral neck bone mineral density over 12 months appear comparable across the 3 treatment groups. Generally, mild reductions in BMD were observed in all treatment groups. These BMD changes are unlikely to be associated with increased fracture risk. An association with increased fracture risk has been shown only with much higher BMD decreases. For each standard deviation decrease in age-adjusted BMD, the risk for any fracture has been shown to increase by a factor of about 1.5 (Marshall 1996).

Overall, the incidence of osteoporosis in the OCA trial is low compared to that reported in previous PBC studies. It may be that most series in the past included either a small number of patients or the analysis was performed in the eighties or early nineties, when the disease was diagnosed in patients with significant cholestasis with advanced liver damage and more bone loss (Guanabens 2005).

Fractures

The Division was asked to analyze fractures as a potential adverse event for OCA. To put fractures in context, the System Organ Classes (SOCs) of Musculoskeletal and connective tissue disorders and Injury, Poisoning and Procedural Complications presenting as treatment-emergent AEs (TEAEs) in this study by preferred term are shown in Table 1:

Table 1: TEAEs occurring in $\geq 5\%$ of subjects Protocol 747-301 by relevant System Order class

Musculoskeletal and Connective Tissue Disorders			
TEAEs	Placebo (N=73)	OCA Titration (N=70)	OCA 10 mg (N = 73)
Subjects (Events)			
Arthralgia	3 (4)	4 (6)	7 (10)
Back Pain	8 (11)	4 (6)	4 (5)
Injury, Poisoning and Procedural Complications			
Procedural pain	1 (1)	4 (6)	1 (1)
Fractures	3 (4)	2 (3)	4 (5)

Reviewer Comment: Discounting one subject in the OCA 10 mg group who sustained a sternal fracture before dosing, 3.4% of subjects treated with OCA had fractures, as did 4% of placebo-treated subjects. These rates are consistent with background fracture rates documented in the age and sex-matched general population (discussion below).

Subject-level fracture data are provided by treatment group in Table 2:

Table 2: Subjects with fractures in Protocol 747-301

Subject	Gender/Age/Race	Fracture Site	Exposure Day(s)	Fragility Fracture	Comments
Placebo					
105002	Female/67 /white	Tibia	220	No	History clavicle fracture, hyperparathyroidism
174018	Female/76 /white	Pubis (2x)	114 122	Yes	Osteoporosis, history of fracture humerus
186005	Female/51 /white	Arm	50	No	Fall
OCA Titration					
162002	Female/62/white	Wrist	260	Yes	Hypothyroidism
172002	Female/63/Cuban	Ulna	248	No	
OCA 10 mg					
142022	Male/34 /white	Clavicle	75	No	Fall; required O.R.I.F.
159003	Female/53/white	Radius (2x)	16 243	Yes	Thyroidectomy, hysterectomy (2005)
161001	Female/51/white	Wrist	208	Yes	Hashimoto's disease
192003	Female/75/white	Sternum	-32	No	Withdrew consent prior to dosing

Source: Compiled by reviewer from dataset ADAE.

For the placebo group, 4 fractures (1 tibia fractures, 2 pubis fractures [same subject], and 1 upper limb fracture) were experienced by 3 subjects (Subjects 105002, 174018, and 186005); in the OCA titration group, 2 fractures (1 wrist fracture and 1 ulna fracture) were experienced by 2 subjects (Subject 162002 and Subject 172002); in the OCA 10 mg group, 7 fractures were listed. These included 2 clavicle fractures, 2 radius fractures, 2 wrist fractures, and 1 skeletal injury [sternal fracture]) that were experienced by 4 subjects (Subjects 159003, 161001, 142022, and 180007). The pubis fractures experienced by Subject 174018 were the result of an accidental fall. One subject (Subject 192003) randomized to OCA 10 mg, had a sternal fracture that occurred 32 days prior to initiation of investigational product, and withdrew study consent. None of these fractures were considered by investigators to be study-related.

Laboratory data were searched for factors independent of chronic liver disease that may have had an effect on fracture risk. Parathyroid hormone assays were not performed. Thyrotropin levels were assessed. Low thyrotropin (as in hyperthyroidism) is a risk factor for osteoporosis primarily because there are thyrotropin receptors on osteoblasts. All of the 8 subjects in the study with fractures each had thyrotropin levels assessed on 8 separate occasions during the study. Thyrotropin levels (mIU/L) were normal in all subjects.

The distribution of fractures by anatomic location across treatment groups is shown in Table 3 (untreated Subject 192003 not included):

Table 3: Fractures by anatomic site across treatment groups, Safety population N=216

Site	Placebo (N=73)	OCA Titration (N=70)	OCA 10 mg (N=73)
Clavicle	0	0	1
Radius	0	0	2 (same subject)
Tibia	1	0	0
Wrist	0	1	1
Ulna	0	1	0
Pubis	2 (same subject)	0	0
Arm	1	0	0

Reviewer comment: Radius, wrist and pubis fractures are generally considered fragility fractures due to loss of bone quality. The 2 pubis fractures in one subject (174018) were due to falling, and qualify as fragility fractures. There is no narrative for this subject, and the timeframe is unclear. Fractures of 2 pubic rami sustained simultaneously could be looked at as one fracture. These 2 pubic fractures were reported only 8 days apart and most likely represent one fracture. Therefore there were 5 fragility fractures in 4 subjects out of 8 subjects with fractures. The other fractures, (clavicle, ulna, arm and tibia) were most likely traumatic in origin. This fracture incidence (4%) is less than reported historically with PBC.

DEXA scan results for subjects sustaining fractures during the study are shown below in Table 4. DEXA scan results for 1 subject in the OCA titration group and 2 subjects in the OCA 10 mg group who sustained fractures are not available (NA).

Table 4: DEXA Scan Results for Subjects with TEAEs of Fractures, Safety population N=216

Subject Site/Days to Onset	Visit	Lumbar Spine			Femoral Neck		
		T-score	Z-score	BMD (g/cm ²)	T-score	Z-score	BMD (g/cm ²)
Placebo							
105002 (Tibia) 220	Day 0	-2.1	-0.2	0.815	-1.2	0.5	0.717
	Month 12	-2.1	-0.1	0.819	-1.9	-0.2	0.641
	Change (%)			0.004 (5)			-0.76 (-8)
174018 (Pubis x 2) 114, 122	Day 0	-4.8	-2.3	0.599	-4.2	-1.9	0.476
	Month 12	-5	-2.4	0.585	-4.3	-1.9	0.465
	Change (%)			-0.014 (-3)			-0.011 (-3)
186005 (Arm) 50	Day 0	1.6	2.7	1.393	0.4	1.4	1.025
	Month 12	1.3	2.5	1.356	0.5	1.6	1.036
	Change (%)			-0.037 (-3)			0.011 (10)
OCA Titration							
172002 (Ulna) 248	Day 0	-1.6	-0.5	0.993	-1.9	-0.7	0.775
	Month 12	-1.5	-0.3	1.008	-2	-0.8	0.756
	Change (%)			0.015 (0.02)			-0.19 (-2.5)
162002 (Wrist) 260	N/A						
OCA 10 mg							
142022 (Clavicle) 102	Day 0	-1.1	-1.1	0.967	-1.1	-0.8	0.779
	Month 12	-1.4	-1.4	0.934	-1.1	-0.8	0.774
	Change (%)			-0.033 (-3)			-0.005 (-1)
161001 (Wrist- scaphoid) 240	N/A						
159003 (Radius x 2) 16, 243	N/A						

Source: Compiled by reviewer from dataset ADMEAS

NA: Not performed or available

In the placebo fracture group, the mean percent change in lumbar spine BMD was -1% g/cm²; mean change in femoral neck BMD was -0.33%. In the one fracture subject with available DXA data from the OCA titration group, the changes respectively were 0.02% and -2.5%. For the 1 subject with available DXA data in the OCA 10 group, lumbar and femoral neck BMD changes were -3% and -1% respectively.

Reviewer Comment: No clear association between BMD changes and fracture risk can be shown with these sparse data. These changes are comparable to the means of all subjects in the 3 treatment groups, and therefore to the means of the age-related general population. As expected, Z-score and T-score changes don't appear to correlate in many cases.

Discussion

Osteoporosis and increased fracture risk are well-recognized sequelae of chronic liver disease, and worsen with the duration and severity of cholestasis. The DXA and fracture data from Protocol 747-301 do not indicate a bone safety issue with OCA:

DXA scan results

At Baseline, subjects generally had normal to low bone mass and most remained within the same range at 12 months in all treatment groups. Only 16 subjects had osteoporosis at Baseline; 20 subjects had osteoporosis at 12 months. The incidence of osteoporosis in this study is low compared to published literature in PBC. The prevalence of osteoporosis among patients with PBC is usually reported as significantly higher than in the age- and sex-matched population (Menon 2001). Varying but significant rates of osteoporosis in PBC have been reported (Table 3):

Table 3: Incidence of osteoporosis in PBC

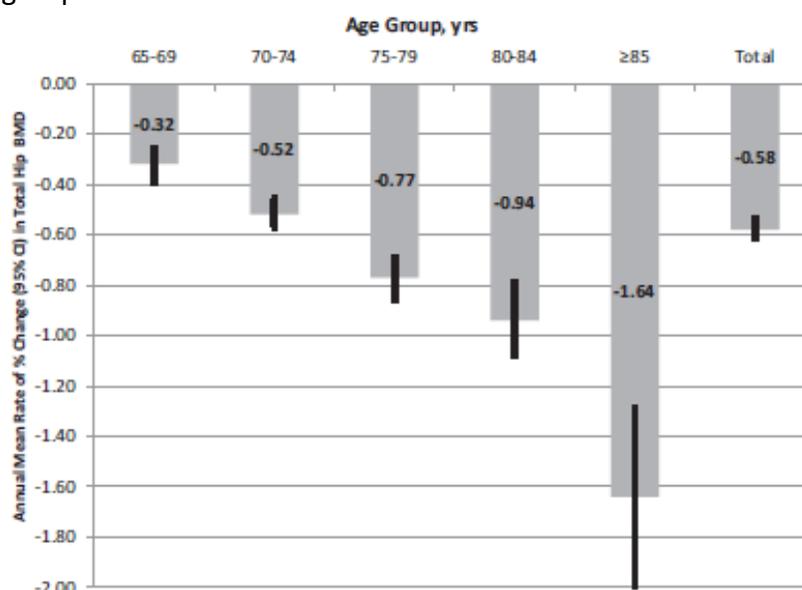
Author	Number of patients	Age (years)	Incidence (%)
Springer [5]	72	55 (34–81)	24
Parés [6]	61	54 ±1.1	21
Menon [7]	176	53 (29–72)	20
Newton [8]	272	62 ±11	31
Solerio [9]	133	53 (21–81)	35
Guañabens [10]	142	54 ±0.8	31
Guichelaar [11]	156	53 ±0.7	44
Guañabens [12]	185	56 (28–79)	32
Average	149	55	30

Source: Wyszomirska 2014

Overall, the incidence of osteoporosis in the OCA trial is low compared to that reported with PBC. A possible explanation is that most series in the past included either a small number of patients or the analysis was performed in the eighties or early nineties, when the PBC was diagnosed in patients with significant cholestasis, with advanced liver damage and more bone loss (Guanabens 2005).

Longitudinal studies in older adults have consistently observed that rates of bone loss increase with advancing age. A woman aged 65-69 can be expected to lose an average of 0.32% in total hip BMD annually. Background loss of bone mineral density in women by age group in the general population is shown in Figure 3:

Figure 3: Annual mean rate of percent change (95% confidence interval) in total hip BMD in women by age group



Source: Cooper 1992

In the OCA clinical trial, the mean (SD) age was 56 (11) years, with a range from 29 to 86 years. The rate of bone loss, comparable across treatment groups, appears to align with that of the age-matched general population. The relative roles of PBC and menopausal status in driving this bone loss are unclear.

Fracture

As with osteoporosis, increased fracture risk is a well-known complication of PBC. Vertebral and nonvertebral fractures occur in about 1 out of 5 patients with PBC. In one series 28 out of 132 PBC patients (21.2%) had fragility fractures; 18 of them had vertebral fractures, and 14 patients had peripheral fractures or both vertebral and peripheral fractures (Guanabens 2010). When compared with the general population, the absolute increase in fracture risk in patients with PBC is increased with an absolute excess fracture rate of 12.5 per 1,000 person-years (Solaymani-Dodaran 2006).

In the OCA trial, 3.4% of subjects treated with OCA had fractures, as did 4% of placebo-treated subjects. These rates are consistent with background fracture rates documented in the age and sex-matched general population (Table 4).

Table 4: The incidence of metaphyseal fractures per 10 000 population per annum related to age and gender (Singer 1998)

Age (yr)	Proximal humerus		Elbow		Wrist		Hip		Knee		Ankle	
	M	F	M	F	M	F	M	F	M	F	M	F
15 to 19	2.62	0.57	9.92	5.16	22.08	9.36	0.75	0.38	0.19	0.57	28.34	15.16
20 to 24	0.84	1.10	15.93	8.38	23.90	10.36	0.63	1.32	1.89	2.21	20.75	12.35
25 to 29	1.05	0.64	8.97	3.18	10.91	6.21	1.20	0.48	0.90	0.48	12.11	6.68
30 to 34	1.70	0.35	5.09	2.64	10.34	8.64	2.54	0.18	0.17	1.06	12.89	3.35
35 to 39	2.74	1.18	4.50	4.52	9.01	7.27	0.39	0.59	1.37	0.79	10.96	4.91
40 to 44	1.33	1.68	5.13	3.74	9.11	6.54	0.95	0.75	0.57	0.56	9.87	7.10
45 to 49	4.31	3.97	5.50	4.20	9.33	16.58	4.31	3.50	0.96	0.70	10.53	8.87
50 to 54	3.30	5.78	2.28	8.66	10.40	25.51	2.03	4.09	2.54	0.96	9.89	15.88
55 to 59	5.21	8.52	5.48	12.28	6.03	37.35	5.48	5.01	1.10	2.51	7.13	18.30
60 to 64	5.55	13.62	4.67	8.83	6.13	46.66	4.96	8.32	0.29	2.02	7.30	16.39
65 to 69	7.60	12.64	5.38	8.25	6.33	57.25	11.40	15.73	1.27	2.84	6.65	19.86
70 to 74	11.96	24.57	4.14	10.39	16.10	69.92	28.53	48.50	1.84	2.20	6.44	19.53
75 to 79	4.68	30.61	2.92	11.22	9.35	69.72	29.81	70.74	4.09	3.40	7.60	11.22
80 to 84	12.32	37.21	8.21	10.70	17.45	74.88	70.83	143.72	2.05	3.26	7.19	9.77
85 to 89	16.57	36.24	2.76	12.08	13.80	100.09	132.52	276.10	0.00	5.18	13.80	13.81
90 to 94	0.00	39.09	42.64	17.59	31.98	91.87	223.88	385.07	0.00	1.95	0.00	19.55

The fracture rate in the OCA trial is less than reported in past clinical experience with PBC. Again, this may be reflective of earlier intervention and enrollment of subjects with less liver-related bone damage than in past series.

Urso[®], (ursodiol, ursodeoxycholic acid, NDA 20675), is the only approved treatment for PBC. In Urso labeling there are no bone-related Warnings and Precautions or Adverse Reactions. In the 3 registration trials for Urso, a total of 452 subjects were exposed to test medication for a maximum of 733 days. Medical Reviews for approval (December, 1997) made no mention of fractures as a safety concern.

Summary and conclusion

This reviewer sees no evidence of a safety signal for bone health or fracture risk for OCA. The DXA scan results are generally consistent with the disease state, although they indicate less osteoporosis than reported in earlier series of PBC patients. The rate of bone loss is comparable to the age-related general population.

The fracture incidence is consistent with clinical experience with PBC and with background rates in the general population. Aside from routine DXA monitoring of PBC patients, as recommended by in the EASL cholestatic liver disease clinical practice guidelines (EASL 2009), no focused postmarketing bone monitoring for OCA is warranted.

References

Goel V, Kar P. Hepatic osteodystrophy. *Trop Gastroenterol*. 2010; 31:82–6.

Shibata H, Nakao K: Bone disease in primary biliary cirrhosis. *Clin Calcium*. 2015; 25 (11):1633-8

Raszeja-Wyszomirska J, Miazgowski T: Osteoporosis in primary biliary cirrhosis of the liver. *Prz Gastroenterol*. 2014;9 (2):82-7

Guanabens N et al.: Severity of cholestasis and advanced histological stage but not menopausal status are the major risk factors for osteoporosis in primary biliary cirrhosis. *J Hepatol*. 2005 Apr; 42(4):573-7

Guanabens N, et al. Low bone mass and severity of cholestasis affect fracture risk in patients with primary biliary cirrhosis. *Gastroenterology* 2010; 138: 2348-2356.

Guanabens N, Parés A. Management of osteoporosis in liver disease. *Clin Res Hepatol Gastroenterol*. 2011; 35:438–45.

Pares A et al.: Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. *Gastroenterology*. 2006 Mar; 130(3):715-20.

Mounach A et al.: Primary biliary cirrhosis and osteoporosis: a case-control study. *J Bone Miner Metab*. 2008; 26(4):379-84.

Wyszomirska J, Miazgowski T. Osteoporosis in primary biliary cirrhosis of the liver. *Gastroenterology Review*: 2017; 9 (2): 82-87

Cooper C, Melton LJ 3rd. Epidemiology of osteoporosis. *Trends Endocrinol Metab*. 1992; 3:224–229.)

EASL. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. *Journal of Hepatology*. 2009; 51(2):237-67.

Solaymani-Dodaran M, et al. Fracture risk in people with primary biliary cirrhosis: a population-based cohort study. *Gastroenterology* 2006; 131:1752-1757.

Singer B et al. Epidemiology of fractures in 15 000 adults. *J Bone Joint Surg (Br.)* 1998; 80-B: 243-8.

Stellon A et al. Low bone turnover state in primary biliary cirrhosis. *Hepatology*. 1987;7: 137-42

Guichelaar M et al. Bone metabolism in advanced cholestatic liver diseases: analysis by bone histomorphometry. *Hepatology* 2002; 36:895-903.

Marshall D et al. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996, 312:1254-1259.

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