Gastrointestinal Drug Advisory Committee (GIDAC) Meeting

April 7th, 2016

The committee will discuss New Drug Application (NDA) 207999 submitted by Intercept Pharmaceuticals, Inc. for obeticholic acid (OCA) proposed for the treatment of Primary Biliary Cirrhosis (PBC).

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the data from the clinical development program for obeticholic acid (OCA) for treatment of Primary Biliary Cirrhosis (also referred to as Primary Biliary Cholangitis) (PBC), as well as FDA's analyses of data from the Global PBC Study Group to this Advisory Committee in order to gain the Committee's insights and opinions on various issues that FDA has identified in reviewing this marketing application. The background package may not include all issues relevant to the final regulatory recommendation; instead, it is intended to focus on issues identified by the FDA for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Office of Drug Evaluation III, Division of Gastroenterology and Inborn Errors of Metabolism (DGIEP)
and
Office of Translational Sciences, Office of Biostatistics, Division of Biometrics 3

Background Package prepared March 15th, 2016

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
M E M O R A N D U M

Date:	March 15th, 2016
From:	Dragos Roman, MD Associate Director, Division of Gastroenterology and Inborn Errors of Metabolism (DGIEP) Office of Drug Evaluation III
To:	Chair, Members and Invited Guests Gastrointestinal Drug Advisory Committee (GIDAC)
Subject:	Review of Obeticholic Acid for the Treatment of Primary Biliary Cirrhosis (PBC)

Reviewers:

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1 DIVISION DIRECTOR MEMORANDUM

1.1 Introduction

In this New Drug Application, Intercept Pharmaceuticals Inc. (further referred to as the Applicant), is seeking approval of obeticholic acid (OCA) for the indication of "treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA."

Obeticholic acid is an analog of the naturally occurring bile acid chenodeoxycholic acid (CDCA), to which a single α-ethyl group was added to the 6-carbon position. CDCA is the natural ligand of the farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine, which regulates bile acid homeostasis. Obeticholic acid (OCA) is approximately 100-fold more potent than CDCA.

OCA is manufactured as 5 mg and 10 mg tablets, to be administered orally once daily. The Applicant is proposing a dosing regimen starting with a dose of 5 mg daily for the first 3 months followed by titration up to 10 mg daily based on tolerance to the medication (primarily pruritus) and biochemical response. Obeticholic acid (OCA) is a new molecular entity, and as such has not been approved for any other indication.

The Obeticholic acid (OCA) Phase 2 and Phase 3 clinical trials in Primary Biliary Cirrhosis

The OCA clinical program included two phase 2 and one phase 3 clinical trial, which will be summarized next (they will be discussed extensively in the following sections of this Advisory Committee Briefing Package).

1.2 Phase 2 Trials

The two phase 2 clinical trials were trials 747-201 and 747-202. Trial 747-201 was a dose ranging trial that studied OCA as monotherapy in patients with PBC. The second trial (747-202) was a dose ranging trial in patients with PBC in combination with ursodeoxycholic acid (UDCA).

Trial 747-201 was a dose-ranging trial that explored the efficacy and safety of OCA as monotherapy. Three months in duration, it evaluated two OCA daily doses (10 mg and 50 mg) against placebo in a randomized, double-blind, parallel group trial which enrolled 59 adult PBC patients (approximately 20 patients per arm) with alkaline phosphatase (ALP) levels between 1.5 x ULN and 10 x ULN, but excluded patients with direct bilirubin > 2 x ULN. The majority of

patients had early stage PBC; the mean baseline ALP was elevated at 433 U/L,[1] and the majority of patients had normal total bilirubin (TB) at baseline with a mean TB of 12 µmol/L (range 4 – 43 µmol/L). Efficacy was evaluated in this short trial by comparing the percent change in a biomarker, alkaline phosphatase (ALP), between groups, at the end of the 3-months treatment period. This trial showed a statistically significant decrease in mean alkaline phosphatase (ALP) in both dose groups relative to placebo: the OCA 10 mg group showed a mean reduction from baseline in ALP of 44.5%; the 50 mg group showed a 38% mean reduction from baseline, while the placebo group remained practically unchanged. In this small clinical trial, the 50 mg dose did not appear to offer additional evidence of efficacy over the 10 mg dose, and was less well tolerated. Pruritus, the most common adverse event observed during the trial, was seen more frequently in the 50 mg arm (94% vs. 70% with the 10mg dose and 30% with placebo). As many as 44% of patients discontinued the trial in the 50 mg arm, and all but one listed pruritus as a reason for discontinuation. Refer to Section 5 for a full review of the efficacy and safety data from this trial.

The second phase 2 clinical trial (747-202) evaluated three daily doses of OCA (10 mg, 25 mg, and 50 mg) in a randomized, double-blind, placebo-controlled clinical trial conducted in 165 adult patients with PBC (approximately 40 patients per arm). The duration of the trial was similar to that of trial 747-201 (3 months) as were the main biochemical inclusion criteria (ALP of 1.5 to 10 x ULN and exclusion of patients with direct bilirubin of > 2 x ULN). The mean ALP level at baseline was elevated (288 U/L). Again the majority of subjects had normal TB levels at baseline with a mean of 13 µmol/L (range 4 – 35 µmol/L). The study evaluated response to treatment by measuring biochemical improvements in alkaline phosphatase. Over 96% of patients in this trial had early stage PBC at baseline, characterized by normal total bilirubin and an elevated ALP but no higher than 3 x ULN. The main difference from trial 747-201 was that the three OCA doses were evaluated as an add-on to a standard ursodeoxycholic acid regimen (13-15 mg/kg/day) which patients had to have received for at least 6 months. Treatment with all three doses resulted in similar mean and median reductions of alkaline phosphatase relative to baseline (21-27%; the placebo arm showed a negligible reduction of 3%); there was no evidence for a better biochemical response with the 25 and 50 mg OCA dose over the 10 mg dose. While these results indicated that, when used in addition to a standard UDCA regimen, OCA resulted in additional reduction in ALP, and provided a rationale for proceeding to a phase 3 clinical trial, they did not support the use of the 25 mg and 50 mg regimens from an efficacy perspective. As seen in trial 747-201, pruritus was the most common treatment-emergent adverse event; it was more frequent in OCA treated patients than in the placebo arm, and occurred at higher rates with OCA doses greater than 10 mg. Several hepatic adverse events (new onset jaundice, variceal bleeding, significant worsening of hepatic biochemistries), were seen more frequently with the 25 and 50 mg OCA doses (hepatic adverse events will be discussed later in this memorandum).

[1] ALP ULN 117 U/L (females), 129 U/L (males); TB ULN 24 µmol/L

1.3 **Phase 3 Program**

Efficacy

The phase 3 clinical program consisted of a one-year, randomized, placebo-controlled, clinical trial (747-301), which was followed by an open-label, long-term extension. In addition to a placebo arm, trial 747-301 included two different OCA dosing regimens: a fixed-dose, 10 mg arm and a titration arm in which OCA treatment was initiated at a lower dose (5 mg) that was up titrated to 10 mg at month 6, depending on patient's tolerance to treatment and biochemical response, the latter being prespecified as a reduction in ALP and total bilirubin. The patients enrolled in this trial were adults with PBC who had been receiving UDCA for at least 12 months, with the UDCA dose stable for ≥ 3 months. The design of the trial was similar to that of trial 747-202 (placebo-controlled, OCA add-on to a standard of care UDCA regimen), except that it excluded OCA doses > 10 mg, and extended the evaluation of biochemical response up to 12 months. Another difference was that it allowed enrollment of some patients who could not tolerate UDCA , but this group of patients who received OCA as monotherapy was small (n = 16) and formed only a fraction of the 216 patients enrolled. To ensure balanced distributions of this subgroup of patients among treatment arms, they were stratified at randomization. Another criterion for stratification was related to the severity of patients' initial biochemical characteristics (ALP, total bilirubin and liver enzymes). Randomization ratio was 1:1:1; the number of patients per arm was around 70.

Clinical trial 747-301 planned to enroll patients with PBC and abnormal liver chemistries (specifically: ALP ≥ 1.67x upper limit of normal (ULN); total bilirubin greater than the ULN but below 2x ULN), and evaluate the biochemical response to OCA on both ALP and total bilirubin. The mean ALP level at baseline was elevated at 323 U/L[2] and the mean total bilirubin (TB) of 11 µmol/L was within the normal range (2 – 39 µmol/L). However, because the inclusion criteria specified that PBC patients had to have an elevated ALP **OR** an elevated total bilirubin, patients could be enrolled with an abnormality in only one of these analytes. This led to enrollment of a population of patients with PBC and elevated ALPs but with mostly normal bilirubin levels. Specifically, 198/216 (92%) of patients had bilirubin in the normal range at baseline, and only 18 (8%) had total bilirubin >ULN (all but 2 patients had ALP ≥ 1.67x ULN). Therefore, it is important to recognize that **the results of clinical trial 747-301 apply only to a subgroup of PBC patients, i.e. patients with relatively milder disease**, and that the subgroup of patients with **both** abnormal ALP and total bilirubin (patients with more severe biochemical manifestations) is too small to analyze and provide meaningful conclusions.

The pre-specified primary analysis was a responder analysis, and the definition of the response was a composite of three criteria:

- a reduction of ALP below 1.67×ULN at Month 12 **and**

[2] ALP ULN 118.3 U/L (females), 124.2 U/L (males); TB ULN 19.32 µmol/L (females), 25.48 µmol/L (males)

- a reduction of ALP ≥ 15% at Month 12 **and**
- a reduction of total bilirubin to < ULN at Month 12

Please note that given the fact that 92% of patients were enrolled with normal bilirubin, the primary endpoint evaluated in essence changes in only 2 of the 3 criteria, both related to changes in the same biomarker (alkaline phosphatase). This limitation and its implication will be discussed further in the Endpoint Section, below.

The results of the pre-specified primary efficacy analysis conducted by FDA (see table below) indicate that both OCA treatment groups showed a superior difference in the proportion/percentage of patients achieving response at Month 12 when individually compared to placebo. This analysis is further supported by multiple sensitivity analyses (e.g., completer and per protocol analyses, different imputation strategies such as "worst case scenario" and "ultra-worse-case imputation," etc.). For details, see Section 4 of this briefing document; secondary and exploratory analyses are further discussed in the same section.

Table 1: Proportion of Patients who Achieved Response at Month 12 (ITT)

Statistics	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)
Response at Month 12 – n (%) [1]	34 (46.6%)	32 (45.7%)	7 (9.6%)
Corresponding 95% Wald CI	36.5%, 59.4%	34.0%, 57.4%	2.8%, 16.3%
CMH Test p-value [2]	<0.0001	<0.0001	
Corresponding Breslow-Day Test p-value	0.9072	0.5045	

Source: Reviewer's Table 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]: Pair-wise comparison made between given OCA treatment group and Placebo adjusted for both randomization stratification variables.

1.4 Discussion of the Alkaline Phosphatase Endpoint

During the development of the obeticholic acid program in PBC, the Applicant and FDA had several face-to-face meetings, and multiple communications in which aspects of the clinical program such as trial design, dose selection, and selection of particular endpoints were discussed. The relative rarity of the disease, the wide spectrum of manifestations ranging from biochemical elevations (e.g., alkaline phosphatase in early disease, total bilirubin in more advanced disease) to the severe clinical phenotype (cirrhosis) in late stages, and the long and slow progression of the disease posed significant challenges in designing this clinical program.

Early on, FDA emphasized the limitations of using a biomarker (such as ALP) as an endpoint in a phase 3 clinical trial seeking marketing approval. The reservations were primarily related to the fact that specific reductions in ALP had not been demonstrated to predict clinical benefit (i.e., an improvement in how patients feel, function or survive). Therefore, the Division did not agree that ALP alone would be considered an appropriate endpoint to demonstrate clinical efficacy, and recommended that additional data would be needed to support an appropriate endpoint.

To this end, the Applicant helped establish and subsequently collaborated with the Global PBC Study Group, an academic research group founded in January 2012 by an independent research group whose principle investigators are located at the Erasmus MC University Medical Center in Rotterdam, Netherlands. The Global PBC Study consists of a combination of prospective and retrospective, multinational, multicenter registries that followed nearly 5,000 adult PBC patients until they achieved a clinical outcome of death or liver transplant. Data from this registry proposed that achievement of a reduction in elevated levels of ALP and TB at 12 months predicts clinical benefit (transplant-free survival; Lammers et. al., 2014[3]). The applicant subsequently leveraged the results from this independent study to construct the composite endpoint used in study 747-301.

The choice of specific cut-points for the phase 3 program (such as an ALP ≤ 1.67×ULN) was also based on analyzing additional data generated by other investigators in the PBC field (Kumagi et al., 2010[4]) and on a final determination that the "Toronto II" criteria (i.e., ALP ≤ 1.67×ULN and TB ≤ ULN) appear to be the most discriminating in predicting transplant-free survival in preliminary studies. In addition to the Toronto II criteria, a minimum % reduction in ALP was also included in the composite endpoint to ensure that patients enrolled with ALP values above but close to the 1.67 cut-point show at least a 15% reduction from baseline to be considered a responder.

Although the published data from the PBC Study Group propose that achievement of combined cut-points of ALP and TB predict transplant-free survival, it should be noted that such cut-points were derived from a PBC patient population that was different from the one evaluated in trial 747-301. The patients in the PBC Study Group represented a broader spectrum of the disease (i.e., those having early, moderate, or even late stage disease, including patients with elevated total bilirubin, not just elevated alkaline phosphatase). As already presented in this memorandum, the patients enrolled in trial 747-301 only had ALP elevations, a finding consistent with early stage PBC. In addition, the vast majority of patients in trial 747-301 also received concomitant UDCA treatment. As such, the cut-points purported to predict transplant-free survival in the PBC Study Group (ultimately chosen by the Applicant for the phase 3

[3] Lammers, W. J., et. al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with PBC: an international follow-up study. Gastroenterology 2014:1-12

[4] Kumagi, et. al., Baseline ductopenia and treatment response predict long-term histological progression in Primary Biliary Cirrhosis, American Journal of Gastroenterology 2010:105:2186-2194

program) could not be necessarily applied to the trial 747-301 patient population without further scrutiny.

Therefore, a determination as to whether ALP reduction **alone** (rather than in combination with TB) can be linked to a reduction in death or need for transplantation is critical to the interpretation of the efficacy data generated in the whole OCA clinical program, and in particular in the Phase 3 program. With this concern in mind, FDA conducted a thorough statistical evaluation of ALP reduction **alone** in a subset of patients from the aforementioned Global PBC Study who met similar inclusion criteria to those of patients enrolled in trial 747-301. This analysis is presented in detail within Section 4 below, and is fundamental to addressing the first question the FDA has for the Advisory Committee:

1. Discuss whether you think 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. Comment on the strength of evidence that supports the stratified responder criteria that were developed by the FDA statistical team's review of Global PBC Study Group data.

1.5 OCA Dosing Regimen

Several doses and dosing regimens were evaluated in the OCA clinical program. The Phase 2 dose-response clinical trials explored doses in excess of the to-be-marketed dose. Lack of a clear advantage from an efficacy standpoint and decreased tolerance (pruritus), along with an increase in hepatic adverse events, made the 25 mg and 50 mg daily OCA doses poor candidates for further study. In contrast, the 10 mg dose was better tolerated, was associated consistently and across clinical trials with better reductions in ALP over placebo.

While the OCA 10 mg daily regimen was supported by the phase 2 data, the Applicant appropriately explored an additional dosing regimen, the OCA titration regiment, in trial 747-301, where treatment was initiated at a dose of 5 mg, and subsequently up titrated to 10 mg if tolerability allowed and if the target reduction in alkaline phosphatase was not achieved by 6 months of treatment.

Based on the observed time course of alkaline phosphatase reduction and other observations detailed in the clinical pharmacology review, the Applicant has proposed a different dosing schema for clinical use. Specifically, while the 5 mg initial dosing and subsequent up titration to 10 mg were preserved, the newly proposed regimen recommends that up titration should be initiated earlier, at 3 months rather than at 6 months as was done during the phase 3 trial. This recommendation is triggered by the observation that the majority of patients who achieved a biochemical response did so prior to month 3 (see the Clinical Pharmacology Review in Section

12 for a full discussion of this topic). This information constitutes the basis of the second question the FDA is posing to the Advisory Committee:

2. Discuss the appropriateness of the Applicant's proposed dosage schema, i.e., a starting dose of 5 mg of obeticholic acid 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).

1.6 OCA as Monotherapy in PBC

In the phase 3 trial 747-301, only 16 (7.5%) patients received OCA as monotherapy. Use of OCA as monotherapy was also evaluated in the phase 2, dose-ranging clinical trial 747-201. Given the small number of patients who received OCA monotherapy and the different durations of the two trials, the FDA evaluated the response to OCA at 3 months in a post-hoc analysis that pooled patients from the phase 2 and the phase 3 trials. Using the Applicant's choice of primary endpoint, the pooled data showed a responder rate of 38% for monotherapy at 3 months, which was comparable to that achieved with OCA in patients on UDCA (41%). There was also a sustained reduction in ALP with OCA monotherapy in the phase 3 trial up to 12 months, not unlike that seen with OCA combination therapy with UDCA. Based on this evidence (detailed in Section 10), the FDA has the following question for the Advisory Committee:

3. 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.

1.7 OCA Dosing in Patients with Hepatic Impairment

The Applicant initially proposed that patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) cirrhosis be treated with the same dose as patients without cirrhosis. The FDA clinical pharmacology team performed modeling that shows that patients with moderate and severe cirrhosis have much greater systemic and hepatic exposure to OCA. In addition, safety data from the early phase 1 and 2 trials suggested that higher doses of OCA were associated with an increase in hepatic adverse events and elevations in transaminases. Therefore, for safety reasons, the FDA team recommends a reduced OCA dose for patients with moderate and severe hepatic impairment. Specifically, we recommend a starting dose of 5 mg 2 times a week, and then up titration to 3 times a week based on tolerability and biochemical response. See the clinical pharmacology review in Section 12 and the integrated summary of safety in Section 9 for a complete discussion of this topic. The FDA has the following request for the Advisory Committee:

4. 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.

5. Discuss whether you think the available evidence (i.e., PK modeling, dose response) supports the FDA's proposed dosage of obeticholic acid in PBC patients with moderately advanced (Child-Pugh B) and advanced (Child-Pugh C) cirrhosis.

1.8 Continuation of OCA in Patients without a Biochemical Response

The review team discussed whether a recommendation should be made for continued dosing in patients who do not exhibit a biochemical response to OCA after an adequate time on the maximally tolerated dose. The safety issues of pruritus, and OCA induced dyslipidemia favor discontinuation of OCA if there is no biochemical response. See the discussion in the clinical pharmacology review in Section 12.

6. Discuss the pros and cons of continuing obeticholic acid 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.

1.9 Safety Summary

The safety of OCA is reviewed in detail in Section 5 for trial 747-201, in Section 6 for trial 747-202, in Section 8 for the trial 747-301, and in Section 9 for an integrated summary of safety. The most common treatment-emergent adverse event was pruritus. Pruritus was not only a tolerability issue, but also severe enough to result in clinical trial discontinuation. Both the incidence and the severity of pruritus were dose-dependent. The significance of pruritus as a drug-related adverse event is further underscored by the fact that patients with severe pruritus due to their underlying PBC disease were excluded from the phase 3 trial. During the trial, patients who developed pruritus or had worsening of pruritus were offered treatment with bile acid sequestrants, antipruritic agents or had a drug holiday or attempts at dose reduction such as dosing every other or every third day. The majority of patients were able to tolerate OCA with these interventions, although 8 patients discontinued from the phase 3 trial secondary to pruritus (1 from the titration arm; 7 from the 10 mg OCA arm).

In addition, increases in low density lipoprotein cholesterol (LDL-C) and decreases in high density lipoprotein cholesterol (HDL-C) were seen in the majority of healthy volunteers and PBC patients treated with OCA in clinical trials. The clinical meaningfulness of these changes in cholesterol is not apparent in these relatively short-term trials, but will need to be considered in the overall risk benefit balance.

Elevations in transaminases and bilirubin were seen in OCA trials, especially with OCA doses higher than 10 mg daily, and some patients with underlying liver disease developed transaminase elevations and hepatic related adverse events at the 10 mg daily dose. As detailed in the integrated review of safety (Section 9), a total of 14 OCA-treated patients had 25 TEAEs that were classified as the Hepatic Disorder terms. There was a difference in the incidence of TEAEs in the MedDRA "hepatic disorders" System Organ Class (SOC) between OCA and placebo (5% and 1%, respectively). In addition, patients who were administered OCA 50 mg had a 2-fold higher incidence in adverse events of "hepatic disorders" compared with placebo and all other OCA dose groups. Although there were no cases of idiopathic drug-induced liver injury or liver failure, it will be important that patients with PBC be followed closely when started on OCA or when undergoing dose increases. It may even be necessary to discontinue drug if there is deterioration in hepatic function or evidence of hepatic injury with OCA use.

According to the Food and Drug Administration Safety and Innovation Act, FDA may grant accelerated approval to:

> . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit… taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

For purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.

Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. For effectiveness, the standard is substantial evidence based on adequate and well-controlled clinical investigations. For safety, the standard is having sufficient information to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling.

For drugs granted accelerated approval, postmarketing confirmatory trials have been required to verify and describe the anticipated clinical benefit.

The Applicant has started a confirmatory trial and the design of this trial is described in section 10. The confirmatory trial will enroll patients with a diagnosis of PBC based on the following biochemical criteria:

- mean ALP > 5×ULN **and/or**
- mean total bilirubin > ULN and ≤ 3×ULN.

Therefore the patients enrolled in this trial may be similar to the patients enrolled in the phase 3 trial, and have predominantly early stage PBC. In addition the Applicant states that they expect that more than 90% of patients enrolled will be on concomitant UDCA.

The clinical benefit to be measured in the confirmatory trial is a composite endpoint consisting of the following:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥ 15 (patients enrolled at ≤ 12)
- Hospitalization for new onset or recurrence of:
    - Variceal bleed
    - Encephalopathy
    - Spontaneous bacterial peritonitis
- Uncontrolled ascites
- Hepatocellular carcinoma

Given the evidence of efficacy seen in the phase 2 and phase 3 clinical program for OCA in patients with PBC, the issues discussed in Questions 1-6, and the overall safety observations made in the OCA clinical program, the FDA has the following question for the Advisory Committee members:

7. Taking into account the risks and benefit of OCA in the population studied, do you think there is the necessary substantial evidence to support accelerated approval of OCA for the treatment of PBC, based on its effect on alkaline phosphatase?
YES or NO

8. Discuss what if any changes in the enrollment criteria or design of the postmarketing confirmatory trial would be necessary to obtain any missing 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 missing data or information that has not been provided.

2 DISEASE BACKGROUND - APPROVED THEREAPIES - ENDPOINTS IN PBC CLINICAL TRIALS

2.1 Disease Background

Primary Biliary Cirrhosis (PBC) is a chronic, cholestatic liver disease which inevitably progresses to hepatic fibrosis, cirrhosis, hepatic decompensation, and eventually death, in the absence of liver transplantation. Typically, the clinical progression is relatively slow, and extends over many decades. The pathological signature of PBC is non-suppurative destruction of the small intralobular bile ducts ultimately leading to ductopenia, progressive impairment of hepatic bile flow, increased hepatocellular bile concentrations, and cell injury. Although the exact pathogenesis of PBC remains unknown, it is thought to be secondary to a combination of genetic predisposition and environmental triggers.

PBC is a rare disease. Incidence rates for Europe, North America, and Australia range from 0.33 to 5.8 per 100,000 inhabitants and prevalence is 1.91 to 40.2 per 100,000 inhabitants, respectively.[5,6] PBC disproportionately affects women (10:1 women to men ratio). The typical age of diagnosis is between 40 and 60 years; recent data suggest that young age at diagnosis (i.e., < 30 years of age) and male gender indicate a poor prognosis. [4] Racial and ethnic differences in PBC patients have not been clearly identified.

Early on, patients are typically asymptomatic, and suspicion of a potential PBC diagnosis is raised by an elevation of alkaline phosphatase noted on screening blood tests obtained during routine office visits. However, currently, patients are more likely to be diagnosed at earlier stages of the disease, secondary to the current practice guideline that include screening of liver biochemistries during routine physical exams.[7,8]

A diagnosis of PBC is confirmed when two of the following three criteria are met[9]:

1. Biochemical evidence of cholestasis with elevation of ALP activity (for more than 6 months)
2. Presence of antimitochondrial antibodies (AMA) (AMA directed against the E2 subunit of the pyruvate dehydrogenase complex are a sensitive serologic hallmark of PBC; they

[5] 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.
[6] 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.
[7] Prince MI, Chetwynd A, Craig WL, Metcalf JV et.al, Asymptomatic primary biliary cirrhosis: clinical features, prognosis, and symptom progression in a large population based cohort. Gut 2004; 53: 865-70.
[8] Floreani A, Caroli D, Variola A, Rizzotto ER, Antoniazzi S, Chiaramonte M, Cazzagon N, et al. A 35-year follow up of a large cohort of patients with primary biliary cirrhosis seen at a single centre. Liver Int 2011; 31: 361-8
[9] http://www.aasld.org/sites/default/files/guideline_documents/PrimaryBillaryCirrhosis2009.pdf

are seen in ~95% of patients, and can be detected years before the clinical signs of PBC appear)

3. Histologic evidence of chronic non-suppurative cholangitis of small and medium size bile ducts (if a biopsy is performed).

A classification of disease stage using biochemical parameters (Kuipers[10], et.al) has been proposed and utilized in clinical practice as follows:

- **Early stage disease**: normal total bilirubin, normal albumin, elevated ALP
- **Moderately advanced stage disease**: either elevated total bilirubin or low albumin, with elevated ALP
- **Advanced stage disease**: both low albumin and elevated total bilirubin, with elevated ALP though ALP may return to normal with end-stage cirrhosis.

Clinical signs and symptoms of PBC include the following:

1. Fatigue: It is the most common symptom, and is reported 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.
2. Pruritus: It occurs in 20%-70% of patients. Pruritus can be local or diffuse, is worse at night, and is often exacerbated by contact with certain fabrics (wool), heat, etc. Pruritus typically diminishes as disease progresses and disappears when patients develop cirrhosis and liver failure. Intractable pruritus can be an indication for liver transplantation.
3. Portal hypertension: It 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[11]. Complications of portal hypertension develop as the disease advances; they include esophageal varices/bleeding, ascites, and hepatic encephalopathy.
4. Hyperlipidemia: It is seen in PBC, with disproportionately elevated high density lipoprotein cholesterol. Historically patients with PBC have not been thought to be at increased risk of death from atherosclerosis.[12,13] This traditional view has been recently challenged.

[10] 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.
[11] Shapiro JM, Smith H, Schaffner F. Serum bilirubin: a prognostic factor in primary biliary cirrhosis. Gut 1979; 20: (2):137-40.
[12] 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
[13] 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

5. Hepatocellular carcinoma (HCC): The risk for HCC is increased in advanced PBC and is also associated with decreased survival. In the Global PBC Study Group, 123 out of 4845 PBC patients developed HCC, and data suggested that biochemical non-response to UDCA therapy is the strongest predictive risk factor for development of HCC.[14]
6. Autoimmune diseases: These are observed in patients with PBC. More than 80% of patients have been reported to exhibit features of at least one non-hepatic autoimmune disease sometime during the clinical course of the disease. Sicca syndrome is seen in up to 70% of PBC patients. Patients may also have Sjogren's syndrome, CREST (Calcinosis, Raynaud's, Esophageal dysfunction, Sclerodactyly, Telangectasia) and Raynaud's disease. Thyroid disease can also be seen with PBC.
7. Osteoporosis: This occurs in up to a third of patients. The relative risk of developing osteoporosis in PBC compared to age matched healthy patients is 4.4%. The cause of osteoporosis in PBC is uncertain.

Survival is reduced in patients with PBC. Once total bilirubin reaches 2 mg/dL mean survival is 4 years, and it declines to 2 years when bilirubin reaches 6 mg/dL. Without therapeutic intervention (pharmacological [e.g., nonselective beta-blockers for variceal bleeding], surgical portal-venous shunting, transcutaneous intrahepatic portacaval shunt) liver impairment progresses inexorably to liver failure and death, unless patients can undergo liver transplantation. The survival of individuals who develop esophageal varices is poor, with a 5-year survival rate without liver transplant of 63%.

Liver transplantation itself is associated with mortality and complications during and after the procedure (bleeding, rejection, infection, side effects of immunosuppressants, etc.).

2.2 Approved Therapies

The only pharmacologic agent approved for the treatment of PBC is ursodeoxycholic acid (UDCA), which was approved in the US in 1997 (the formal UDCA indication is "treatment of primary biliary cirrhosis"). UDCA was approved on the basis of 3 clinical trials.[15] In the first trial (a 2-year, placebo-controlled trial) the clinical endpoints evaluated in the trial were death, transplant, histologic progression by two stages or to cirrhosis, development of varices, ascites or encephalopathy, marked worsening of fatigue or pruritus, inability to tolerate the drug, doubling of serum bilirubin and voluntary withdrawal. This trial showed statistically significant improvement in these endpoints in the UDCA treated group. The second trial was a 2-year placebo controlled trial; it showed a statistically significant improvement in favor of UDCA in reducing the proportion of patients exhibiting a more than 50% increase in serum bilirubin; median percent increase in bilirubin, transaminases, and alkaline phosphatase; in

[14] Lammers, W. J., et. al. Levels of Alkaline Phosphatase and Bilirubin are surrogate end points of outcomes of patients with PBC: an international follow-up study. Gastroenterology 2014:1-12
[15] UDCA Labeling at Drugs@FDA.gov

discontinuations from the trial for any reason, increase in total bilirubin to greater than 1.5 mg/dL, and development of ascites or encephalopathy. However, other clinical benefit endpoints were unable to be evaluated at the 4 year follow-up secondary to high dropout rates. A third study, a 6-month study evaluating two different doses of UDCA failed to show a significant difference in outcomes of changes in liver biochemistries or Mayo risk score.

Several different meta-analyses of UDCA trials have subsequently been published in the literature and have reached variable conclusions regarding the potential benefits of UDCA in PBC on mortality and/or liver transplantation. Limitations of these trials included small sample sizes and short duration of trials. Trials were also limited to small and select populations contributing to selection bias.[16, ,5] Moreover, trials were often performed in major centers focusing on complex PBC phenotypes, potentially limiting generalizability to the broader spectrum of PBC patients.

However, subsequent publications with longer durations of follow up of patients treated with UDCA show a clear survival benefit. While UDCA therapy has a marked impact on clinical outcomes in PBC, up to 40% of UDCA-treated patients have a suboptimal or absent response to UDCA and, as such, are at significantly increased risk of an adverse outcome (death, requiring a liver transplant, or other clinical complications).[16,6,17] Several studies have shown that UDCA-treated patients with early stage disease, who respond biochemically to UDCA treatment, have survival rates comparable with a standardized general population.[17,6,16,17]

2.3 **Biochemical prognostic factors**

It is well established that serum total bilirubin[11] is one of the most powerful prognostic indicators in PBC and this variable has been incorporated in most scoring and prediction models. Albumin[17] is regarded as another important and powerful biochemical predictor of liver decompensation. Low serum albumin and high bilirubin values were shown to be independent predictors of the development of cirrhosis and mortality. However, it is apparent that bilirubin levels are more important in later disease stages than in early disease where they are generally normal.[11,17]

Angulo and colleagues were the first to report on the prognostic impact of changes in ALP values upon treatment with UDCA, showing that ALP values ≥ 2x upper limit of normal (ULN) after 6 months of treatment predicted future treatment failure. Since then, various biochemical responder criteria have been proposed as shown in Table 2 below.

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[16] Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008;48:871-877.

[17] 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 2006; 101: 2044-50.

Table 2: Biochemical Response Criteria for Risk Stratification in UDCA Treated Patients (Responder Criteria)[18]

Criteria	Definition of biochemical response	Evaluation time point	Number of patients
Mayo criterion, 1999[19]	ALP < 2.0xULN	6 months	180
Barcelona criterion, 2006[20]	> 40% decrease of ALP or normalization	1 year	192
Paris-1 criterion, 2008[21]	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, 2010[22]	ALP ≤ 1.67xULN	2 years	69
Toronto criterion, 2010	ALP <1.76x ULN or TB < ULN	10	69
Toronto criterion, 2011[23]	ALP <1.76x ULN AND TB <ULN	8.2	683
Paris-2 criterion,* 2011[24]	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[25]	ALP ≤ 1.67xULN and bilirubin ≤ 1mg/dL	1 year	73

*early disease patients only; **Japanese patients

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

[19] Angulo P, Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Kamath PS, Dickson ER. Utilization of the Mayo risk score in patients with primary biliary cirrhosis receiving ursodeoxycholic acid. Liver 1999; 19: 115-21.

[20] Pares A, Caballeria L, Rodus J. Excellent Long-Term Survival in Patients with Primary Biliary Cirrhosis and Biochemical Response to Ursodeoxycholic Acid. Gastroenterology 2006; 130:715- 720.

[21] Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008; 48:871-877.

[22] Kumagi T, Guindi M, Fischer SE, et al. Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. Am J Gastroenterol. 2010; 105(10):2186-2194.

[23] Meaney C, and Hirschfield G. Toronto Western Hospital PBC Study – Response Criteria Analysis. October 25, 2010, Internal Communication.

[24] Corpechot C, Chazouilleres O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. J Hepatol 2011; 55: 1361-7.

[25] Momah N, Silveira MG, Jorgensen R, Sinakos E, Lindor KD. Optimizing biochemical markers as endpoints for cli nical trials in primary biliary cirrhosis. Liver Int 2012; 32: 790-5.

2.4 **Summary**

PBC is a rare and potentially fatal disease leading to liver failure and the need for liver transplant to avoid death. There is only one drug approved for treatment of PBC at this time, ursodeoxycholic acid (UDCA). Approximately 50-60% of patients will respond to UDCA with improvement in liver biochemistries and symptoms. These responders appear to have a close to normal life expectancy, though meta-analyses of different trial data do not always generate consistent conclusions. For the remaining 40-50% of patients who do not respond to UDCA there is a clear slow but exorable progression to liver failure and the need for liver transplant, or death. The risk for hepatocellular cancer is also increased in non-responders to UDCA.[26]

Several scoring systems for assessment of baseline PBC status and treatment response have been developed by different academic institutions over the years; none of these have been validated; however, they are commonly used in clinical practice and to assess treatment response in clinical trials. **ALP as a stand-alone biomarker has not been validated in randomized clinical trials to predict clinical outcomes**.

[26] Boonstra, et. al, Increased cancer risk in a large population-based cohort of patients with primary biliary cirrhosis: follow-up for up to 36 years, Hepatology International, 2014:8:266-274

3 REGULATORY HISTORY

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 relative and absolute 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.

Based on the findings from the Global PBC Study Group[27], 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 ≤ ULN, and ALP decrease of ≥ 15% from baseline at Month 12.

[27] Lammers, W. J., et. al. Levels of Alkaline Phosphatase and Bilirubin are surrogate end points of outcomes of patients with PBC: an international follow-up study. Gastroenterology 2014:1-12

4 REVIEW OF PBC STUDY GROUP DATA

4.1 Summary For Global PBC Study Group Data

The Applicant submitted three efficacy trials (i.e., phase 2 trial 747-201, phase 2 trial 747-202, and phase 3 trial 747-301, respectively) to support the accelerated approval for obeticholic acid in treating adult patients with primary biliary cirrhosis. To date, the only drug therapy approved for PBC is ursodeoxycholic acid (UDCA), and the 747-202 and 747-301 trials allowed concomitant usage of this approved therapy.

Following FDA's advice, the Applicant collaborated with the Global PBC trial Group to investigate whether any liver-related biochemical variables, particularly for the endpoints used in the Phase 3 trial 747-301, i.e., alkaline phosphatase (ALP) and total bilirubin (TB), could be surrogates that would be reasonably likely to predict clinical benefit. Overall, the analyses of the Global PBC Study Group database supported the proposition that TB and ALP at 12 months and other time points after study enrollment are predictors for transplant-free survival in patients with PBC. The Applicant subsequently leveraged this finding to provide support for a Subpart H application based on the primary composite endpoint of ALP <1.67x ULN, total bilirubin ≤ULN, and ALP decrease of ≥15% from baseline at Month 12 for Phase 3 trial 747-301.

During the NDA review, the FDA noted that trial 747-301 primarily enrolled the early disease stage PBC patients, whose baseline ALPs were at least 1.67xULN and TB measurements were within the normal range (92% of patients enrolled). However, patients in the overall Global PBC database had a much broader disease spectrum than those included in trial 747-301. It remains unclear as to whether a patients' ALP at 12 months alone is reasonably likely to predict clinical outcome (i.e., death or liver transplant) in the patient population studied in trial 747-301. In addition, even if it could be used for this purpose, it appeared that it was difficult to clearly pre-specify a suitable cutoff. Therefore, we analyzed the PBC data by sub-setting patients with similar clinical demographics as those in trial 747-301 to better understand if evidence existed to support the use of ALP alone at 12 months to predict clinical outcomes for an early stage clinical population.

After sub-setting patients with normal TB at enrollment, we obtained 909 patients with 131 events from the Global PBC Study Group data for our analyses. Recall that in the original Global PBC study, there were 4845 patients with 1118 events of liver transplantation or death. In order to increase the reliability and generalizability, we randomly divided 909 patients into three small groups; (1) 25% of the data was used for model selection (2) 50% of the data served as the training set and (3) the rest 25% of the data was used as testing set. We conducted the analyses for seventeen cutoffs and 5 covariates to select the best fit model(s) and suitable cutoff(s).

After thorough evaluation, the model with the factors of the **age** and **baseline ALP raw lab values and ALP at 12 months** had been chosen as the best predictive performance for death or liver transplantation based on the smallest point estimate of the Akaike Information Criterion (AIC) value; note that the AIC is a measure of the relative quality of statistical models for a given set of data, and is commonly used for model selection. The distribution of ALP at time 0 or at 12 month is skewed. We have performed the model diagnosis and explored log transformation of ALP. We found that ALP at 12 months is an important predictive factor in the subset of subjects whose baseline ALP is at least 1.67xULN. Although the distributions of all ALP measurements (e.g., ALP and ALP lab raw values) are not perfectly symmetric, the same model was chosen based on log transformation. To be consistent with Lammer's paper, we presented results based on the original scale in this review.

Trial 747-301 used a combination cutoff which is ALP at Month 12 less than 1.67xULN and at least 15% decrease from baseline (we call it protocol defined cutoff in this review). As one inclusion criterion of trial 747-301 was baseline ALP at least 1.67xULN, patients whose baseline ALPs (as a multiple of ULN) are between 1.67 and any other derived ALP value (i.e., >1.67xULN) can only be responders if including the additional percent reduction criterion. In other words, any other absolute derived ALP value (>1.67xULN) will restrict some subset of patients who become responders only based on the additional percent reduction of ALP criterion. According to the results shown in Table 5.4 and 5.5 of the Appendix, the combination of 2.0xULN and either 15% or 40% reduction performed better than 1.67xULN and 15% reduction, we propose the following stratified cutoff to take into account the aforementioned patients in our cutoff selections:

> (1) ALP less than 1.67xULN at Month 12 and at least 15% decrease from baseline for the patients whose baseline ALP were between 1.67 and 2.0xULN; **or**
> (2) ALP less than 2.0xULN at Month 12 and at least 40% decrease from baseline for the patients whose baseline ALP were at least 2.0xULN)

From the above definition, our proposed stratified cutoff resulted in similar point estimates of C-statistic compared to other combined cutoffs of (a) 2.0xULN and 15%, (b) 2.0xULN and 40%, (c) 1.67+2.0xULN and 15%, (d) 1.67+2.0xULN and 40% (i.e., 0.68 to 0.69 in the training sets and 0.68 to 0.70 in the testing sets, respectively). We examined the robustness of our proposed stratified cutoff's predictability of transplant-free survival in comparison with protocol defined cutoff (i.e., ALP <1.67 ULN and 15% reduction) through subgroup analyses, including those by age, age at diagnosis, year of diagnosis, region and baseline ALP raw lab values. We found that the point estimates (hazard ratios) of the association between the cutoffs and the clinical outcome appeared to be consistent even though some of the 95% confidence intervals were narrower or wider than those in Global PBC Study, which can be mainly due to the smaller size of the subgroups. In conclusion, we believe that our proposed stratified cutoff appears more reasonable as a predictor for transplant-free survival.

4.2 Background

The Global PBC Study Group was 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 were located at the Erasmus MC University Medical Center in Rotterdam, Netherlands. Based on the findings from the Global PBC Study Group project[28], the applicant conducted one pivotal phase 3 trial 747-301 using the primary endpoint of achievement of ALP < 1.67x ULN, total bilirubin ≤ ULN, and ALP decrease of ≥ 15% from baseline at Month 12 for the accelerated approval for obeticholic acid (OCA) in the treatment of primary biliary cirrhosis (PBC) in adult patients.

During the NDA review, we noted the enrolled trial patients only represented the early disease stage PBC population; this population typically exhibits elevated ALP only and TB is within the normal range. The enrolled trial population was not directly comparable to the entire Global PBC Group (see Table 3). Therefore, we proposed sub-setting the Global PBC Group in order to address our main concern, which is whether ALP at 12 months is predictive of clinical outcome (i.e., death or liver transplant).

Table 3: Baseline Patient Characteristics for Global PBC Data and Trial 747-301

	Global PBC data (N=4845)	**Trial 747-301 (N=216)**
Age at entry (year)	54.5±12.0	55.8±10.5
Female	4348 (90%)	196 (91%)
AMA positive	4280 (88%)	194 (90%)
Year of diagnosis	1959-2012	1980-2012
Early disease stage	**2040 (42%)**	**198 (92%)**
Moderately advanced disease stage	**989 (15%)**	**18 (8%)**
Advanced disease stage	**259 (5%)**	**0 (0%)**
Bilirubin (>ULN)	**974 (26%)**	**18 (8%)**
ALP (×ULN)	2.10 (1.31-3.72)	2.40 (1.21-6.85)

Source: Applicant's 301-report-body.pdf and Lammers et al. 2014 paper's Table 1.

[28] Lammers, W. J., et. al. Levels of Alkaline Phosphatase and Bilirubin are surrogate end points of outcomes of patients with PBC: an international follow-up study. Gastroenterology 2014:1-12

4.3 Data Limitations

4.3.1 Limitations of Global PBC Data

To evaluate the use of the ALP and identify the best cutoff, we met and negotiated with the Global PBC Study Group's statistician and the applicant regarding the submission of the PBC study data. Even though we have thoroughly examined and tried our best to analyze the submitted data, we found that their data have the following limitations due to confidentiality/non-disclosure agreements that participating clinical sites made with the Global PBC Group, which disabled full/complete disclosure of all study data to FDA: (1) only the "years" of all the important dates (e.g., date of first visit, date of birth, UDCA date of start therapy, date of diagnosis of PBC, date of decompensation and end of follow-up date) were provided. (2) region information was only categorized as USA, Canada and Europe not as exact countries. (3) Global PBC database composed of an observation and retrospective registry data, therefore a lot of data were missing without any imputations. For the comparable subset, we have 7.92% (72 out of 909) missing ALP values (raw and derived) at 12 months (4) lab data were collected locally without centralization.

4.4 Statistical Evaluation

Our model selection was performed based on cross-validation prediction errors and Akaike Information Criterion (AIC) for 25% of the matched subset of Global PBC data, optimal cutoff (s) based on C-statistics and hazard ratios for the training set which has 50% of the data and the analysis set for the rest 25% of the data. The subgroups analyses were conducted to explore the robustness of the chosen optimal cutoff(s) for different region, age, age at diagnosis, baseline ALP and diagnosis year groups. Kaplan Meier curves were used to demonstrate the predictive ability of the chosen optimal cutoff(s).

4.4.1 Model selection

Data considerations

All but one patient in trial 747-301 have baseline ALP ≥ 1.67xULN; however, 92% of patients have normal TB, thus are in early stage PBC. Therefore, the medical review team determined that the analyses conducted based on a subset of Global PBC data with comparable clinical demographics to those in the trial 747-301 (see Table 8 in the Appendix) would be more applicable. In other words, it is necessary to re-analyze the PBC data by limiting to patients with baseline ALP ≥ 1.67xULN and normal TB thus are in the early stage (SG_DSRDAM=1) with UDCA use (UDCA=1). This subsetting resulted in 909 patients with 131 events, compared to 4845 patients with 1118 events of liver transplantation or death conducted by Global PBC group. Patients in the PBC subset had a much lower event rate of 14% compared to the event rate of 23% in the entire Global PBC study. This finding is in line with clinical expectations given the

course of disease. For this model selection, 25% (227 with 29 events) of 909 patients were randomly selected.

Comment:
It would be expected that patients with early stage disease would have a lower rate of clinical events of death and liver transplant than the entire PBC global study group which included patients with all stages of disease.

Candidate models
PBC is a female dominant disease, hence only age, year of diagnosis, ALP at baseline (raw or derived), duration of PBC and region were explored in the candidate models as covariates. Of note, we found that age and age at diagnosis was highly correlated and thus the age at diagnosis is not considered. Table 4 displays all different types of ALP at Month 12 which we considered. Note that in our analyses, the models including percentage changes from baseline were all adjusted for baseline ALP raw lab values and the absolute changes were all calculated based on the already derived data after they were converted to the ULN.

Table 4: Candidate Models Based on Different Types of Measurements for ALP and Covariates

ALP at 12 months	Covariates
Percentage change from baseline based on ALP lab raw values	Total 47 models: Age, diagnosis year and duration of PBC, region, ALP raw values at baseline
Absolute ALP	Total 61 models: Age, diagnosis year, ALP at baseline, region and duration of PBC

Best fit models based on cross-validations and AIC values
For the Cross validation (CV), we used 5-fold method. Our analyses were implemented through the R package "pec".

The statistical reviewer searched for the best fit models through candidate models using covariates age, baseline ALP and diagnosis year, region and duration of PBC. Based on the cross validation prediction errors and AIC (see Table 9 and Table 10 in the Appendix), the best fit model included terms of age and raw ALP values at baseline in addition to the percentage change from baseline. Here we only listed results for the models including ALP at 12 months and ALP at baseline (raw or derived values). Although the distributions of all ALP measurements (e.g., ALP and ALP lab raw values) are not perfectly symmetric, the model with the factors of the **age** and **baseline ALP raw lab values and ALP at 12 months** was also chosen based on log transformation.

4.4.2 Exploration of Potential Cutoff(s)

About 75% (682 with 102 events) of 909 patients were randomly selected for searching the optimal cutoff(s) by using ten random splits (training vs. testing is 2:1) and 5-fold cross validation methods. Both methods give the largest C-statistic and hazard ratio to our proposed combined cut-off, i.e., 1.67 x ULN and 15%, or 2.0 x ULN and 40%.

Ten random splits

Total of 682 patients were randomly split into two parts ten times: training set (455) and testing set (227). C-statistics and hazard ratios were calculated for each random split for both testing and training sets. We found that the combined cutoff: (1.67 x ULN and 15% decrease), or (2.0xULN and 40% decrease) can best predict patient outcomes based on C-statistics and hazard ratios (see Table 5 below and Table 11 in Appendix).

Table 5: Summary of C-statistics and hazard ratios (10 random splits)

Cut offs	C-statistic (mean)	Hazard ratio (mean)	Hazard ratio 95% CI (mean)	#significant p-values
10 Training sets				
1.67xULN and 15%	0.6395	1.82	(1.06, 3.13)	7/10
1.67xULN and 15% or 2.0xULN and 40%	0.6884	2.29	(1.33, 3.97)	10/10
10 Testing sets				
1.67xULN and 15%	0.6844	2.42	(1.08, 5.51)	4/10
1.67xULN and 15% or 2.0xULN and 40%	0.7000	2.54	(1.15, 5.69)	8/10

5-fold

Total of 682 patients were randomly split into 5 mutually exclusive subsets of approximately the same size of 135 patients per subset. After the first four subsets were combined, C-statistics and hazard ratios were calculated and then compared with the results in the fifth subset. The entire process was performed five times to allow each combination of 4 subsets to be pooled to serve as the training set and each subset not used in the training set to serve as the testing set. We also observed that the combined cutoff (1.67xULN and 15% decrease or 2.0xULN and 40% decrease) best predicted patient outcomes based on C-statistics and hazard ratios (see Table 7 below and Table 12 in Appendix).

Table 6: Summary of C-statistics and hazard ratios (5-fold)

	C-statistic (mean)	Hazard ratio (mean)	Hazard ratio 95% CI (mean)	#significant p-values
5 Training sets				
1.67xULN and 15%	0.6531	1.95	(1.19, 3.21)	5/5
1.67xULN and 15% or 2.0xULN and 40%	0.6924	2.32	(1.42, 3.80)	5/5
5 Testing sets				
1.67xULN and 15%	0.6775	2.38	(0.78, 7.44)	2/5
1.67xULN and 15% or 2.0xULN and 40%	0.6849	2.68	(0.89, 7.21)	1/5

4.4.3 **Subgroup analyses**

To assess the consistency and robustness, subgroup analyses for two cutoffs (i.e., our proposed stratified cutoff: 1.67xULN and 15% or 2.0xULN and 40% decrease from baseline for ALP at Month 12 and the protocol defined cutoff: 1.67xULN and 15% reduction) were conducted and displayed in Table 5.6 in the Appendix based on the total 909 patients. We used the best fitted model including age, raw ALP at baseline and percentage change from baseline for ALP at Month 12 to perform the subgroup analyses.

We obtained similar results between our proposed stratified cutoff and the protocol defined cutoff for Trial 747-301 except the diagnosis year < 1990. Due to the insufficient study duration and thus only 9 events observed for patients diagnosed after Year 2000, we only considered two subsets for patients' diagnosis year (i.e., < 1990 & 1990-2009). Although some of the 95% confidence intervals were narrower or wider, it can be mainly due to the smaller size of the subgroups. Figure 3 and Figure 4 display the Kaplan Meier survival curves for the protocol defined cutoff and our proposed stratified cutoff, respectively. It appears that the two curves in Figure 4 have a slight bigger separation after 10 years.

Table 7: Summary of subgroup analyses for hazard ratios (HRs)

			1.67xULN and 15% decrease		**1.67xULN and 15% decrease or 2.0xULN and 40% decrease**	
		N	HR	95% CI	HR	95% CI
Age (years)	≥ 65	179	1.415	(0.72, 2.78)	1.547	(0.80, 2.98)
	< 65	730	2.282	(1.38, 3.79)	2.757	(1.66, 4.58)
Age at diagnosis (years)	>45	677	2.201	(1.41, 3.43)	2.471	(1.58, 3.86)
	≤45	232	1.236	(0.50, 3.0)	1.810	(0.77, 4.26)
ALP baseline raw values (u/l)	≤277.5	314	1.417	(0.62, 3.23)	1.276	(0.59, 2.76)
	>277.5 and ≤465.5	215	1.076	(0.48, 2.39)	1.495	(0.69, 3.25)
	>465.5	380	4.475	(2.10, 9.54)	4.915	(2.32, 10.41)
Region	USA and Canada	270	1.573	(0.61, 4.07)	1.198	(0.49, 2.91)
	Europe	639	2.049	(1.31, 3.20)	2.603	(1.67, 4.07)
Diagnosis year	<1990	244	1.791	(0.98, 3.29)	2.366	(1.28, 4.37)
	1990-2009	631	1.923	(1.13, 3.28)	2.066	(1.22, 3.49)

Due to small number of events in diagnosis year 2000-2009, it was merged with 1990-1999 as one category.

4.4.4 **Forest and Kaplan-Meier Plots**

Figure 1: Forest plot for subgroup analyses
Cutoff: 1.67xULN and 15% decrease from baseline for ALP at 12 months

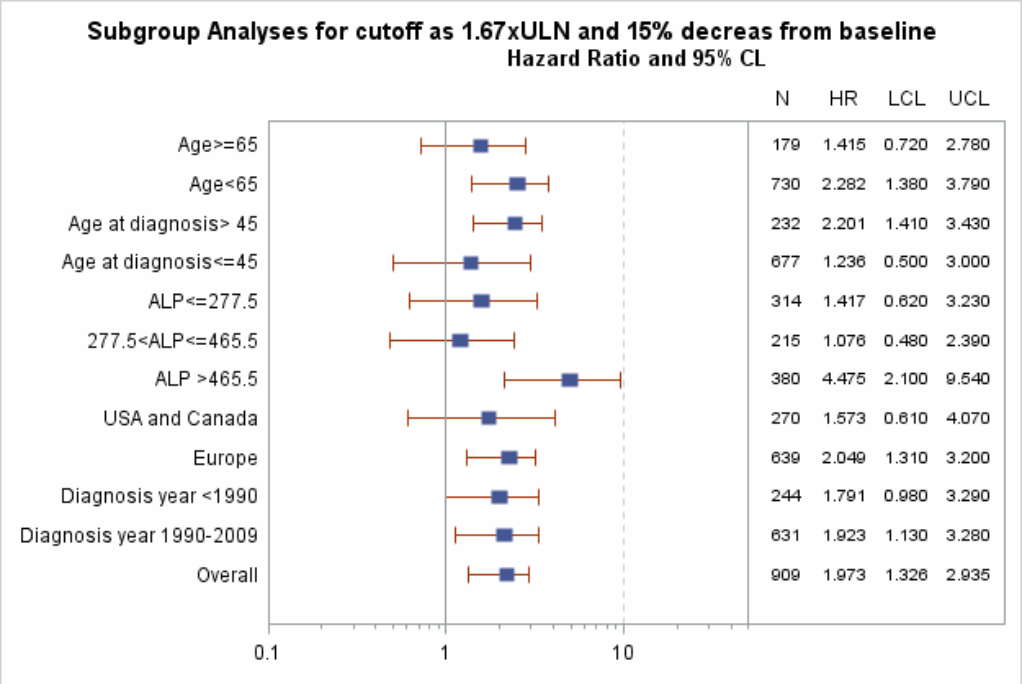


Figure 2: Forest Plot for Subgroup Analyses
Cutoff: 1.67 x ULN and 15% or 2.0 x ULN and 40% Decrease from Baseline for ALP at 12 Months

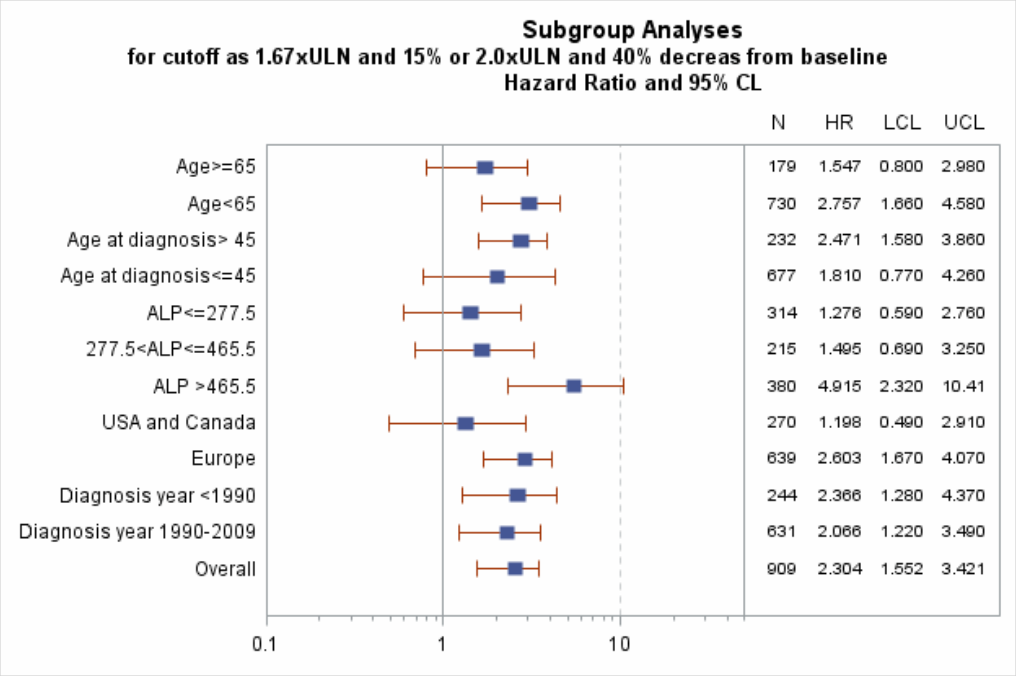


Figure 3: Kaplan-Meier Plot for Transplant-free Survival Probability
Cutoff: 1.67xULN and 15% Decrease from Baseline for ALP at 12 months

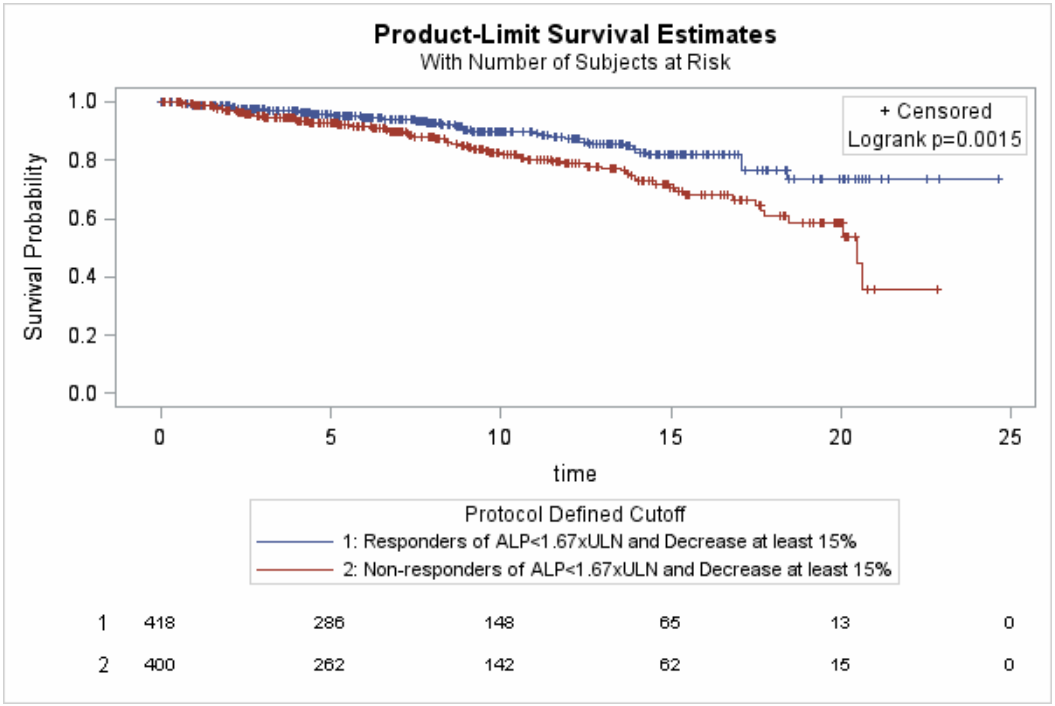
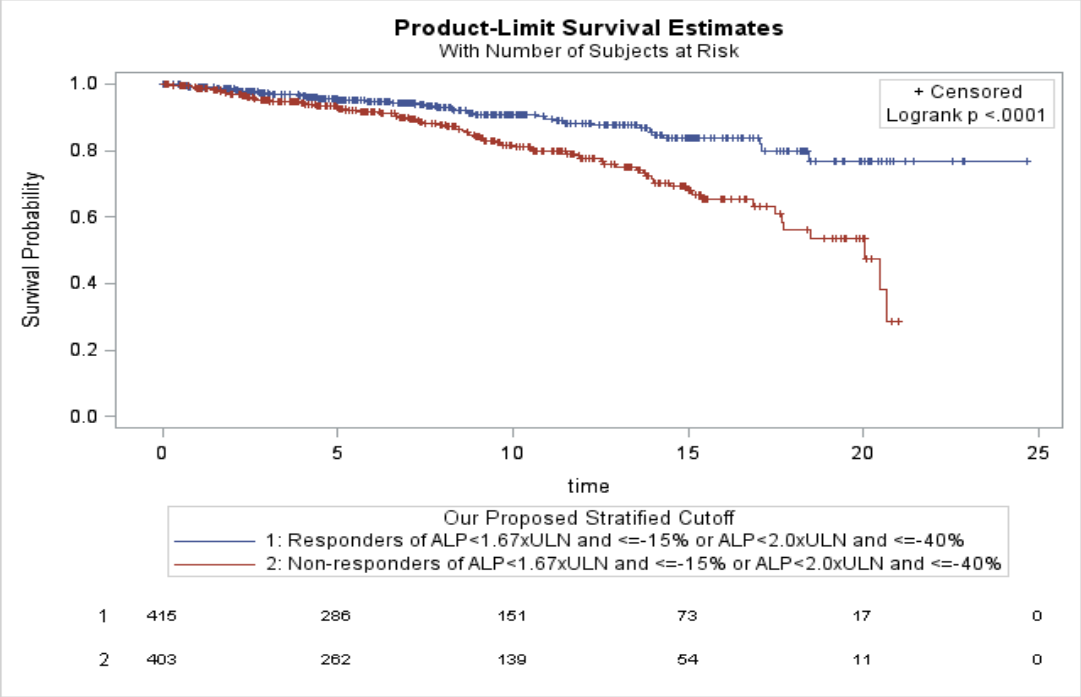


Figure 4: Kaplan-Meier plot for transplant-free survival probability
Cutoff: 1.67xULN and 15% or 2.0xULN and 40% decrease from baseline for ALP at 12 months



4.4.5 Summary of Findings

After sub-setting patients with similar clinical demographic as those in trial 747-301 (i.e. that had a normal TB at trial entry) we included a subset of 909 patients with 131 events in our analysis, compared to 4845 patients with 1118 events of liver transplantation or death in Global PBC database. Of these 909 patients, we randomly divided them into three parts: 25% for model selection, 50% for training set and the rest 25% as testing set. Seventeen cutoffs and 5 covariates were considered.

Our first step was to select the best fit model for each of two types of ALP at Month 12, among all the candidate models (61 models for the absolute ALP and 47 models for percentage change from baseline) by AIC and cross validation prediction error. The chosen models include the age and baseline ALP raw values when percentage from baseline was used.

Our second step was to select the optimal cutoff(s) based on C-statistics and hazard ratios by using the ten random splits and 5-fold methods. A fitted survival model including age, baseline ALP raw values and ALP at 12 months had the best predictive performance of death or liver transplantation (based on the point estimates of C-statistics and hazard ratios for time-to-event natural history data submitted by the Global PBC group) for the two types of patients: 1) those patients with baseline ALPs between 1.67 and 2.0 x ULN whose ALPs at

Month 12 were larger than or equal to 1.67 x ULN and had less than 15% decrease from baseline; or 2) for those patients with baseline ALPs at least 2.0 x ULN whose ALPs at Month 12 were larger than or equal to 2.0 x ULN and had less than 40% decrease from baseline.

Our final step is to check the robustness of the predictive ability of two cutoffs by subgroup analyses. The subgroups we explored include age, age at diagnosis year, region, diagnosis year and baseline ALP raw values.

Our proposed stratified cutoff resulted in similar point estimates of C-statistic compared to other combined cutoffs of (a) 2.0 x ULN and 15%, (b) 2.0 x ULN and 40%, (c) 1.67+2.0 x ULN and 15%, (d) 1.67+2.0 x ULN and 40% (i.e., 0.68 to 0.69 in the training sets and 0.68 to 0.70 in the testing sets, respectively). To allow the responder definition captures improvement of those subjects with baseline ALP between 1.67 x ULN and 2.0 x ULN as well as those with at least 2.0 x ULN, our proposed stratified cutoff appears more reasonable. Furthermore, this stratified cutoff had demonstrated numerically better performance than the protocol originally defined cutoff as 1.67 x ULN and 15% decrease from baseline in terms of point estimates of C-statistic and hazard ratios. Also the analysis results based on 10 random splits and 5-fold were similar. Our subgroup analysis results demonstrated that the point estimates (hazard ratios) of association between the cutoffs and the clinical outcome appeared to be consistent. Although some of their 95% confidence intervals were narrower or wider, it could be mainly due to the smaller size of the subgroups. The Kaplan Meier survival curves for our proposed stratified cutoff appears to have a slight bigger separation after 10 years.

4.5 **Appendix**

Table 8: 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 GPBC lab 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 8 continued: 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	1.7, 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)	7.02 (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 9: AIC values and prediction errors (33 models for absolute ALP)

Models	AIC	Prediction Error (5-fold)
Age	249.604	0.119
alp12	223.134	0.119
alp0+alp12	224.718	0.119
Diag_yr+alp12	224.892	0.119
Age+alp12	**219.955**	**0.114**
Region+alp12	225.111	0.123
Disease_duration_at0+alp12	225.072	0.121
alp0+alp12+Age	221.772	0.115
alp0+alp12+Diag_yr	226.270	0.123
alp0+alp12+Region	226.630	0.125
alp0+alp12+Disease_duration_at0+alp12	226.619	0.121
Diag_yr+Age+alp12	221.845	0.116
Diag_yr+Region+alp12	226.892	0.127
Diag_yr+Disease_duration_at0+alp12	226.830	0.124
Age+Region+alp12	221.894	0.119
Age+Disease_duration_at0+alp12	221.940	0.116
Disease_duration_at0+alp12+Region	227.059	0.126
Diag_yr+Age+alp0+alp12	223.561	0.117
Diag_yr+Region+alp0+alp12	228.253	0.130
Diag_yr+Disease_duration_at0+alp0+alp12	228.113	0.125
Age+Region+alp0+alp12	223.670	0.121
Age+Disease_duration_at0+alp0+alp12	223.767	0.117
Region+Disease_duration_at0+alp0+alp12	228.554	0.128
Age+Region+Diag_yr+alp12	223.817	0.122
Age+Disease_duration_at0+alp12+Diag_yr	223.373	0.120
Disease_duration_at0+alp12+Region+Diag_yr	228.830	0.129
Disease_duration_at0+alp12+Region+Age	223.868	0.121
Diag_yr+Region+Age+alp0+alp12	225.514	0.124
Disease_duration_at0+Diag_yr+Age+alp0+alp12	224.941	0.121
Disease_duration_at0+Region+Diag_yr+alp0+alp12	225.361	0.132
Disease_duration_at0+Region+Age+alp0+alp12	225.657	0.124
Disease_duration_at0+Diag_yr+Age+alp0+alp12	224.941	0.121
Disease_duration_at0+Regio+Diag_yr+alp0+alp12+Age	226.915	0.129

Table 10: AIC Values and Prediction Errors (17 models for percentage change for ALP)

Models	**AIC**	**Prediction Error (5-fold)**
Age+labalp0	251.017	0.123
Percent_change_alp12+labalp0	227.522	0.128
Percent_change_alp12+labalp0+Age	**224.851**	**0.122**
Percent_change_alp12+labalp0+Diag_yr	228.733	0.134
Percent_change_alp12+labalp0+Region	229.405	0.128
Percent_change_alp12+labalp0+Disease_duration_at0	229.302	0.129
Percent_change_alp12+Diag_yr+Age+labalp0	226.304	0.126
Percent_change_alp12+Diag_yr+Region+labalp0	230.755	0.136
Percent_change_alp12+Diag_yr+Disease_duration_at0+labalp0	230.614	0.136
Percent_change_alp12+Age+Region+labalp0	226.754	0.123
Percent_change_alp12+Age+Disease_duration_at0+labalp0	226.815	0.123
Percent_change_alp12+Region+Disease_duration_at0+labalp0	231.223	0.131
Percent_change_alp12+Diag_yr+Region+Age+labalp0	228.281	0.128
Percent_change_alp12+Disease_duration_at0+Diag_yr+Age+labalp0	227.749	0.129
Percent_change_alp12+Disease_duration_at0+Region+Diag_yr+labalp0	232.604	0.124
Percent_change_alp12+Disease_duration_at0+Region+Age+labalp0	228.732	0.129
Percent_change_alp12+Disease_duration_at0+Diag_yr+Age+labalp0+Region	229.736	0.131

Table 11: Summary of C-statistics and Hazard Ratios (10 random splits)

Cut offs	C-statistic (mean)	Hazard ratio (mean)	Hazard ratio 95% CI (mean)	#significant p-values
10 Training sets				
1.0xULN	0.5783	2.43	(0.88, 6.99)	3/10
1.67xULN	0.6515	1.92	(1.14, 3.25)	6/10
1.76xULN	0.6614	2.07	(1.22, 3.49)	7/10
2.0xULN	0.6218	2.28	(1.36, 3.82)	10/10
3.0xULN	0.6311	2.92	(1.64, 5.23)	7/10
15%	0.6557	2.20	(1.24, 3.89)	7/10
30%	0.6280	1.75	(1.04, 2.96)	5/10
40%	0.6587	2.0	(1.19, 3.34)	9/10
60%	0.6073	1.68	(0.82, 3.51)	1/10
1.67xULN and 15%	0.6395	1.82	(1.05, 3.13)	7/10
1.67xULN and 40%	0.6509	2.12	(1.18, 3.81)	9/10
2.0xULN and 15%	0.6804	2.07	(1.22, 3.52)	10/10
2.0xULN and 40%	0.6877	2.55	(1.44, 4.50)	10/10
1.67+2.0xULN and 15%	0.6761	2.03	(1.19, 3.44)	10/10
1.67+2.0xULN and 40%	0.6841	2.51	(1.43, 4.44)	10/10
1.67 and 15% or 2.0 and 40%	0.6883	2.29	(1.33, 3.97)	10/10
1.67 and 40% or 2.0 and 15%	0.6746	2.15	(1.26, 3.66)	10/10
10 Testing sets				
1.0xULN	0.6087		(0.50, 6.89)	1/10
1.67xULN	0.6840	2.57	(1.15, 5.80)	4/10
1.76xULN	0.6880	2.52	(1.16, 5.53)	4/10
2.0xULN	0.6930	2.76	(1.31, 5.83)	7/10
3.0xULN	0.6730	3.67	(1.64, 8.23)	5/10
15%	0.6914	2.31	(1.05, 5.13)	6/10
30%	0.6749	2.27	(1.09, 4.76)	5/10
40%	0.6967	2.38	(1.13, 5.00)	6/10
60%	0.6336	2.33	(0.73, 7.83)	3/10
1.67xULN and 15%	0.6844	2.42	(1.08, 5.51)	4/10
1.67xULN and 40%	0.6849	2.69	(1.09, 6.86)	6/10
2.0xULN and 15%	0.7004	2.54	(1.19, 5.46)	6/10
2.0xULN and 40%	0.6992	2.82	(1.22, 6.64)	8/10
1.67+2.0xULN and 15%	0.7007	2.48	(1.16, 5.32)	6/10
1.67+2.0xULN and 40%	0.6986	2.78	(1.20, 6.54)	8/10
1.67 and 15% or 2.0 and 40%	0.7000	2.54	(1.15, 5.69)	8/10
1.67 and 40% or 2.0 and 15%	0.7053	2.57	(1.19, 5.59)	7/10

Table 12: Summary of C-statistics and Hazard Ratios (5-fold)

	C-statistic (mean)	Hazard ratio (mean)	Hazard ratio 95% CI (mean)	#significant p-values
5 Training sets				
1.0xULN	0.592	2.06	(0.91, 4.68)	1/5
1.67xULN	0.663	1.98	(1.23, 3.20)	5/5
1.76xULN	0.669	2.09	(1.30, 3.36)	5/5
2.0xULN	0.641	2.34	(1.47, 3.73)	5/5
3.0xULN	0.642	3.06	(1.81, 5.18)	5/5
15%	0.6620	2.22	(1.32, 3.72)	4/5
30%	0.6413	1.88	(1.17, 3.02)	4/5
40%	0.6582	2.05	(1.29, 3.27)	5/5
60%	0.6055	1.68	(0.89, 3.17)	1/5
1.67xULN and 15%	0.6531	1.95	(1.19, 3.21)	4/5
1.67xULN and 40%	0.6526	2.18	(1.28, 3.70)	5/5
2.0xULN and 15%	0.6893	2.21	(1.36, 3.58)	5/5
2.0xULN and 40%	0.6919	2.54	(1.52, 4.22)	5/5
1.67+2.0xULN and 15%	0.6877	2.16	(1.33, 3.50)	5/5
1.67+2.0xULN and 40%	0.6917	2.50	(1.50, 4.16)	5/5
1.67 and 15% or 2.0 and 40%	0.6924	2.32	(1.42, 3.80)	5/5
1.67 and 40% or 2.0 and 15%	0.6839	2.26	(1.39, 3.66)	5/5
5 Testing sets				
1.0xULN	0.581		(0.33, 8.49)	0/5
1.67xULN	0.666	1.79	(0.82, 6.53)	0/5
1.76xULN	0.673	2.42	(0.87, 6.76)	1/5
2.0xULN	0.725	2.67	(0.99, 7.24)	1/5
3.0xULN	0.692	3.70	(1.13, 12.5)	1/5
15%	0.6796	2.68	(0.86, 8.57)	1/5
30%	0.6989	2.91	(0.92, 9.51)	1/5
40%	0.6945	2.61	(0.88, 8.02)	1/5
60%	0.6404	2.09	(0.52, 8.63)	0/5
1.67xULN and 15%	0.6775	2.38	(0.78, 7.44)	2/5
1.67xULN and 40%	0.6628	2.35	(0.77, 7.25)	0/5
2.0xULN and 15%	0.7014	2.54	(0.88, 7.42)	1/5
2.0xULN and 40%	0.6967	2.74	(0.91, 8.42)	1/5
1.67+2.0xULN and 15%	0.6989	2.49	(0.86, 7.27)	1/5
1.67+2.0xULN and 40%	0.6961	2.71	(0.90, 8.31)	1/5
1.67 and 15% or 2.0 and 40%	0.6849	2.68	(0.89, 8.26)	1/5
1.67 and 40% or 2.0 and 15%	0.6962	2.50	(0.88, 7.21)	1/5

CLINICAL SUMMARIES

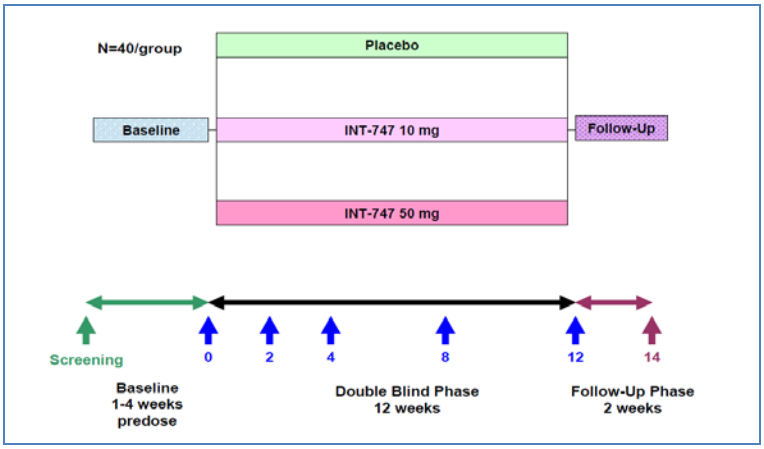
5 PHASE 2 TRIAL 747-201 USE OF OCA AS MONOTHERAPY

Trial 747-201: OCA monotherapy (no UDCA use for at least 3 months before screening)

5.1 Trial Design

Study 747-201 was a double-blind, placebo-controlled, 12 week, multicenter trial, which enrolled 60 patients with early disease stage PBC, out of which 59 patients were randomized 1:1:1 in three parallel groups (23 patients in placebo; 20 patients in OCA 10 mg; and 16 patients in OCA 50 mg w). It studied two doses of OCA (10 mg, and 50 mg) vs. placebo for a period of 12 weeks (85 days). The study was completed by 48 patients and PK data are available for 34 patients. All 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. There was a 2-week follow-up period, i.e., up to day 99.

Figure 5: Graphical representation of study



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Key Inclusion criteria:

1. Age >18 years,
2. Both male and female had to use one effective method of contraception,
3. Proven or likely PBC demonstrated by patient presenting with at least 2 of the 3 diagnostic criteria
   1. History of increased ALP
   2. Positive AMA

3. Liver biopsy consistent with PBC
4. Screening ALP value between 1.5 and 10 X ULN.

Key Exclusion Criteria

1. The following drugs were contraindicated: ursodeoxycholic acid (UDCA), colchicine, methotrexate, azathioprine, or systemic corticosteroids
2. Conjugated bilirubin >2 XULN; ALT or AST > 5X ULN and serum creatinine >133 µmol/L (1.5 mg/dL)
3. History or presence of hepatic decompensation
4. History of presence of concomitant liver diseases such as Hepatitis B or C; HIV; primary sclerosing cholangitis, alcoholic liver disease, definite autoimmune liver disease or biopsy proven nonalcoholic steatohepatitis (NASH).
5. Pregnancy

Primary efficacy endpoint

1. The primary efficacy endpoint: Percent change (%) in serum ALP from Baseline to End of Study (EOS). 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 applying the Paris I, Toronto I, Toronto II, Toronto III, Toronto IV, Mayo II, and Barcelona disease prognostic risk criteria at Day 85/ET (see Section on Disease Background for a definition of these criteria)

- 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)

Safety Endpoints

2. Study duration
3. Dose and compliance with study medication
4. Status at the end of study; reasons for withdrawal

5. Treatment-emergent adverse events (TEAEs) including overall incidence, severity, relationship to study drug, relationship by severity, action taken, outcome
6. Vital sign measurements
7. 12-lead electrocardiograms
8. Physical examinations
9. Concomitant medications
10. Clinical laboratory assessments
11. Safety parameters of special interest for OCA were as follows:
    a. Pruritus-related assessments:
        i. Pruritus adverse events (AEs)
        ii. Clinically significant interventions for pruritus
        iii. 5-Dimensional (5-D) questionnaire as it relates to pruritus
    b. Investigator assessment of pruritus per visual analog scale (VAS)
        i. Hepatic AEs
        ii. Changes in lipids and cardiovascular events

Mandatory discontinuation: Development of the following clinical laboratory values:

- ALT or AST ≥3x average predose value, and >ULN or
- Conjugated [direct] bilirubin >2x average predose value [average of screening and baseline], and >1.5 mg/dL [25.7 µmol/L].

5.2 Study Results

Patient Disposition

Of the 59 randomized patients included in the ITT Population, 23 patients were randomized to placebo, 20 patients to OCA 10 mg, and 16 patients to OCA 50 mg. Overall, 48 patients (81%) received at least 1 dose of investigational product, and participated through the end of the double-blind phase, i.e., Day 85 (Completer Population: 23 patients [100%], 16 patients [80%], and 9 patients [56%], in the placebo, OCA 10 mg, and OCA 50 mg groups, respectively).

Table 13: Subject Disposition:

	Placebo	OCA 10 mg	OCA 50 mg	Total
Completed Double-Blind Phase of Study [c]				
Yes	23 (100)	16 (80)	9 (56)	48 (81)
No	0 (0)	4 (20)	7 (44)	11 (19)

c The Completer Population included all randomized subjects who received at least 1 dose of investigational product based on the treatment group assignment and participated through the end of the study Day 85/ET.

A total of 11 OCA-treated subjects and no placebo-treated subjects withdrew from the study prior to Day 85. The primary reason for study discontinuation was due to AEs of pruritus, which was dose-related with 3 subjects from the OCA 10 mg group and 6 subjects from the OCA

50 mg group. One additional subject from the OCA 10 mg group withdrew consent, while a subject from the OCA 50 mg group was discontinued due to a major protocol violation of a failure to return to the study clinic.

Demographics: The mean (standard deviation [SD]) age of the ITT Population was 54.8 (9.5) years, and ranged from 34 years to 73 years; the mean ages of all 3 treatment groups were comparable. As expected with PBC, the study population was predominantly female (85%). There were 9 (15%) male subjects enrolled in placebo (n = 3) and OCA 10 mg (n =6) groups; none in the OCA 50 mg group. The majority of the population reported race as white (95%). Overall, the demographics of the enrolled population were consistent with the PBC population, and excluding sex and modest differences in BMI, all other baseline characteristics were well balanced across all treatment groups.

5.3 Efficacy Results

Table 14: Primary Efficacy Endpoint – Percent Change in ALP from Baseline to End of Study: ITT Population (N = 59)

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

[a]Per SAP, comparisons of OCA treatment groups versus Placebo are regarded as confirmatory analyses (applying for a hierarchical order): Step 1 - OCA 10 mg versus placebo; Step 2 - OCA 50 mg versus placebo.
[b]Wilcoxon-Mann-Whitney p-value compared to placebo.
Source: CSR 747-201, Section 14, Table 14.2.1.2.

Other Exploratory Efficacy Analyses

Absolute change in ALP at day 85

The OCA treated patients achieved a greater ALP reduction relative to placebo. There was no dose-response relationship between the two OCA treatment groups.

Table 15: ALP Levels (U/L) at Baseline and Day 85/ET: ITT Population (N = 59)

	Placebo (n = 23)	**OCA 10 mg (n = 20)**	**OCA 50 mg (n = 16)**
Baseline			
Mean (SD)	408.4 (223.0)	461.6 (298.7)	431.1 (177.2)
Median	320.5	366.3	379.0
Day 85/ET			
Mean (SD)	420.1 (253.5)	228.1 (117.0)	269.8 (158.9)
Median	288.0	196.5	197.5
Change from Baseline to Day 85/ET, Mean (SD)	11.7 (63.0)	-233.5 (212.3)	-161.3 (129.7)

The ULN of ALP reference range for the female population was 117 U/L (Appendix 16, Listing 16.2.7.1). Source: CSR 747-201, Section 14, Table 14.2.1.1 and Table 14.2.1.3.

Reductions in GGT and ALT and AST

1. GGT levels decreased, relative to placebo, at all-time points from day 15 to Day 85/ET in both the OCA 10 mg and OCA 50 mg groups. In the ITT Population, the mean (SD) GGT levels decreased from 653 (370) U/L at baseline to 184 (203) U/L at Day 85/ET in the OCA 10 mg group, and from 455 (418) U/L at baseline to 202 (300) U/L at day 85/ET in the OCA 50 mg group. Placebo GGT levels were 466 (321) U/L at Baseline and 502 (383) U/L at Day 85/ET.

2. ALT levels decreased, relative to placebo, from baseline to Day 85/ET in both OCA 10 mg and OCA 50 mg groups. The mean (SD) ALT levels decreased from 86 (44) U/L at baseline to 54 (41) U/L at Day 85/ET in the OCA 10 mg group, and similarly decreased from 71 (38) U/L at baseline to 49 (29) U/L at Day 85/ET in the OCA 50 mg group. There was no change in the levels of ALT in the placebo group from baseline to Day 85/ET.

3. The mean (SD) AST levels at Day 85/ET were 54 (40) U/L and 56 (28) U/L in OCA 10 mg and OCA 50 mg groups compared to baseline levels of 67 (33) U/L and 66 (29) U/L, respectively. There was no change in the levels of AST in the placebo group from Baseline to Day 85/ET.

5.4 Safety Results

1. All placebo subjects (n = 23) completed the study. In the OCA 10 mg group, 3 of 20 subjects were discontinued due to an AE of pruritus; of the 16 subjects in the OCA 50

mg group, 6 discontinued due to pruritus, and 1 subject was discontinued due to a major protocol violation of failing to return to the clinic. One of the 6 OCA 50 mg subjects who discontinued from the study due to pruritus, also had an AE of nausea.

2. A total of 16 (80%) out of 20 patients completed the 3 month trial in the OCA 10 mg arm. Three of the 4 patients who dropped out did so because of pruritus. One patient withdrew consent.
3. TEAEs were reported by 90%, 94%, and 91% of subjects treated with OCA 10 mg, OCA 50 mg, and placebo, respectively. The majority of these TEAEs were mild or moderate in severity.
4. There were no deaths in this study.
5. There was one SAE (rash) in the placebo group, and none in the OCA treatment groups.
6. The most commonly reported TEAE across all treatment groups was pruritus.
    a. The incidence and severity of pruritus were dose-related, and were higher in the OCA-treated subjects compared with placebo-treated subjects.
    b. The median time to the onset of first episode of clinically significant (defined as requiring intervention or discontinuation of drug) 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.
    c. Intervention for pruritus (bile acid sequestrants, treatment interruptions) were successful in 3 placebo subjects (100%), 6 OCA 10 mg subjects (67%), and 7 OCA 50 mg subjects (54%).
7. One OCA 50 mg subject who had a deviation that should have resulted in a mandatory discontinuation (conjugated bilirubin level was 2x ULN) was granted a waiver, and completed the study.
8. Adverse events that were possibly/probably hepatic-related included 2 subjects (13%) in the OCA 50 mg group and 1 subject each in the OCA 10 mg and placebo groups with the following TEAEs: hepatic pain (1 subject - 50mg), faeces discolored (1 subject - 50mg), and faeces pale (2 subjects 10mg and placebo).
9. Changes in serum lipids were observed across all treatment groups including placebo, but the magnitude of HDL-C change was greater in the OCA treatment groups. Mean HDL-C levels decreased from 1.73 (0.45) mmol/L at baseline to 1.57 (0.46) mmol/L at the end of treatement (ET) in the OCA 10 mg arm. In the OCA 50 mg arm, the mean (SD) HDL-C decreased from 1.95 (0.55) mmol/L at baseline to 1.86 (0.56) mmol/L at ET. In the placebo arm the mean HDL-C decreased from 1.84 (0.52) mmol/L at baseline to 1.70 (0.44) mmol/L at ET. The effect of HDL-C lowering is not as prominent in the OCA 50 mg treatment group, perhaps due to a 44% dropout rate which occured early in treatment (<1 month). At Day 85/ET, a mean change in LDL-C of -0.08 (0.43) mmol/L was observed in the placebo group compared to mean changes of +0.10 (0.58) mmol/L and +0.23 (0.52) mmol/L in the OCA 10 mg and OCA 50 mg groups, respectively.

Table 16: TEAEs by System Organ Class (SOC) and Preferred Term Reported ≥2 Subjects in Any Treatment Group: 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)
	n (%)	n (%)	n (%)
Subjects with any TEAEs	21 (91)	18 (90)	15 (94)
Skin and subcutaneous tissue disorders			
Pruritus[a]	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			
Nasopharyngitis	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)

Source: CSR trial 747-201 study report body Table 38

[a] Pruritus and Pruritus generalized were defined as separate MedDRA preferred terms.

[b] TEAEs with MedDRA preferred terms Pruritus and Pruritus generalized

5.5 Trial 747-201 Summary of Results

This 3-month trial conducted in patients with early stage PBC demonstrated ALP reductions with OCA 10 mg and 50 mg monotherapy, which were greater then placebo (on average approximately 40% for each OCA dose vs. minimal change in placebo). The adverse events reported were consistent with the known safety profile of the drug, with pruritus and headache being the most frequent AEs reported. Fatigue was reported infrequently in this trial, perhaps due to the short duration of this trial.

6 PHASE 2 TRIAL 747-202: DOSE RANGING TRIAL OF OBETICHOLOC ACID AS AN ADD-ON TO URSODEOXYCHOLIC ACID (UDCA)

6.1 Trial Overview

Phase 2 trial: A 3-month, international, multi-center, randomized, double- blind, placebo-controlled, multi-dose, parallel group trial for efficacy and safety of obeticholic acid (OCA) in combination with ursodeoxycholic acid (UDCA) in subjects with primary biliary cirrhosis

The primary objectives of the study were to measure the effect of OCA on alkaline phosphatase and to assess its safety in PBC patients.

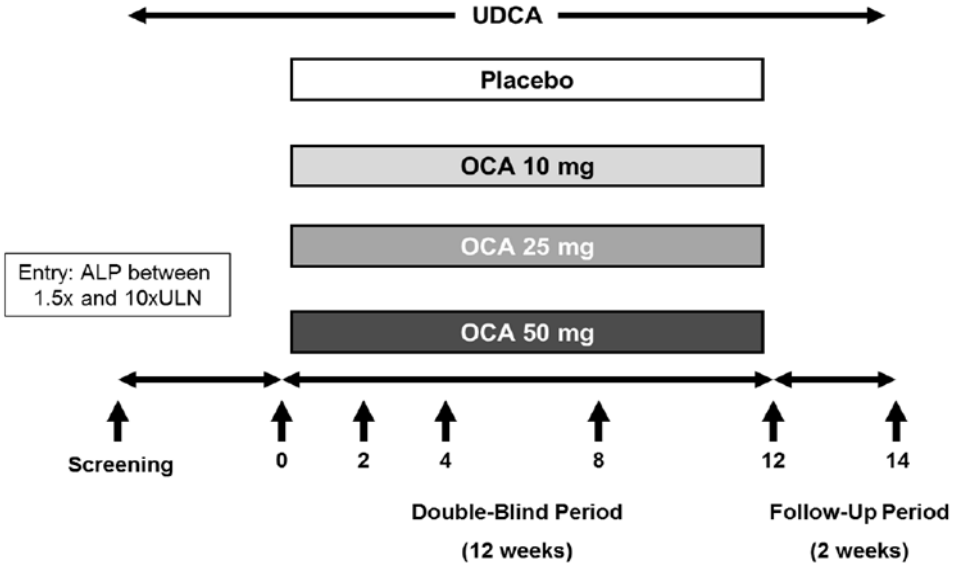
The secondary objectives were to assess the effects of OCA in subjects with PBC on the following:

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)

Trial Design

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. Subjects who met the enrollment criteria were randomized in a 1:1:1:1 ratio to placebo, OCA 10 mg, OCA 25 mg, or OCA 50 mg groups. A total of 222 subjects were screened, of which 165 subjects met the study entry criteria and were randomized: placebo (n = 38), OCA 10 mg (n = 38), OCA 25 mg (n = 48), and OCA 50 mg (n = 41). The study design is graphically described below.

Figure 6: 747-202 – Trial Design



Key Inclusion Criteria

1. Male or female age 18 - 75 years and on a stable dose of UDCA for at least 6 months prior to screening
2. Screening ALP level between 1.5x upper limit of normal (ULN) and 10x ULN
3. Proven or likely PBC, as demonstrated by the subject 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 (>1:40 titer on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay) or PBC-specific antinuclear antibodies (antinuclear dot and nuclear rim positive)
    c. Liver biopsy consistent with PBC

Key Exclusion criteria

1. Use of colchicine, methotrexate, azathioprine, or systemic corticosteroids
2. Screening conjugated (direct) bilirubin >2x ULN; ALT or AST >5 X ULN; serum creatinine >1.5 mg/dL (133 µmol/L)
3. History or presence of hepatic decompensation (e.g., variceal bleeds, encephalopathy, or poorly controlled ascites)
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

Mandatory discontinuation

1. ALT or AST ≥3x average predose value (average of screening and baseline values) and >ULN
2. Conjugated (direct) bilirubin >2x average predose value (average of screening and baseline values) and >1.5 mg/dL (25.7 µmol/L)

3. Other reasons included: patient decides to withdraw, any clinical or laboratory AEs to justify discontinuation, major violation, non-compliance, development of exclusion criteria, inability to provide blood samples

Special considerations

1. One site (Mayo Clinic, USA) instituted titration schedule that allowed investigational product to be administered once every 3 days in the first week, moving to once every 2 days in the second week, and daily from the third week onwards. Fourteen subjects were enrolled at the Mayo clinic study site, using this titration strategy.
2. As clinically indicated, investigators could attempt to decrease the severity of a subject'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: Bile acid binding resins: cholestyramine, colestipol, colesevelam, anti-histamines and other anti-pruritic agents
    e. Decreasing the concomitant dose of UDCA

Primary Efficacy endpoints

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

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

7. 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
8. Absolute and percent change in fibroblast growth factor-19 (FGF-19) levels from Baseline to Day 85/ET

Post-Hoc Efficacy Endpoint

Percentage of subjects who met the disease prognostic risk criteria defined as ALP <1.67x ULN and total bilirubin ≤ULN, and ALP decrease of ≥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

- 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-Dimentional Pruritus Questionnaire:
    - Pruritus VAS

The original Protocol for trial 747-202, dated 08 Aug 2007 was amended 10 times and had 6 addenda. No significant changes were made to the protocol objectives or to data collection for primary and secondary measures of efficacy or safety.

6.2 Study Results

Populations Analyzed

Overall, 165 subjects (100%) received at least 1 dose of investigational product (ITT and Safety Populations) and 136 subjects comprised the Completer Population. One hundred sixty-one subjects (98%) were included for the analysis of the primary efficacy endpoint (mITT Population) as measured by the percent change in ALP from Baseline to EOS; the mITT Population for sensitivity analysis of the primary endpoint included 163 subjects. It should be noted that the mITT population was defined for the primary analysis as all patients randomized who received at least one dose of study medication and had at least one post-baseline ALP evaluation which was taken at most seven days after their last dose of study medication. The mITT Population for the sensitivity analysis of the primary endpoint included ALP assessments obtained up to 15 days after the last investigational product use (unlike 7 days for primary endpoint). The number of subjects was -balanced across all groups in all analysis populations with the exception of the Completer Population due to the higher proportion of discontinuations with OCA 50 mg.

Patient Disposition

A total of 222 subjects were screened, of which 165 subjects met the study entry criteria and were enrolled. Of the 165 randomized subjects, 38 subjects were randomized to placebo, 38 subjects were randomized to OCA 10 mg, 48 subjects were randomized to OCA 25 mg, and 41 subjects were randomized to OCA 50 mg. A total of 136 (82%) subjects completed the study. Of the 29 (18%) subjects who did not complete the study, 23 (14%) discontinued due to a clinical or laboratory TEAE, 12 (11.3%) of whom were in the OCA 50 mg group. 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 subjects in OCA 50 mg group, and 1 subject in OCA 10 mg group) or elevated AST/ALT levels (1 subject in OCA 50 mg group). Two patients discontinued due to withdrawal of consent (1 subject) and lost to follow-up (1 subject).

Demographic and Baseline Characteristics

The demographic characteristics, including sex, ethnicity, and age variables were well balanced across treatment groups. The majority of patients were female (95%) and white (95%), but this is expected for the PBC population.

There were 7 (4%) patients who had moderately advanced PBC per Rotterdam criteria. There were 2 (5%) patients in the placebo group, 3 (8%) patients in the OCA 10 mg arm, no patients in the OCA 25 mg arm, and 2 (5%) patients in the OCA 50 mg arm (2 patients or 5%). There was only one patient with advanced liver disease per Rotterdam criteria; this patient was randomized to OCA 10 mg arm.

The baseline variables indicate that the PBC patients enrolled in the study had early stage of disease (i.e., without liver decompensation), which was expected because the protocol excluded subjects with conjugated bilirubin levels >2x ULN, as well as ALT/AST>5x ULN, or history or presence of hepatic decompensation. The duration of disease was balanced across the treatment groups with about 50-60% of patients having disease for less than 7.5 years.

Baseline ALP values were balanced across treatment groups. The mean baseline ALP values were 2.4x to 2.5x ULN. The majority of subjects had baseline total and direct bilirubin values < upper limit of normal (ULN). GGT was elevated across all treatment groups. Mean (SD) baseline GGT levels were slightly higher in the OCA treatment groups compared with placebo. The mean baseline GGT levels ranged from 3.8 to 5.5 X ULN. Serum transaminase (ALT and AST) levels were generally around the ULN across treatment groups. Mean albumin levels were within the normal range across all treatment groups. In addition, the baseline international ratio (INR) and partial thromboplastin time parameters were also within normal ranges. All three parameters were balanced across all treatment arms. Medical history abnormalities reflected the underlying disease and were generally similar across treatment groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was similar across treatment groups and for each study visit. 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 subjects taking these medications was similar between treatment groups. Mean daily UDCA dose at study entry was similar (approximately 15 to 16 mg/kg) across treatment groups.

6.3 Efficacy Results

Primary Endpoint

The primary efficacy endpoint for this trial was the percent change (%) in serum ALP from Baseline to EOS in the mITT Population.

Figure 7: Percent Change in ALP Levels from Baseline to EOS: mITT Population (N = 161)

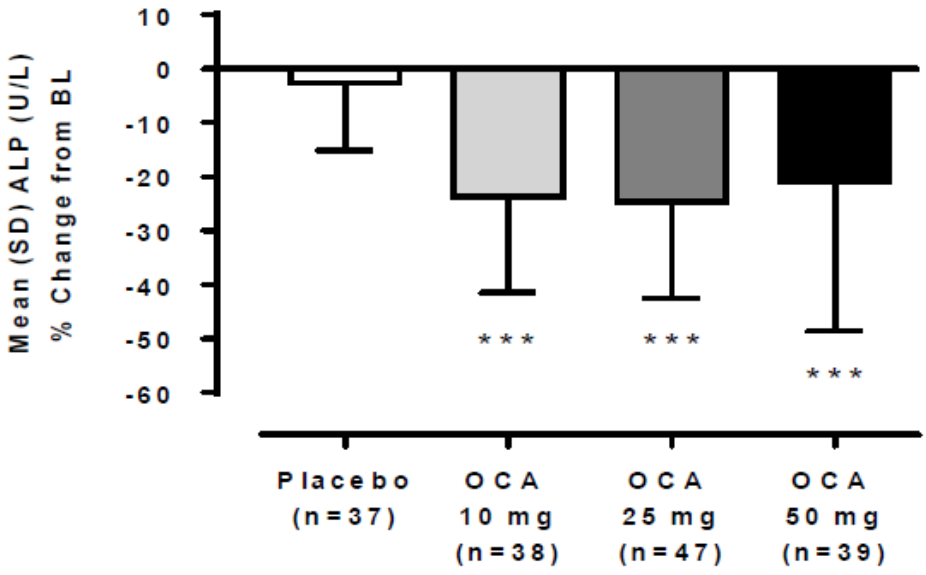


Table source: CSR 747-202 page 69-1652

p-value compares OCA treatment groups 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 17: 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

Table source: CSR 747-202 page 69-1652

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

Comment:

The ALP mean and median percent reduction in the OCA-treated patients was generally similar across all OCA dose groups and was statistically significantly different than placebo. From an efficacy standpoint, OCA doses of 25 mg and 50 mg added little over the 10 mg daily dose. Therefore, the OCA 10 mg dose was chosen by the Applicant for the phase 3 program and marketing approval. The sensitively analysis of the primary endpoint performed by the Applicant (not shown here) supports the primary analysis.

Secondary Endpoint

The secondary endpoint of change in ALP from baseline to day 85 showed decrease in ALP for all 3 doses (**Table 18**).

Table 18: ALP (U/L) at Baseline to Day 85/ET: ITT Population (N = 165) and Completer Population (N=136)

	Placebo	OCA 10 mg	OCA 25 mg	OCA 50 mg
ITT Population	**(n = 38)**	**(n = 38)**	**(n = 48)**	**(n = 41)**
Baseline				
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
Day 85/ET				
Mean (SD)	270.7 (118.7)	219.0 (113.5)	225.0 (169.1)	227.9 (115.9)
Median	234.5	177.5	187.5	197.0
Mean (SD) Change	-4.6 (34.9)	-75.4 (81.5)	-65.0 (91.3)	-62.9 (101.9)
Median Change	-6.3	-47.5	-69.3	-56.5
Mean (SD) Percent Change	-2.6 (12.4)	-23.3 (17.1)	-24.0 (18.8)	-20.0 (27.4)
Median Percent Change	-3.2	-21.0	-27.8	-22.7
P-value	NA	<0.0001	<0.0001	<0.0001
Completer Population	**(n = 37)**	**(n = 32)**	**(n = 42)**	**(n = 25)**
Baseline				
Mean (SD)	276.4 (103.8)	298.6 (159.5)	274.9 (80.2)	279.3 (110.5)
Median	250.0	234.8	255.8	236.5
Day 85/ET				
Mean (SD)	272.1 (120.0)	212.3 (120.2)	199.0 (59.8)	179.1 (63.6)
Median	235.0	175.0	187.5	158.5
Mean (SD) Change	-4.3 (35.3)	-86.3 (83.7)	-76.0 (48.8)	-101.8 (85.5)
Median Change	-6.0	-61.3	-71.3	-76.0
Mean (SD) Percent Change	-2.5 (12.6)	-26.7 (16.0)	-26.6 (14.7)	-32.5 (20.1)
Median Percent Change	-3.1	-23.5	-28.2	-33.9

Table source 747-202 Page 73-1652

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

The ULN of ALP reference range for the female population was 117 U/L

mITT population excludes 4 patients who missed the time frame for the ALT level at month 12

The effect of OCA treatment on ALP serum levels was observed as early as the first Post-baseline visit (Day 15), followed by continued improvement through Day 29, after which ALP levels were generally maintained. At the Follow-Up Visit (Day 99), the mean ALP levels increased slightly in all 3 OCA treatment groups compared to Day 85/ET. However, at follow-up, the ALP levels in the OCA treatment groups were still lower than at baseline: the ALP levels were 16.7% to 19.3% lower than baseline levels in the OCA treatment groups, compared to 5.1% in placebo.

Figure 8: ALP Levels from Baseline to Day 99/Follow-Up: ITT Population (N = 165)

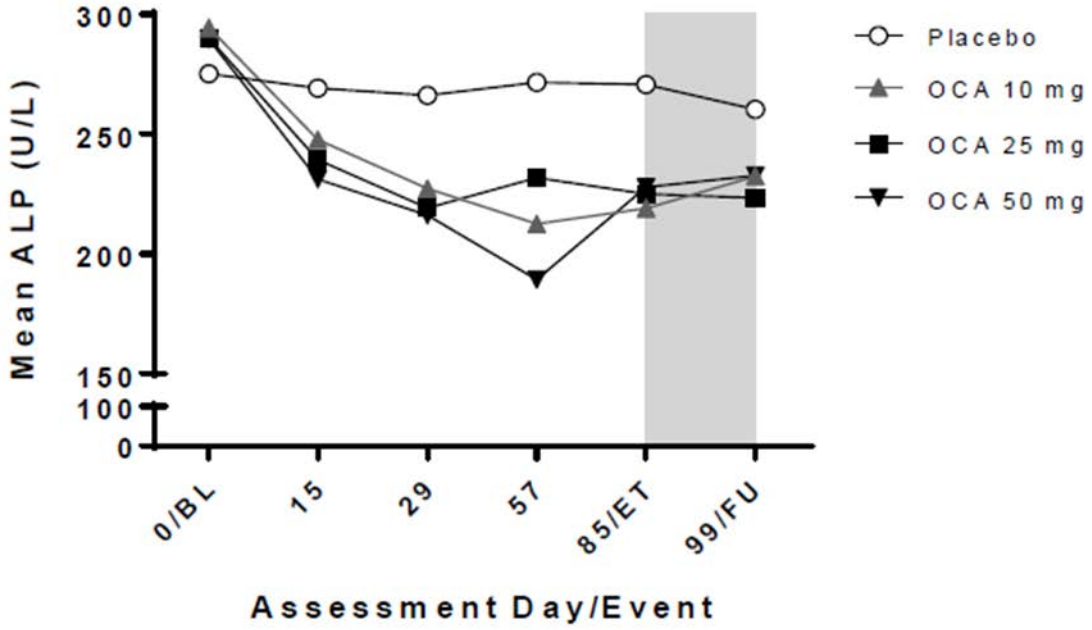


Table source: 747-202 CSR page 74-1652

Responders Based on Mayo II plus 15% ALP Reduction Composite Endpoint

A post-hoc analysis was performed to determine the percentage of subjects achieving the proposed prognostic disease risk criterion of ALP < 1.67 x ULN [with a ≥ 15% reduction] and bilirubin ≤ ULN. Overall, 41% of the OCA-treated subjects achieved the composite endpoint at Day 85/ET compared to 9% of the placebo-treated patients. OCA 10 mg dose showed similar efficacy in achieving ALP reduction as OCA 25 mg and OCA 50 mg treatment groups.

Subgroup analysis of ALP reduction by age (<50 years versus 50-65 years versus >65 years), geographic region (Canada versus Europe versus US) and years since diagnosis (<7.5 years versus ≥7.5 years) did not show any meaningful difference in response. There were too few male subjects to make a meaningful conclusion about differences in response by gender

6.4 Safety Review

Overall Exposure: A total of 165 subjects were exposed to investigational product (IP): 38 subjects received placebo, 38 subjects received OCA 10 mg, 48 subjects received OCA 25 mg, and 41 subjects received OCA 50 mg.

Serious Adverse Events

Overall, 7 subjects (4%) experienced an SAE in the study. The incidences of SAEs reported in the study were as follows: 1 subject (3%) in the placebo group had an SAE of dyspnea, 1 subject (2%) in the OCA 25 mg group had an SAE of salivary gland neoplasm, 2 subjects in the OCA 50 mg

group experienced angina pectoris and angioedema, and 3 subjects in the 50 mg group experienced GI hemorrhage, jaundice, and PBC flare.

The incidence of TEAEs leading to discontinuation was higher in the OCA 50 mg group (37%) compared with placebo, OCA 10 mg, and OCA 25 mg groups (3%, 16%, and 10%, respectively). The most common reason for study discontinuation was pruritus, which occurred most notably in the OCA 50 mg group (10 subjects). The overall incidence of the TEAE of pruritus was higher in the OCA 25 mg and OCA 50 mg treatment groups compared with the OCA 10 mg and placebo groups (47%, 85%, 80%, and 50% of subjects in the OCA 10 mg, OCA 25 mg, OCA 50 mg, and placebo groups, respectively).

Hepatic Adverse Events

Two subjects (both in the OCA 50 mg group) were discontinued from the study due to a hepatic related SAE (GI hemorrhage and jaundice). One of these subjects (previously reported as an SAE) who had advanced PBC and cirrhosis, who was on the 50mg dose experienced a PBC flare with nausea, vomiting, pruritus, hepatomegaly and elevated transaminases and total bilirubin which started 9 days after starting treatment.

Five subjects (1 subject [3%] each in the placebo and OCA 10 mg group, and 3 subjects [7%] in the OCA 50 mg group) met the criteria of mandatory protocol discontinuation (elevated AST/ALT or conjugated bilirubin levels); 3 of them discontinued, while the remaining 2 received a waiver and completed the study.

Reviewer Comment:

It is concerning that these hepatic-related events occurred in the higher dose group and no hepatic adverse events occurred in the placebo group. The transaminase and bilirubin elevations occurred more commonly in the 50mg group and 3 patients in this group met criteria for discontinuation. The modeling done by the FDA clinical pharmacology reviewers noted that obeticholic acid systemic and liver exposures are higher in patients with cirrhosis, and in the early phase 1 trials using higher doses, dose dependent increases in transaminases and bilirubin were observed. Therefore we cannot conclude that these events and some events of transaminase elevations are not related to study drug. See the integrated summary of safety in Section 9 for a complete discussion of this topic.

Pruritus Related Adverse Events

Pruritus appears to be the most common dose-related AE associated with OCA. Both the severity and the frequency of pruritus are dose-related. In addition, pruritus is the most common cause for discontinuation of treatment (See **Table 19**, below). 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 groups, respectively. The Applicant reports that the most common medications used to treat pruritus were bile acid sequestrants (e.g., cholestyramine), and antihistamines alone or in combination with a bile acid sequestrant.

Table 19: Pruritus safety population - N=165

Pruritus	Placebo (n=38)	OCA 10mg (n=38)	OCA 25mg (n=48)	OCA 50mg (n=41)
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%0	15 (45%)
Total	**19 (50%)**	**18 (47%)**	**41 (85%)**	**33 (80%)**

Source: CSR 747-202, page 117-1652

Other Common Adverse Events

Other common TEAEs (reported by ≥10% of subjects in any group) were headache, fatigue, nausea, abdominal distention, pain in extremity, and epistaxis.

Lipid-Related Adverse Events

Hypercholesterolemia, typically characterized by elevated HDL-C levels, has been previously observed in subjects with PBC. A dose-related decrease in mean total cholesterol was observed in all OCA treatment groups compared to placebo. In all OCA treatment groups, the mean reductions in the HDL-C levels seen on day 85/ET were greater than that in placebo. At day 85/ET, mean changes from baseline HDL-C were -0.25 (0.28) mmol/L, -0.26 (0.48) mmol/L, -0.47 (0.45) mmol/L, and +0.09 (0.29) mmol/L in the OCA 10 mg, OCA 25 mg, OCA 50 mg, and placebo groups, respectively. The mean HDL-C levels remained within the normal range, and were reversible within 2 weeks off treatment. There was no change in the mean levels of low-density lipoprotein cholesterol levels (LDL-C), triglyceride, or very low-density lipoprotein cholesterol (VLDL-C) levels from baseline to day 85/ET in any treatment group. One subject in the OCA 10 mg group had a shift in LDL-C from normal to abnormal values that were clinically significant. No shifts from normal to clinically significant values were observed in any of the treatment groups for HDL-C, VLDL-C, or triglycerides.

Reviewer Comment:
PBC patients are known to have dyslipidemia, but in most meta-analyses do not appear to have a higher incidence of cardiovascular events. It is unknown at this time if the changes in LDL-C and HDL-C will increase cardiovascular events in this population.

6.5 Summary of Trial 747-202 Results

This was a phase 2, placebo-controlled trial that evaluated 3 OCA doses (10 mg, 25 mg, and 50 mg) as add-on to UDCA.

The percent change in ALP from baseline to EOS was statistically significantly greater with each of the three OCA doses relative to placebo; however, there was no meaningful difference in percent reduction in ALP between the 3 doses of OCA.

There was an increase in incidence and severity of pruritus with increasing dose. There was an increase in the incidence of hepatic related adverse events and elevations in liver biochemistries with increasing dose. There were small changes in cholesterol levels with decreases in HDL-C, the clinical significance of which is unknown.

7 PHASE 3 TRIAL 747-301 - COMBINED CLINICAL AND STATISTICAL EFFICACY REVIEW

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

7.1 Trial Design

Trial Centers

Fifty nine investigators from 13 countries participated in this trial including 15 sites in the Unites 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.

Trial Design

Trial 747-301 was a randomized, double-blind, placebo-controlled, parallel-group, 12-month trial evaluating OCA in patients with PBC who:
1) were on ursodeoxycholic acid (UDCA) for at least 12 months (and on stable dose for ≥3 months), or
2) were unable to tolerate UDCA, and did not receive UDCA for ≥3 months prior to Day 0.

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

- 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)

- 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).

<u>Key inclusion criteria</u>

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 anti-mitochondrial antibody (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 ≥ 1.67x ULN

    OR

    b. Total bilirubin > ULN but < 2x ULN
3. Age ≥ 18 years
4. 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.
5. Contraception: Female patients had to be postmenopausal, surgically sterile, or if premenopausal, had to use ≥ 1 effective (≤ 1% failure rate) method of contraception during the trial and for 30 days after the EOT Visit.

<u>Key exclusion criteria</u>

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 ≥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 µmol/L)
2. Competing etiology for liver disease (e.g., 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. Patients who had previously participated in a clinical trial of OCA were not allowed to participate
6. Prolonged QT interval, pregnancy or lactation.
7. If female: known pregnancy, or had a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
8. Known history of human immunodeficiency virus infection
9. 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).
10. Medical conditions that could cause non-hepatic increases in ALP (e.g., Paget's disease)

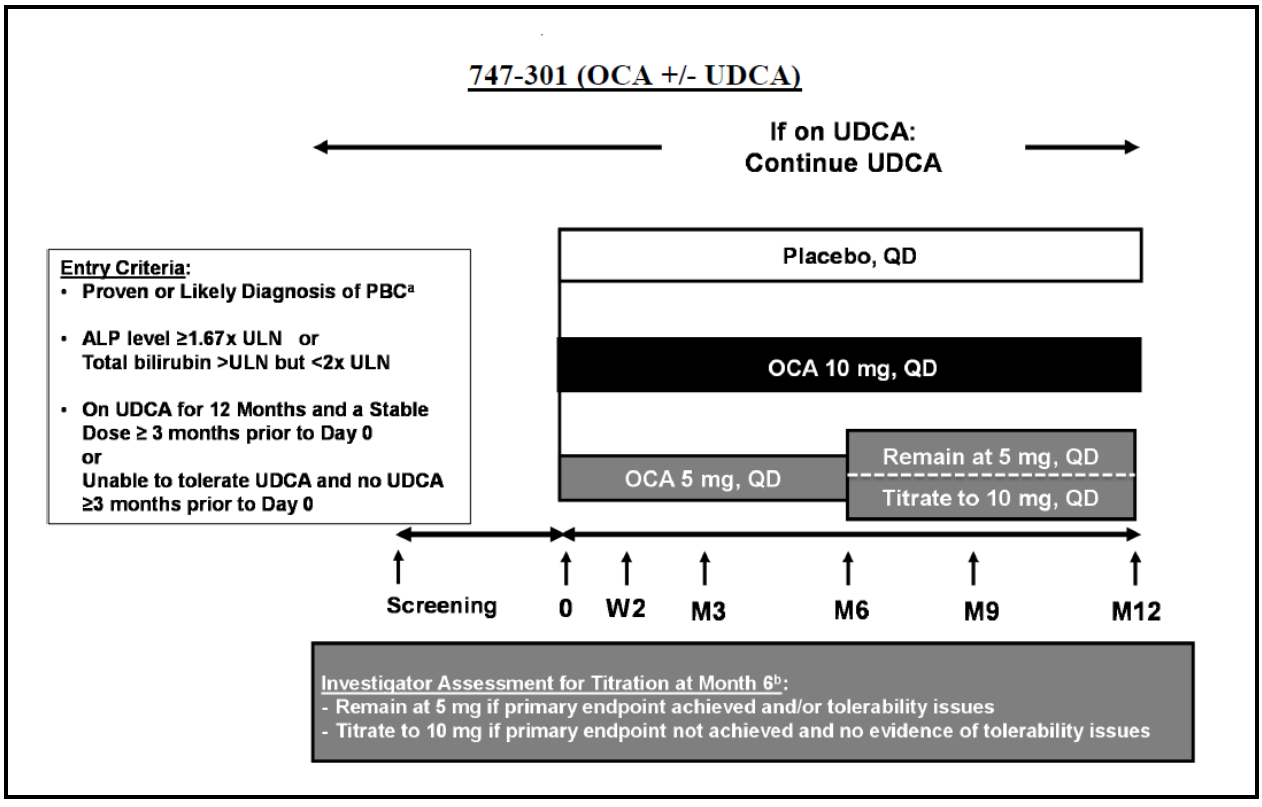
or that could diminish life expectancy to < 2 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphocytic leukemia)

Removal of Patients from Therapy or Assessment

Female patients who became pregnant were required to stop taking investigational product and were to be withdrawn from the trial. The following additional events led to discontinuation of patient from the trial:

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 trial.
3. Patient experienced an AE that in the opinion of the investigator or medical monitor was caused by or exacerbated by any of the trial procedures or investigational product, and was of sufficient intensity to warrant discontinuation.
4. Patient refused to comply with the requirements for trial participation.
5. Investigator's or Sponsor's decision.
6. Patient initiated a new therapy for PBC.

Figure 9: Trial Design for the Double-Blind, Placebo-Controlled Phase of Trial 747-301



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

Screening Period

Patients were screened during a ≤ 1 to 8 week, to establish baseline laboratory values for serum ALP and total bilirubin. Eligible patients within each randomization stratum were randomized, via Interactive Voice-Response System/Interactive Web-Response System (IVRS/IWRS), 1:1:1 to 1 of 3 treatment arms:

(a) placebo
(b) 10 mg OCA, or
(c) 5 mg titrating to 10 mg OCA

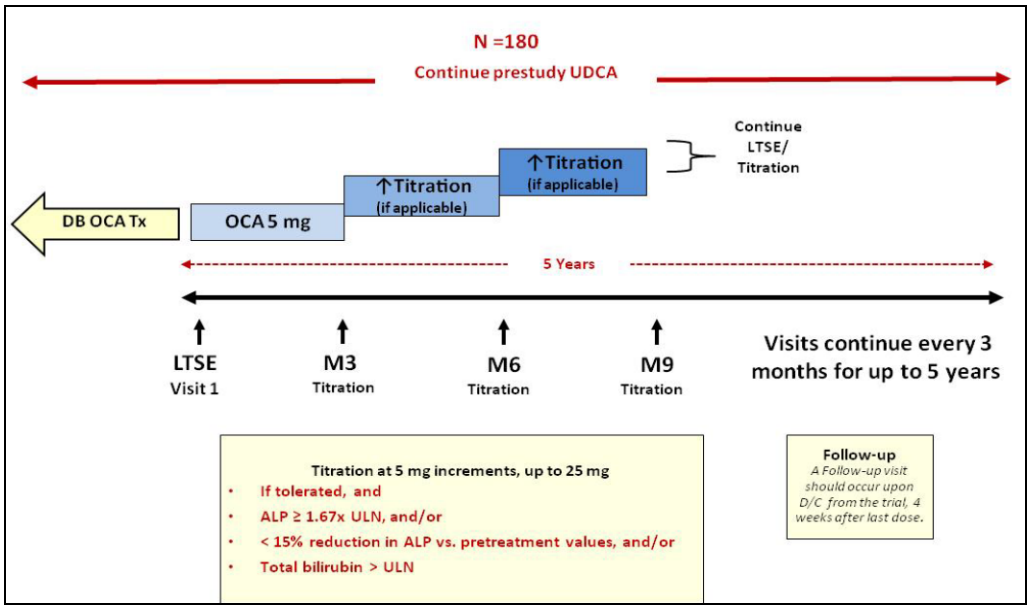
Double-blind Phase

OCA was administered orally, once daily for 12 months. Following randomization, patients had 5 at-clinic trial visits at Week 2 and Months 3, 6, 9 and 12 to evaluate efficacy, safety, tolerability and compliance with trial medication. Patients randomized to the OCA 10 mg treatment group received 10 mg throughout the entire 12-month duration. Patients randomized to the OCA titration group received OCA 5 mg for the initial 6-month period. At Month 6, patients in the OCA titration group who did not meet the criteria for the composite endpoint and did not have evidence of tolerability issues were to titrate from OCA 5 mg to OCA 10 mg for the final 6 months of the double-blind phase. Investigators remained blinded to treatment and assessed all patients for up-titration at month 6.

Long term safety extension (LTSE) Phase

Upon completion of the DB phase all eligible patients were offered to continue in the OCA open label LTSE phase trial during which patients who received 5 mg OCA were titrated up to receive 10 mg of OCA for up to 5 years. Patients who were taking UDCA before screening continued UDCA treatment, while patients who were unable to tolerate UDCA before screening received OCA monotherapy.

Figure 10: Schematic Diagram – Open Label LTSE Phase



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

Rationale for Dose Selection

In Phase 2 trials, OCA 10 mg once daily was better tolerated (i.e. less pruritus) than 25 mg or 50 mg once daily. Doses higher than OCA10 mg were not more effective - OCA 10 mg was as effective as OCA 25 mg and OCA 50 mg. A dose-related increase in the incidence and severity of pruritus was observed across OCA doses. There were higher adverse event rates with OCA 25 mg and OCA 50 mg doses, as well as higher rates of discontinuation from the study due to TEAEs. Three patients on OCA 50 mg experienced hepatic adverse reactions (e.g., jaundice, variceal bleeding, worsening liver biochemistries and flare of PBC).

Therefore, the Applicant designed Trial 747-301 to assess the efficacy, safety, and tolerability of lower daily doses of OCA (10 mg) in support of a marketing authorization in patients with PBC. The rationale for an OCA titration arm (OCA 5 mg starting dose titrated to a 10 mg dose) was to identify a better tolerated regimen.

Table 20- 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[8]	
Patient Questionnaires[1]			X	X		X		X	X	X[1]	X[1]	X
Transient Elastography (TE)[2]			X							X	X[8]	
Liver Biopsy[3]	X											
DEXA Scan[10]			X							X	X[8]	
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[8]	
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, Trial 747-301 Protocol submitted on 24 September 2012, page 33/106.

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 trial 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 21: Schedule of Trial Procedures – LTSE 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, Trial 747-301 Protocol: submitted on 24 September 2012, page 33/106.

Footnote:

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

Double-blind Month 6 Dose Titration

To maintain the blind, all patients (i.e., all treatment groups) were assessed by the Investigator for titration eligibility at Month 6 based on achieving the primary endpoint (ALP and bilirubin response) and tolerability of investigational product. A request for "up-titration" by the Investigator via the IVRS/IWRS could be made for patients who failed to meet the pre-specified responder criteria at Month 6; however, the Investigator and patient remained completely blinded to whether or not titration actually occurred.

Prohibited Medications

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

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

Permitted Medications While on Study

1. Topical or inhaled corticosteroids
2. Patients taking herbal supplements or botanical preparations that were purported to affect the liver (e.g., milk thistle) were permitted to take these during the trial, 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 trial 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.
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 trial, where medically appropriate. Patients with other concomitant conditions that were not well controlled or whose medication needs were anticipated to change during the trial were not enrolled in the trial.

Management of Pruritus

The most common AE of OCA is pruritus. The management of pruritus in this phase 3 trial was done by the following:

1. Prescribe bile acid sequestrants (BAS), e.g., cholestyramine, colestipol, colestimide, or colesevelam.
2. Dose frequency modification: Less frequent dosing of study medication
3. Drug holiday: A drug holiday is defined as an investigator 'prescribed' complete interruption of dosing for 1 or more consecutive days (i.e., nondaily dosing, every other day dosing) does not constitute a drug holiday). Patients with drug holidays of > 28 days total during the double-blind phase should be discontinued from the trial.

Duration of Treatment

The double-blind, placebo-controlled phase of the trial consisted of a Screening period ≤ 8 weeks and a 12-month treatment phase. An option to continue receiving open-label OCA for up to 5 years was given to patients completing the 12-month double-blind phase (for a maximum participation duration of 74 months).

Trial Endpoints

EFFICACY

The primary objective of the trial was to demonstrate the efficacy of OCA, relative to placebo, based on its effects on ALP and TB. Other objectives such as assessing safety, histological, bile acid, and biomarker (i.e., not including ALP and TB) parameters were considered exploratory.

Primary Endpoint

ALP and TB composite response criteria at Month 12; a patient was designated as a responder if **all three** of the following conditions were met:

- 12-Month value of ALP < 1.67×ULN
- ALP reduction from baseline at Month 12 ≥ 15%
- 12-Month value of TB < ULN

Secondary Endpoints

1. 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.
2. Percentage of patients with a decrease in ALP of ≥10%, ≥15%, ≥20%, and ≥40% from Baseline or ≤ULN at month 12.
3. Percentage of patients achieving the following biochemical response criteria at month 12:
    a. ALP ≤ 3x ULN and AST ≤ 2x ULN and bilirubin ≤ ULN ((Corpechot 2008); Paris I)
    b. ALP ≤ 1.5x ULN and AST ≤ 1.5x ULN and bilirubin ≤ ULN ((Corpechot 2011), Paris II)

c. ALP ≤ 1.67x ULN and bilirubin ≤ ULN ((Momah 2012), Mayo II)
d. ALP ≤ 1.76x ULN ((Kumagi 2010b), Toronto II)
e. Normal bilirubin (values ≤ ULN) and/or normal albumin (values ≥ lower limit of normal [LLN]; (Kuiper 2009) [Rotterdam criteria])

4. 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
5. Absolute and percent change from Baseline 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
6. Absolute and percent change from Baseline on PBC-40 domains
7. Percentage of patients with each response on the Patient Research Questionnaire at Month 12

Exploratory Endpoints

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

Pharmacokinetic and Pharmacodynamic Endpoints

1. 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)
2. 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
3. Bile acid sequestrant (BAS) concomitant exposure

Safety Assessments

Safety was assessed by:

1. Treatment-emergent adverse events (TEAEs)
2. Vital sign measurements, weight, BMI
3. 12-lead electrocardiograms (ECGs)
4. Physical examinations, clinical laboratory results
5. Dual-emission x-ray absorptiometry (DEXA) scans in a subset of patients
6. Mayo Risk Score (MRS)
7. Model for End Stage Liver Disease (MELD) scores
8. Patient questionnaires (5-dimensional [5-D] pruritus, and pruritus visual analog scale [VAS])

7.2 Study Results

Analysis Methods

Analysis Sets

The primary analysis set used for all efficacy analyses, along with the summarization of disposition along with demographics and baseline characteristics, was the 'Intent-to-Treat' (ITT) analysis set. This analysis set included all randomized patients who received at least one dose of blinded study drug. When utilizing this analysis set, patients were analyzed according to the treatment group that they were randomized to regardless of the actual treatment received. It should be noted that all but one randomized patient received at least one dose of blinded study drug.

For sensitivity analysis purposes, all efficacy analyses were repeated utilizing a 'Completer' analysis set. This analysis set was comprised of all ITT patients who participated through the end of the double-blind period (i.e., through the Month 12 visit). When utilizing this analysis set, patients were analyzed according to the treatment group that they were randomized to, regardless of the actual treatment received.

For additional sensitivity analysis purposes, all efficacy analyses were again repeated utilizing an 'Efficacy Evaluable' (EE) analysis set. This analysis set was comprised of all 'Completer' patients who did not have any major protocol deviations that would potentially affect the efficacy of the study drug. This analysis set definition was finalized in a blinded manner prior to database lock.

For population pharmacokinetic (PK) analysis purposes, the PK analysis set was utilized, which consisted of all patients who had at least 1 confirmed fasted analyzable sample at the Month 6 or Month 12 visit and who did not have any major protocol deviations that could potentially affect exposure levels.

For all safety analyses, the safety analysis set was utilized, which consisted of all patients who received at least 1 dose of investigational product.

Multiplicity Adjustment

In order to control the overall study-wise type I error rate, a step-down/closed sequential testing procedure was pre-specified by the applicant to adjust for the multiple comparisons of the two OCA dose groups individually to placebo on the primary study endpoint alone. Starting with the 10 mg OCA comparison to placebo on the primary endpoint, the applicant stated that the step-down could only be carried to the OCA Titration comparison to placebo (on the primary endpoint), if and only if the 10 mg OCA comparison to placebo was found to be statistically significant (i.e., p-value less than 0.05). 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.

As can be deduced, this pre-specified multiplicity adjustment procedure was narrow in scope in that it only pertained to the individual OCA dose comparisons with placebo on the primary endpoint alone. Hence even if both OCA dose comparisons were found to be statistically significant, then any other hypothesis test would still be deemed as exploratory in nature.

Primary Endpoint Analysis

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, and a 95% Wald Confidence Interval (CI) for the difference of these responder rates (i.e., between the individual OCA groups and placebo) was calculated.

The applicant's pre-specified analysis, based on FDA advice, utilized a Cochran-Mantel-Haenszel (CMH) test which adjusted for both randomization stratification variables as described above. In tandem with the CMH test, a Breslow-Day test was also conducted, by the FDA statistical reviewer in order to test for the homogeneity of the treatment effect across the different randomization strata.

Descriptive Supportive Analyses

There were no formal secondary endpoints. As stated previously, other trial objectives such as assessing safety, histological, bile acid, and biomarker (not including ALP and TB) parameters were considered exploratory from a statistical perspective and hence are not presented in this review.

Several descriptive analyses were presented by the FDA statistical reviewer to further support the primary endpoint analysis. These pertained to descriptively assessing the absolute change-from-baseline and percentage change-from-baseline in ALP and TB concentrations at Month 12 separately for each treatment group. The proportion of patients achieving a decrease in ALP of at least 10%, 15%, 20%, and 40% at Month 12 was presented separately for each treatment group. In addition, the proportion of patients achieving an ALP value of strictly less than ULN and 1.67×ULN at Month 12 was presented separately for each treatment group. The proportion of patients achieving a TB value of strictly less than ULN at Month 12 was also presented separately for each treatment group. Finally, separate figures presenting ALP and TB concentrations over time were presented to assess the durability of biochemical response while continuing long term treatment.

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

All safety analyses were based on the Safety population. TEAEs were summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and preferred term by severity and by causal relationship to OCA. Pruritus was considered an adverse event (AE) of special interest. Safety laboratory parameters, MRS, MELD scores, vital signs, body weight, and body mass index (BMI) values (absolute and change from Baseline) were summarized by treatment group using descriptive statistics at Baseline and at each post-Baseline visit. The 5-D pruritus questionnaire values and change from Baseline were summarized by treatment using descriptive statistics for each domain score and the total score by visit. The pruritus VAS was summarized in the same manner. Correlation analyses and categorical summaries were presented for ECGs.

Handling of Dropouts/Missing Data

To further assess the sensitivity of the results to missing/unavailable Month 12 data, a worst-case (i.e., designating "failure") imputation strategy was espoused by the applicant for the primary endpoint analyses. An additional ultra-worst-case imputation strategy was espoused by the FDA statistical reviewer for the same analyses; this new strategy imputed "failure" at Month 12 for OCA treated patients having missing/unavailable Month 12 data while imputing "success" at Month 12 for placebo treated patients having missing/unavailable data at Month 12. As is discussed below, the final results and conclusions were not influenced by the limited missing data encountered in the study.

Other Analysis Considerations

For the analysis of the primary endpoint, baseline was defined by the applicant as the last measurement prior to the first administration of study drug, or, if multiple pre-treatment measurements were available, the arithmetic mean of the last (up to) three measurements preceding the first administration of study drug. Unscheduled measurements prior to first study drug administration were considered in the calculation of baseline value.

For sensitivity analysis purposes, all relevant primary efficacy analyses were re-conducted by the FDA statistical reviewer utilizing the median (in lieu of the arithmetic mean) of the pre-first dose measurements. In addition, all relevant analyses were again re-conducted by the FDA statistical reviewer utilizing a traditional baseline definition, i.e., choosing the last non-missing value prior to the first administration of study drug.

The enrolled phase 3 trial population primarily consisted of early stage PBC patients (i.e., screening/baseline TB < ULN) who had screening/baseline ALP ≥ 1.67×ULN and who were on UDCA. Due to this circumstance, the applicant's pre-specified primary composite endpoint could not be appropriately applied to assess treatment on this very specific PBC patient population (i.e., patients with early stage disease). The goal to establish a new criterion utilizing ALP reduction alone, after 12 months of observation, to better predict transplant-free survival within a subset of the Global PBC Study subjects that was comparable to the majority of patients

enrolled in the phase 3 trial was undertaken as presented earlier within Section 4. Hence all of the previously described analyses, if applicable/relevant, were repeated by the FDA statistical reviewer (analyzing trial patients who were exclusively early stage PBC patients, who also had screening/baseline ALP ≥ 1.67 × ULN, being administered UDCA) utilizing this newly determined, and relatively best performing, criterion. Other relevant ALP cut points explored and presented in Section 4 were also applied to this subset of trial patients for sensitivity analysis purposes.

Comments:

Diagnostic criteria used for patient enrollment were not consistent with the meeting discussions held between the FDA and the Applicant during the drug development program, in that the FDA recommended the use of a co-primary endpoint of ALP and TB based on enrollment of a broad spectrum of PBC disease stages and the Applicant enrolled primarily only patients with early stage disease

UDCA was approved in December 1997 based on demonstration of clinical benefit (e.g., survival or need for transplant, and progression to esophageal varices, ascites, or encephalopathy), in addition to changes in histological changes at 2 years, liver biochemistries (ALP, TB, albumin),[29] over a period of 2.5 years, in a high risk population. This phase 3 trial (747-301) is the first clinical trial conducted in patients with PBC with use of only biomarkers, i.e., ALP and TB as study endpoints to support efficacy for a marketing application. Most PBC patients enrolled in the clinical trial were in an early stage of disease, as observed by the biochemical profile of the patients, (i.e., 92% of patients had a normal TB at enrollment). The phase 3 trial population (early stage disease) is different from the population analyzed in the data from the Global PBC Study Group (a range of all disease stages) used to evaluate the use of the composite endpoint of ALP and TB as a surrogate for approval. Use of reductions in ALP alone has not been evaluated or agreed upon by the FDA prior to the submission of the NDA. Since PBC is a slowly progressive disease with a clinical course spanning over decades, the change in ALP seen over a 12-month trial and the magnitude of reduction in ALP and its correlation to a clinical outcome was unknown. However, the FDA approached the Applicant and the Global PBC Study Group's principle investigator to request access to subject-level data sets from the Global PBC Study Group which would allow FDA to assess whether a reduction in ALP alone in a similar population with early stage PBC could be used as a surrogate biomarker reasonably likely to predict clinical benefit. Please see Section 4 for discussion of the results of FDA's evaluation of the Global PBC Study Group data.

[29] See labeling for UDCA (Ursodiol) at Drugs@FDA.com

7.3 Patient Disposition

Of the 217 patients enrolled and randomized into this trial 216 were administered at least one dose of study drug. One patient who was randomized to the OCA titration treatment group withdrew consent prior to being dosed.

The disposition information for all ITT patients is displayed in **Table 22** below.

Table 22: Disposition (ITT population)

	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)	Total (N = 216)
Intent-to-Treat (ITT)	73 (100%)	70 (100%)	73 (100%)	216 (100%)
Completer	64 (87.7%)	64 (91.4%)	70 (95.9%)	198 (91.7%)
Efficacy Evaluable (EE)	63 (86.3%)	63 (90.0%)	67 (91.8%)	193 (89.4%)
Pharmacokinetic (PK)	60 (82.2%)	66 (94.3%)	0	126 (58.3%)
Safety	73 (100%)	70 (100%)	73 (100%)	216 (100%)
Discontinued Study Early	9 (12.3%)	6 (8.6%)	3 (4.1%)	18 (8.3%)
Death	0	1 (1.4%)	0	1 (0.5%)
Pruritus	7 (9.6%)	1 (1.4%)	0	8 (3.7%)
Other Adverse Events (AEs)	1 (1.4%)	3 (4.3%)	2 (2.7%)	6 (2.8%)
Withdrew Consent	1 (1.4%)	1 (1.4%)	1 (1.4%)	3 (1.4%)
Participated in LTSE	64 (87.7%)	63 (90.0%)	66 (90.4%)	193 (89.4%)

Source: Reviewer's Table generated from the 747-301 ADSL dataset.
Note: Denominators for percentages are N

Patient discontinuations were higher in the OCA 10 mg group and occurred before month 6; discontinuations in the placebo group were also seen earlier in the trial, prior to 6 months. In the OCA titration group, most patient discontinuations occurred after month 6 in all patients except one patient who discontinued from the trial due to hallucinations within 5 days of starting treatment.

As stated previously, and as displayed above in **Figure 10**, 71 patients were enrolled and randomized to the OCA Titration treatment group with 70 of these patients being administered at least one dose of study medication. With one OCA Titration patient discontinuing prior to Month 6, a total of 37 out of 69 OCA Titration patients were eligible for up-titration at Month 6. Ultimately 33 of these 37 eligible patients were titrated up to the 10 mg dose; hence 36 of the 69 OCA Titration patients remained on 5 mg OCA after Month 6. The 4 patients who were eligible for up titration based on failure to achieve reduction in ALP were not up titrated secondary to intolerance (i.e., pruritus).

7.4 Demographics and Baseline Characteristics

Table 23: Demographic and Baseline Characteristics (ITT)

	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)	Total (N = 216)
Age at Screening (years)				
N	73	70	73	216
Mean (SD)	56.2 (11.00)	55.8 (10.52)	55.5 (10.03)	55.8 (10.48)
Median	56.0	54.5	55.0	55.0
Min, Max	30, 86	29, 83	35, 78	29, 86
Age Category – n (%)				
< 65 years old	56 (76.7%)	60 (85.7%)	60 (82.2%)	176 (81.5%)
≥ 65 years old	17 (23.3%)	10 (14.3%)	13 (17.8%)	40 (18.5%)
PBC Diagnosis Age (years)				
N	73	70	73	216
Mean (SD)	47.1 (10.60)	47.6 (11.65)	47.3 (9.34)	47.3 (10.51)
Median	47.0	48.0	48.0	47.5
Min, Max	24, 78	25, 82	31, 74	24, 82
PBC Diagnosis Age Category – n (%)				
< 45 years old	28 (38.4%)	29 (41.4%)	29 (39.7%)	86 (39.8%)
≥ 45 years old	45 (61.6%)	41 (58.6%)	44 (60.3%)	130 (60.2%)
Diagnosis Year Category – n (%)				
< 1990	4 (5.5%)	2 (2.9%)	0	6 (2.8%)
≥ 1990	69 (94.5%)	68 (97.1%)	73 (100%)	210 (97.2%)
Duration of PBC (years)				
N	73	70	73	216
Mean (SD)	9.2 (6.85)	8.3 (5.79)	8.3 (5.39)	8.6 (6.03)
Median	8.5	7.2	7.4	7.8
Min, Max	0.04, 32	0.3, 27	0.9, 22	0.04, 32
Duration of PBC Category – n (%)				
< 7.5 years	30 (41.1%)	36 (51.4%)	39 (53.4%)	105 (48.6%)
≥ 7.5 years	43 (58.9%)	34 (48.6%)	34 (46.6%)	111 (51.4%)
Gender – n (%)				
Female	63 (86.3%)	65 (92.9%)	68 (93.2%)	196 (90.7%)
Male	10 (13.7%)	5 (7.1%)	5 (6.9%)	20 (9.3%)
Race – n (%)				
Asian	1 (1.4%)	1 (1.4%)	1 (1.4%)	3 (1.4%)
Black or African American	1 (1.4%)	1 (1.4%)	1 (1.4%)	3 (1.4%)
Other	1 (1.4%)	1 (1.4%)	5 (6.9%)	7 (3.2%)
White	70 (95.9%)	67 (95.7%)	66 (90.4%)	203 (94.0%)
Geographical Region – n (%)				
Australia	1 (1.4%)	5 (7.1%)	3 (4.1%)	9 (4.2%)
Europe	51 (69.9%)	45 (64.3%)	49 (67.1%)	145 (67.1%)
North America	21 (28.8%)	20 (28.6%)	21 (28.8%)	62 (28.7%)

Source: Reviewer's Table generated from the 747-301 ADSL and ADLIVER datasets.

Note: Denominators for percentages are N.

Table 23: Demographics and Baseline Characteristics (ITT) - continued

	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 < 3×ULN and AST < 2×ULN and TB < ULN; UDCA Usage	45 (61.6%)	43 (61.4%)	45 (61.6%)	133 (61.6%)
2. ALP < 3×ULN and AST < 2×ULN and TB < ULN; No UDCA Usage	2 (2.7%)	2 (2.9%)	2 (2.7%)	6 (2.8%)
3. ALP ≥ 3×ULN and/or AST ≥ 2×ULN and/or TB ≥ ULN; UDCA Usage	23 (31.5%)	22 (31.4%)	23 (31.5%)	68 (31.5%)
4. ALP ≥ 3×ULN and/or AST ≥ 2×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 (×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 (µmol/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 (×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

Source: Reviewer's Table generated from the 747-301 ADSL and ADLIVER datasets.

Note: Denominators for percentages are N.

Table 23: Demographics and Baseline Characteristics (ITT) - continued

	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)	Total (N = 216)
ALP Baseline Categories – n (%)				
1. 1.0×ULN ≤ ALP < 1.67×ULN	0	1 (1.4%)	1 (1.4%)	2 (0.9%)
2. 1.67×ULN ≤ ALP < 2.0×ULN	20 (27.4%)	13 (18.6%)	16 (21.9%)	49 (22.7%)
3. 2.0×ULN ≤ ALP < 3.0×ULN	33 (45.2%)	37 (52.9%)	33 (45.2%)	103 (47.7%)
4. 3.0×ULN ≤ ALP < 4.0×ULN	12 (16.4%)	10 (14.3%)	15 (20.5%)	37 (17.1%)
5. 4.0×ULN ≤ ALP < 5.0×ULN	6 (8.2%)	8 (11.4%)	5 (6.8%)	19 (8.8%)
6. ALP ≥ 5.0×ULN	2 (2.7%)	1 (1.4%)	3 (4.1%)	6 (2.8%)
TB Baseline Categories – n (%)				
1. TB < 1.0×ULN	66 (90.4%)	66 (94.3%)	66 (90.4%)	198 (91.7%)
2. 1.0×ULN ≤ TB < 2.0×ULN	7 (9.6%)	4 (5.7%)	6 (8.2%)	17 (7.8%)
3. TB ≥ 2.0×ULN	0	0	1 (1.4%)	1 (0.5%)
Relevant Combination Baseline Categories – n (%)				
1. ALP ≥ 1.67×ULN and TB < 1.0×ULN; UDCA Usage	**60 (82.2%)**	**60 (85.7%)**	**61 (83.6%)**	**181 (83.8%)**
2. ALP ≥ 1.67×ULN and TB < 1.0×ULN; No UDCA Usage	6 (8.2%)	5 (7.1%)	5 (6.8%)	16 (7.4%)
3. ALP ≥ 1.67×ULN and TB ≥ 1.0×ULN; UDCA Usage	7 (9.6%)	4 (5.7%)	6 (8.2%)	17 (7.8%)

Source: Reviewer's Table generated from the 747-301 ADSL and ADLIVER datasets.
Note: Denominators for percentages are N.

Note that there were only two patients in the study with baseline ALP < 1.67×ULN, and one of these patients also had a normal baseline total bilirubin concentration as well. It can be seen from the presented demographic and baseline characteristics that there was balance, for all presented variables, between the randomized treatment groups. Note that one of these patients did not meet the pre-specified inclusion criteria and was thus a protocol violation. The other patient meets the inclusion criteria of elevated TB.

The mean (SD) age was 56 (11) years, with a range from 29 to 86 years. A total of 82% of patients 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. The mean (SD) duration of PBC at time of entry was 9 (6) years, with a comparable percentage of patients with a duration of PBC of ≤ 7.5 years versus > 7.5 years. At Baseline, 128 (59%) patients reported pruritus assessed by the Investigator as follows: 43% mild, 15% moderate, and 1% severe.

Baseline biochemical characteristics were well balanced across treatment groups and consistent with PBC, each parameter was > ULN with the exception of total bilirubin. Baseline INR was ≤ 1.3 in 95% (treatment) to 99% (placebo) patients; INR was > 1.3 in 5 patients in the OCA arm.

Table 24: Key baseline Laboratory Values: mean (SD)

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)	ULN[a]
ALP (U/L)	327.5 (115.0)	325.9 (116.2)	316.3 (103.8)	118
Total Bilirubin (µmol/L)	11.8 (7.4)	10.3 (5.5)	11.3 (6.7)	19.3
Conjugated Bilirubin (µmol/L)	5.5 (6.0)	4.5 (4.5)	4.9 (4.4)	3.4
GGT (U/L)	309.6 (449.4)	252.8 (167.0)	261.1 (207.4)	23.6
ALT (U/L)	56.0 (30.3)	61.6 (39.0)	56.3 (39.7)	22.9
AST (U/L)	48.8 (22.4)	52.3 (25.3)	50.5 (31.0)	25.7

Source: Copied and electronically reproduced from Applicant submission 747-301 Clinical Study Report (Double-Blind Phase).

[a]Given that the majority of the population was female, ULN values were based on criteria for females. ALP ULN 118.3 U/L (females), 124.2 U/L (males)

Table 25: Diagnosis of PBC Based on PBC Diagnostic Criteria from PBC Disease history eCRF

	NUMBER OF SUBJECTS MEETING PBC DIAGNOSTIC CRITERIA, n (%)				
		OCA			
	Placebo (N = 73)	Titration (N = 70)	10 mg (N = 73)	Total (N = 143)	Total (N = 216)
Met All 3 Diagnostic Criteria	**50 (68)**	**43 (61)**	**50 (68)**	**93 (65)**	**143 (66)**
Met 2 Diagnostic Criteria	**22 (30)**	**27 (39)**	**23 (32)**	**50 (35)**	**72 (33)**
Increased ALP ≥6 months, AMA Titer	13 (18)	16 (23)	14 (19)	30 (21)	43 (20)
Increased ALP ≥6 months, Liver Biopsy	9 (12)	11 (16)	9 (12)	20 (14)	29 (13)
Liver Biopsy, AMA Titer	0	0	0	0	0
Protocol Violation	0	1 (1)	0	1 (<1)	1 (<1)
Met 1 Diagnostic Criteria	**1 (1)**	**0**	**0**	**0**	**1 (<1)**
Increased ALP ≥6 months	1 (1)	0	0	0	1 (<1)

Source: Response to the clinical response to information request page 4 and 5 of 5 (Sequence 0023 (24) 09/28/2015).

Inclusion criteria: ALP ≥ 1.67 × ULN and/or TB ≥ ULN and < 2 x ULN.

Comment:

The inclusion criteria were met in all, but 2 patients. The 2 protocol violations mentioned above were clarified by the Applicant further. "We do not consider these protocol violations impact the efficacy result, since the patient in OCA titration arm did have a liver biopsy consistent with PBC, and is supportive of the diagnosis. And the patient in placebo arm indeed met two criteria when

eCRFs were reviewed. The trial population met appropriate inclusion criteria for all but one patient who did not meet the biochemical enrollment criteria (i.e., ALP <1.67 × ULN or TB <ULN)."

7.5 Efficacy Results

Primary Endpoint

Table 26: Proportion of Patients who Achieved Response at Month 12 (ITT)

Statistics	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)
Response at Month 6 – n (%) [1]	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]	34 (46.6%)	32 (45.7%)	7 (9.6%)
Corresponding 95% Wald CI	36.5%, 59.4%	34.0%, 57.4%	2.8%, 16.3%
CMH Test p-value [2]	<0.0001	<0.0001	
Corresponding Breslow-Day Test p-value	0.9072	0.5045	

Source: Reviewer's Table 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%.

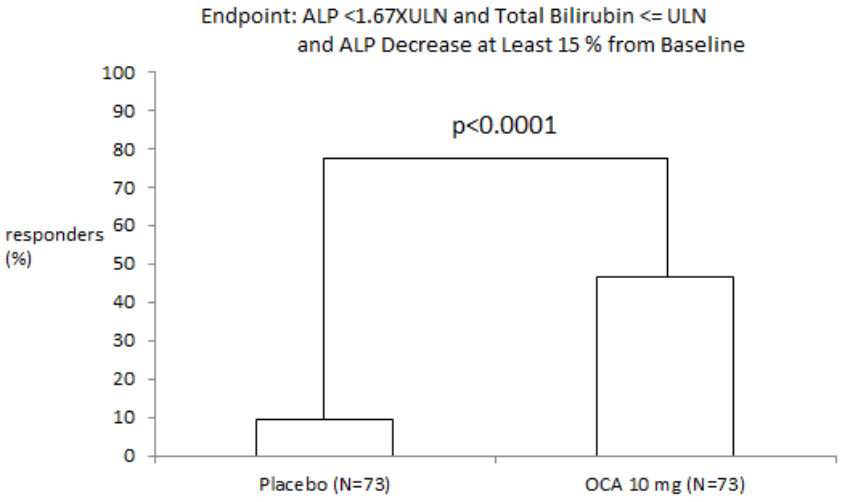
[2]: Month 12 Pair-wise comparison made between given OCA treatment group and Placebo adjusted for both randomization stratification variables.

It can be observed from Table 26 above that 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. The corresponding Breslow-Day test result shows that the treatment effects were homogeneous across the different randomization strata. 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 study conclusions. It is important to note that no single site influenced or drove 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 [30] laboratory values (as presented) and original (i.e.,

[30] Note that the Applicant used two different labs and used "corrected" lab values to account of the differences in the reference ranges in the two labs. The FDA analyzed the correction factors and found that these did not affect the efficacy analyses.

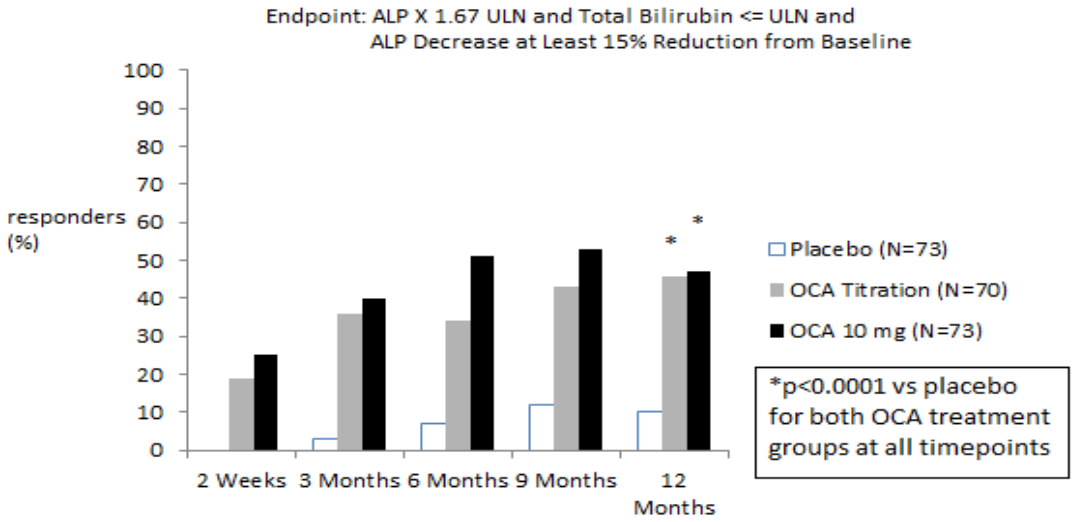
uncorrected) laboratory values. All of the previously presented analyses were re-conducted utilizing a baseline value that was the median of all pre-first dose measurements, and, separately, a traditional baseline definition (both approaches as described above); there was no impact on study conclusions with either approach. Considering the applicant's pre-specified step-down/closed sequential testing procedure as previously described, formal hypothesis testing is stopped at this point. Any subsequent inferential statistic reported below should be considered exploratory. Further pictorial representations of the primary efficacy results are reflected in **Figure 11** and **Figure 12** below.

Figure 11: Percentage of Patients Achieving Primary Efficacy Composite Endpoint at Month 12 (ITT)



Source: FDA reviewer table from data derived from the Applicant's submitted "Clinical Trial report" page 100/3119; Figure 6.

Figure 12: Percentage of Patients Achieving the Primary Composite Endpoint (ITT)



From FDA reviewer from the Applicant's submission Clinical Study Report 747-301 (Double-Blind Phase) page 102/3119
m = month; OCA = obeticholic acid; w = week; Missing values were considered a non-response.

7.6 Secondary Endpoints

Changes in Alkaline Phosphatase Concentrations

See Table below

Table 27: ALP Summary at Month 12 (ITT)

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 ≥ 10% at Month 12 – n (%)	61 (83.6%)	55 (78.6%)	29 (39.7%)
Decrease in ALP ≥ 15% at Month 12 – n (%)	**57 (78.1%)**	**54 (77.1%)**	**21 (28.8%)**
Decrease in ALP ≥ 20% at Month 12 – n (%)	54 (74.0%)	49 (70.0%)	17 (23.3%)
Decrease in ALP ≥ 40% at Month 12 – n (%)	**25 (34.3%)**	**21 (30.0%)**	**1 (1.4%)**
Baseline ALP Concentration (×ULN)			
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 (×ULN)			
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
ALP < 1.0×ULN at Month 12 – n (%)	**5 (6.9%)**	**1 (1.4%)**	**0**
ALP < 1.67×ULN at Month 12 – n (%)	**40 (54.8%)**	**33 (47.1%)**	**12 (16.4%)**

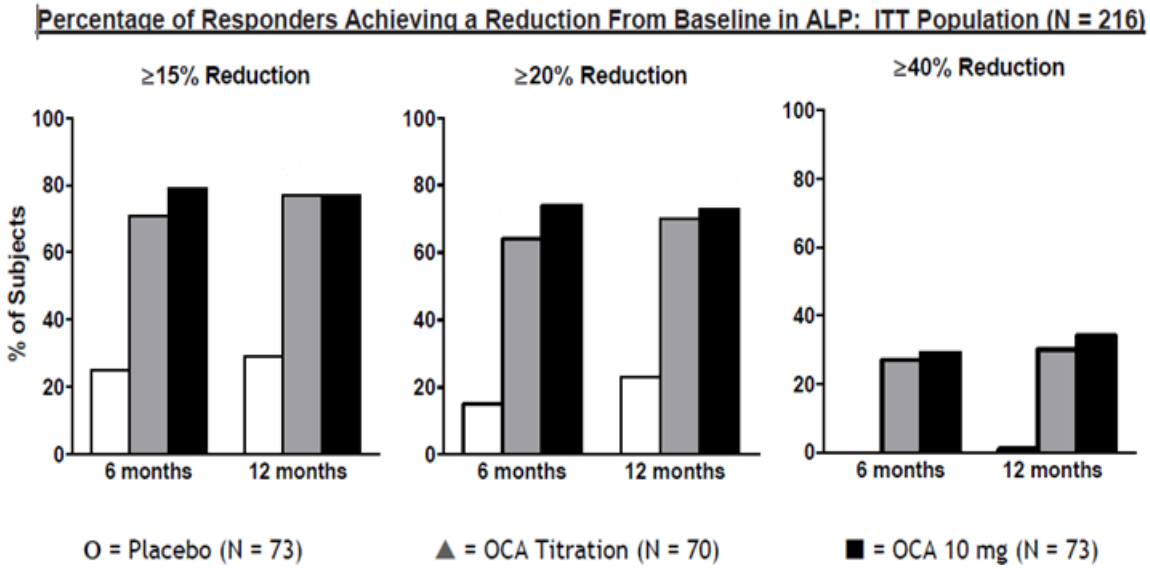
Source: Reviewer's Table generated from ADLIVER dataset.
Note: Denominators for percentages are N.

It can be observed from Table 27 above that both OCA treatment arms reduced ALP relative to placebo. It should be noted that the continuous descriptive statistics pertaining to the baseline, Month 12, absolute change from baseline at Month 12 and percentage change from baseline at Month 12 values utilized only the available data at those time points (i.e., no missing data were imputed). The categorical descriptive statistics (i.e., frequencies and corresponding proportions

at Month 12) utilized the worse-case (i.e., non-response) imputation strategy. The Applicant's baseline definition was used for all presented calculations performed by the FDA statisticians.

At Month 12, 21 (30%) and 25 (34%) patients from the OCA Titration and OCA 10 mg groups, respectively, achieved an ALP reduction from Baseline ≥ 40% compared with 1 (1%) placebo patient. The numbers of patients normalizing ALP values i.e., 118 U/L in females and 124 U/L males at month 12 are as follows: 1 (1%) patient from OCA titration group, 5 (7%) patients from the OCA 10 mg group, and zero placebo-treated patients.

Figure 13: Percentage of Responders Achieving a Reduction from Baseline in ALP (ITT)



Source: Copied and electronically reproduced from the Applicant submission of the 747-301 Clinical Study Report (Double-Blind Phase) page 123 of 3119.

As can be seen in Figure 13 above, a higher percentage of OCA-treated patients achieved the stated percent reduction in ALP compared with placebo at both time points (i.e., at Month 6 and Month 12). Further pictorial representations of these results are reflected in **Figure 14** below.

7.7 Secondary Endpoints

Figure 14: ALP values and Absolute change from baseline over time to month 12 in the ITT population (N=216)

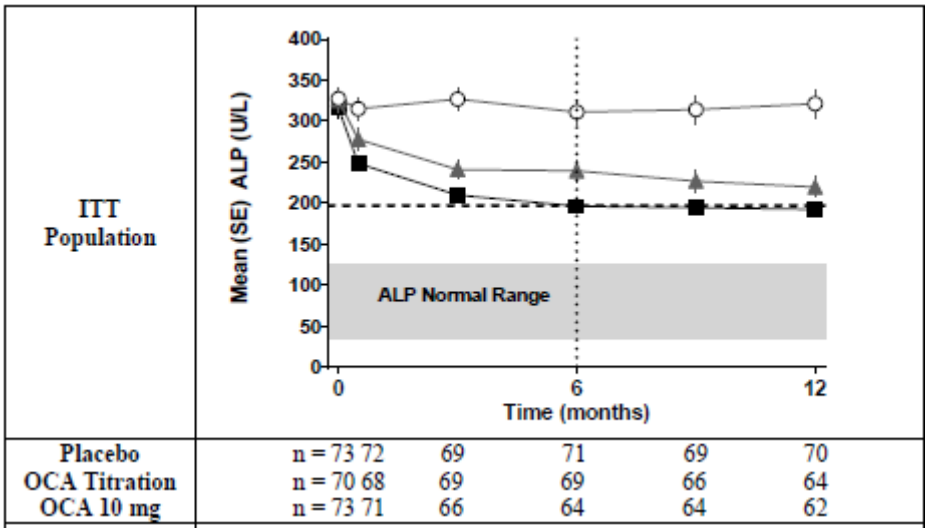


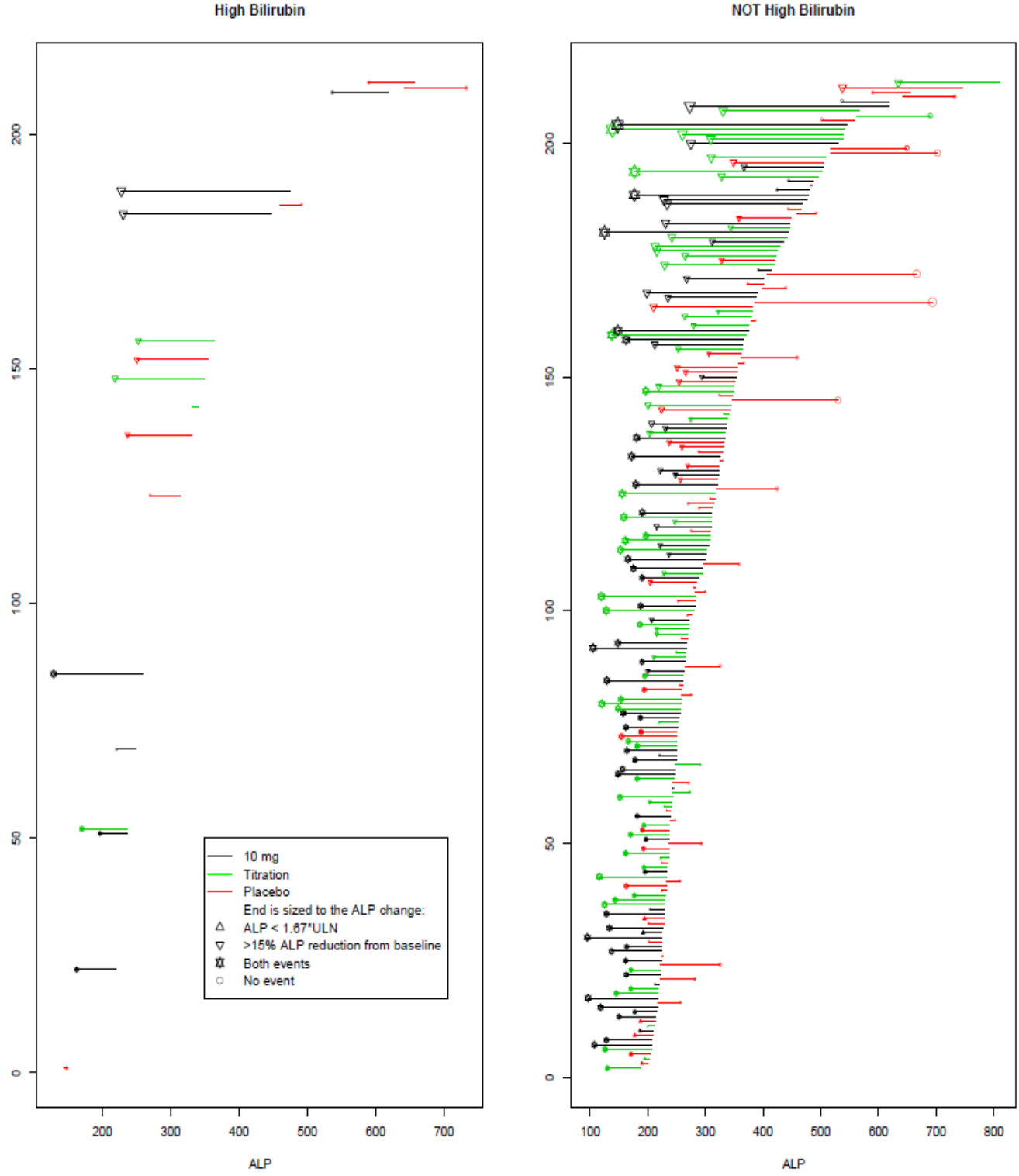
Figure source: Copied and electronically reproduced from the Applicant's submission Clinical Study Report 747-301 (Double-Blind Phase) page 107/3119

Dotted line at ALP of 200 U/L represents ALP of 1.67 x ULN

ALP normal range represents normal range for female patients (ULN 118.3)

Treatment with OCA (titration or 10 mg) resulted in a reduction in ALP levels as early as 2 weeks after treatment initiation with steep early reductions continuing through Month 3. In the OCA 10 mg group, the maximal effect on ALP reduction occurred at Month 6 and was sustained through Month 12.

Figure 15: Individual Patient Profiles for ALP: Change from Baseline to Month 12 by Treatment Group in Patients with Above Normal or Normal Bilirubin at Baseline (ITT)



Source: Statistical Reviewer Figure from ADLIVER dataset.

The length of each line represents the magnitude of ALP response seen during the trial.

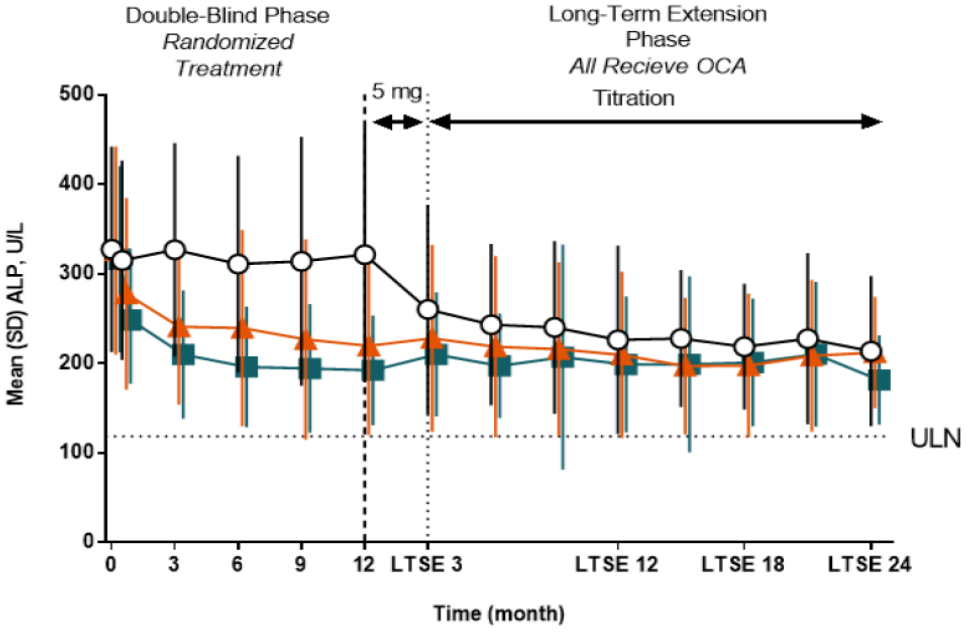
The y-axis represents dummied patient ID number.

Figure 15 above presents the change in ALP concentration (in U/L) for each of the 216 ITT patients from baseline to the end of the 12 month double-blind treatment period; the length of the line represents the magnitude of change in ALP. These graphical patient profiles are presented according to baseline TB status; the figure on the left presents data on the 18 patients with baseline TB ≥ 1.0×ULN, while the figure on the right panel presents data on the 198 early stage PBC patients (i.e., TB < 1.0×ULN).

ALP Concentrations over Time

After completing the 12-month double-blind treatment period, 193 out of the 216 ITT patients (i.e., 64 on 10 mg OCA, 63 on OCA Titration, and 66 Placebo patients) continued on open-label OCA treatment during the LTSE period (note: that all placebo patients were switched to OCA 5 mg at month 12 and then all patients were switched to OCA 10mg at month 15). Figure 16 presents ALP concentrations over time, organized by originally randomized treatment group, up to the latest data cut made on June 29, 2015.

Figure 16: ALP Concentration (U/L) from Randomization through Latest LTSE Data Cut (ITT)



	Month	0	0.5	3	6	9	12	LTSE 3	LTSE 6	LTSE 9	LTSE 12	LTSE 15	LTSE 18	LTSE 21	LTSE 24
Placebo	n	73	72	69	71	69	70	64	60	59	59	55	55	28	12
Titration OCA	n	70	68	69	69	66	64	63	62	62	60	57	56	29	10
OCA 10 mg	n	73	71	66	64	64	62	64	59	61	59	58	59	30	12

Source: Figure 3 of page 13 of the 120 Day Safety Update.

It can be seen that ALP concentration levels are reduced in both OCA treatment groups during the first 12 months, most notably during the first three months; these reduced levels remain

stable during the LTSE period signifying durability of response. It can also be seen that ALP levels for placebo patients are flat during the first 12 months; however, these levels start decreasing upon initiation of OCA therapy, and stabilize during the LTSE period.

Changes in Total Bilirubin Concentrations

Table 28: TB Summary at Month 12 (ITT)

Time Point/Statistics	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)
Baseline TB Concentration (µmol/L)			
N	73	70	73
Mean (SD)	11.3 (6.69)	10.3 (5.51)	11.8 (7.38)
Median	9.2	9.1	9.2
Min, Max	2, 34	2, 36	2, 39
Month 12 TB Concentration (µmol/L)			
N	63	64	70
Mean (SD)	9.6 (4.68)	9.9 (4.82)	13.2 (8.69)
Median	7.9	8.2	9.8
Min, Max	2, 25	4, 28	4, 45
Absolute Change from Baseline to Month 12 (µmol/L)			
N	63	64	70
Mean (SD)	-1.2 (4.36)	-0.62 (3.33)	1.4 (4.13)
Median	-0.46	-0.34	1.3
Min, Max	-18, 7	-9, 7	-7, 20
Percentage Change from Baseline to Month 12 (%)			
N	63	64	70
Mean (SD)	-1.1 (36.19)	1.3 (34.71)	17.0 (41.54)
Median	-5.1	-5.0	12.4
Min, Max	-51, 194	-51, 125	-43, 211
Baseline TB Concentration (×ULN)			
N	73	70	73
Mean (SD)	0.558 (0.3162)	0.514 (0.2490)	0.598 (0.3733)
Median	0.473	0.456	0.478
Min, Max	0.08, 1.78	0.11, 1.43	0.12, 2.03
Month 12 TB Concentration (×ULN)			
N	63	64	70
Mean (SD)	0.479 (0.2332)	0.496 (0.2221)	0.660 (0.4097)
Median	0.407	0.416	0.496
Min, Max	0.12, 1.28	0.22, 1.12	0.23, 1.96
TB < 1.0×ULN at Month 12 – n (%)	**68 (93.2%)**	**68 (97.1%)**	**60 (82.2%)**
TB ≥ 1.0×ULN at Baseline – n (%)	7 (9.6%)	4 (5.7%)	7 (9.6%)
TB < 1.0×ULN at Month 12 – n (%) [1]	**5 (71.4%)**	**2 (50.0%)**	**1 (14.3%)**

Source: Reviewer's Table generated from ADLIVER dataset.

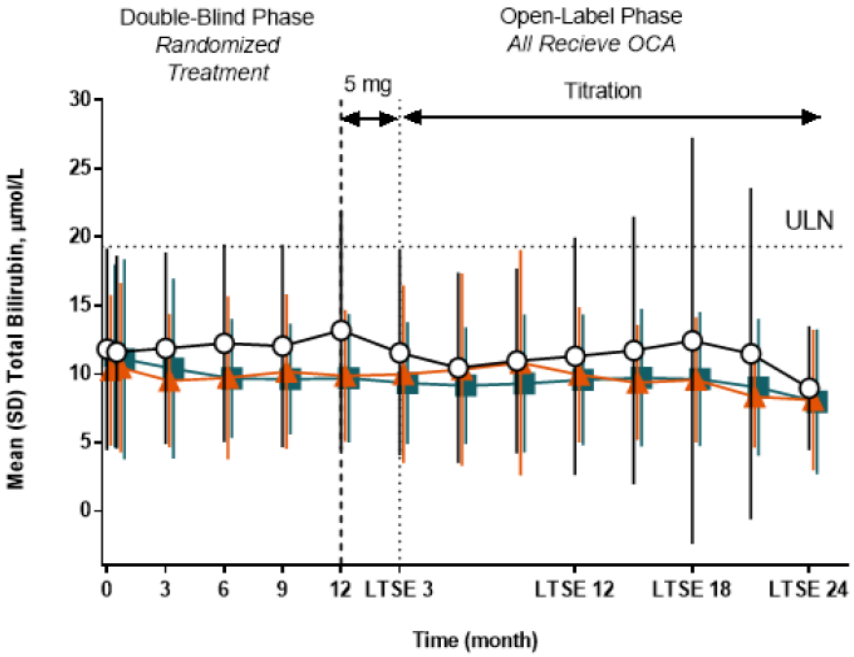
Note: Denominators for percentages are N.

[1]: The denominator for this calculation is the number of patients with TB ≥ 1.0×ULN at baseline.

It can be observed from Table 28 above that reductions from baseline in TB were greater in both OCA treatment groups than in the placebo group. **However, note that very few patients had elevations in TB above ULN at baseline**; therefore, of the 18 patients with baseline elevations in TB, 2 of 7 (28.6%) in the OCA 10 mg arm, 1 of 4 (25.0%) in the OCA Titration arm and 0 of 7 in the placebo arm were designated as responders at Month 12. It should be noted that the continuous descriptive statistics pertaining to the baseline, Month 12, absolute change from baseline at Month 12 and percentage change from baseline at Month 12 values utilized only the available data at those time points (i.e., no missing data was imputed). The categorical descriptive statistics (i.e., frequencies and corresponding proportions at Month 12) utilized the worse-case imputation strategy. The applicant's baseline definition was used for all presented calculations.

Figure 17 below presents TB concentrations over time, organized by originally randomized treatment group (up to the latest data cut made on June 29, 2015) for the 193 ITT patients continuing on open-label OCA treatment during the LTSE period.

Figure 17: TB Concentration (µmol/L) from Randomization through Latest LTSE Data Cut (ITT)



Placebo ± UDCA
Titration OCA ± UDCA
10 mg OCA ± UDCA

Month	0	0.5	3	6	9	12	LTSE 3	LTSE 6	LTSE 9	LTSE 12	LTSE 15	LTSE 18	LTSE 21	LTSE 24
n	73	72	68	71	69	70	64	60	59	59	55	55	28	12
n	70	68	68	69	66	64	63	62	62	60	57	56	29	10
n	73	71	66	64	64	62	64	59	61	59	58	59	30	12

Source: Figure 7 of page 17 of the 120 Day Safety Update.

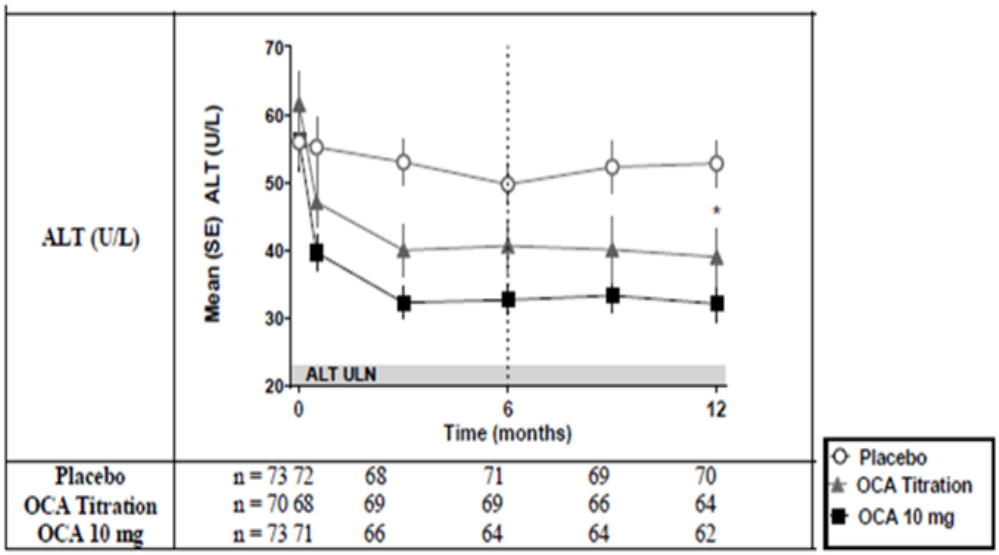
Table 29: GGT Absolute and Percent Change From Baseline at Month 12: ITT Population (N = 216)

	Placebo		OCA Titration		OCA 10 mg	
	N	Mean (SD)	N	Mean (SD)	n	Mean (SD)
GGT (U/L)						
Baseline	73	309.6 (449.36)	70	252.8 (167.04)	73	261.1 (207.40)
Month 12	70	301.8 (427.82)	64	114.2 (99.95)	62	91.9 (80.36)
Absolute Change	70	-8.2 (167.98)	64	-138.2 (145.47)	62	-177.7 (160.67)
Percent Change	70	-1.1 (37.95)	64	-51.2 (28.13)	62	-64.9 (16.66)
GGT ULN: 23.6 U/L (Female) and 35.2 U/L (Male)						

Baseline is defined as the mean of all available evaluations prior to treatment.
Source: CSR 747-301, Section 14, Table 14.2.9.1.1

Table 29 shows GGT reduction followed similar trends as ALP decline. Normalization of GGT (a marker of cholestasis) was not noted in any treatment arm at any time point.

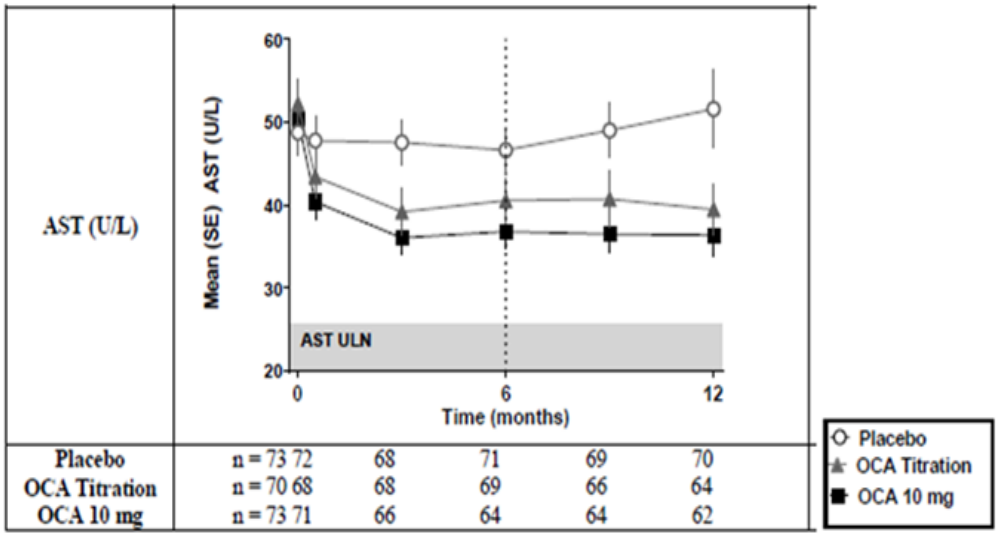
Figure 18: ALT Values and Change from Baseline over Time (ITT)



Given the majority of the population was female; ULN values are based on criteria for females i.e., ALT 22.9 U/L

Source: Copied and electronically reproduced from 747-301 Clinical Study Report (Double-Blind Phase) page 116 of 3119.
ALT: (ALT ULN: 22.9 U/L (Female) and 33.4 U/L (Male))

Figure 19: AST Values and Change from Baseline over Time (ITT)



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

Given the majority of the population was female; ULN values are based on criteria for females i.e., AST 25.7 U/L.

Source: Copied and electronically reproduced from the 747-301 Clinical Study Report (Double-Blind Phase) Clinical Study Report 747-301 (Double-Blind Phase) page 117-3119. AST: (AST ULN: 25.7 U/L (Female) and 33.0 U/L (Male))

Comments:

Markers for hepatocellular damage (AST/ALT) decreased over time, indicating a reduction of the ongoing hepatocellular damage. They did not normalize, however, and the full clinical consequences of these findings are not fully understood at this time.

Secondary Efficacy Laboratory Measures

The albumin and coagulation profile remained normal throughout the trial across the treatment arms. Please note, however, that > 99% of patients had normal albumin (ULN of albumin 4 gm/dL) and normal coagulation profile at baseline. PBC is a slowly progressive disease and it is not expected that these laboratory parameters will worsen in a 12-month period.

Patients with cirrhosis

Since the majority of patients had a liver biopsy at some point of time prior to trial enrollment (ranging from 2-10 years) there were a few patients who were identified as having histological findings consistent with cirrhosis. This included a total of 20 patients distributed as follows among the treatment arms:

- 9 patients in placebo
- 7 patients in the OCA titration arm
- 4 patients in the OCA 10 mg arm

At this time only 20 patients (11 OCA treated patients) enrolled with cirrhosis. Therefore there is not enough patients enrolled with cirrhosis to make any conclusions about efficacy or safety in patients with cirrhosis.

7.8 Exploratory Analysis

Dose Titration: As stated previously, a total of 69 of 70 ITT patients from the OCA titration group completed month 6. Of these, 36 (52%) remained at 5 mg for the duration of the 12-month treatment period and 33 (48%) who did not meet the primary composite endpoint at Month 6, but, because they tolerated the investigational product, were titrated to 10 mg for the last 6 months of the 12-month period. Thirteen (39%) of the patients who up-titrated met the composite endpoint at Month 12 suggesting that incremental benefit can be gained with titration of OCA from 5 mg to 10 mg in those patients who did not respond to the 5 mg dose.

Because for some patients, a response can be achieved with OCA 5 mg, initiating treatment on OCA 5 mg and titrating subsequently to 10 mg if needed and if tolerated appears to be a reasonable dosing strategy. For patients who do not achieve an optimal response within 6 months of treatment with OCA 5 mg, additional incremental benefit may be gained by titrating to OCA 10 mg. Please see Section 13 (Clinical Pharmacology Summary) below for full details.

Effect of Bile Acid Sequestrants (BAS) Exposure on Efficacy

For patients receiving BAS, OCA 5 mg and 10 mg trough concentrations were slightly lower compared to those patients who did not receive BAS. The decreased trough concentrations resulted in a modest attenuation in efficacy in patients receiving OCA 5 mg (despite instruction to dose BS at least 4 hours apart from OCA), but did not appear to affect efficacy in patients receiving OCA 10 mg.

Efficacy of OCA used as Monotherapy

See Section 10 for analysis and discussion of these results.

Subgroup Responder Analyses

The primary efficacy composite endpoint, ALP and total bilirubin, was evaluated in relation to age at baseline, age at time of diagnosis, and years since diagnosis. The effect of OCA was consistent independent of age at diagnosis, duration of PBC, or years since diagnosis. In general, the subgroups were consistent with the observed effect in the overall ITT population. Namely, greater improvements were observed in OCA-treated subjects, compared with placebo subjects. The preponderance of trial patients was female and white thereby precluding any meaningful subgroup analyses by gender or race.

7.9 Exploratory Analysis of ALP response based on Stratified Endpoint Derived from Analysis of the Global PBC Study Group Data

Several different cut points described in Section 5 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 30, which is a representation of Table 5.1 within the appendix of Section 4 above.

Table 30: 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 30 continued: 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.

It can be seen from **Table 30** above that 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 31** 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 31: 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 31** 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 ≥ 2.0×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×ULN*
- *ALP reduction from baseline at Month 12 ≥ 40%;*

Else if baseline ALP was ≥ 1.67×ULN but < 2.0×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×ULN*
- *ALP reduction from baseline at Month 12 ≥ 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 32** above was reproduced and expanded by applying this stratified ALP cut point to the 181 comparable ITT patients for re-analysis purposes.

Table 32: 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%
Baseline ALP ≥ 2.0×ULN – n (%)	42 (70.0%)	47 (78.3%)	46 (75.4%)
ALP < 2.0×ULN at Month 6 – n (%) [2]	30 (71.4%)	24 (51.1%)	8 (17.4%)
Decrease in ALP ≥ 40% at Month 6 – n (%) [2]	10 (23.8%)	13 (27.7%)	0
ALP < 2.0×ULN and Decrease ≥ 40% at Month 6 – n (%) [2]	**9 (21.4%)**	**11 (23.4%)**	**0**
Baseline ALP ≥ 1.67×ULN but < 2.0×ULN – n (%)	18 (30.0%)	13 (21.7%)	15 (24.6%)
ALP < 1.67×ULN at Month 6 – n (%) [3]	17 (94.4%)	10 (76.9%)	3 (20.0%)
Decrease in ALP ≥ 15% at Month 6 – n (%) [3]	16 (88.9%)	11 (84.6%)	1 (6.7%)
ALP < 1.67×ULN and Decrease ≥ 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%
Baseline ALP ≥ 2.0×ULN – n (%)	42 (70.0%)	47 (78.3%)	46 (75.4%)
ALP < 2.0×ULN at Month 12 – n (%) [2]	29 (69.1%)	28 (59.6%)	9 (19.6%)
Decrease in ALP ≥ 40% at Month 12 – n (%) [2]	13 (31.0%)	16 (34.0%)	1 (2.2%)
ALP < 2.0×ULN and Decrease ≥ 40% at Month 12 – n (%) [2]	**12 (28.6%)**	**13 (27.7%)**	**1 (2.2%)**
Baseline ALP ≥ 1.67×ULN but < 2.0×ULN – n (%)	18 (30.0%)	13 (21.7%)	15 (24.6%)
ALP < 1.67×ULN at Month 12 – n (%) [3]	16 (88.9%)	11 (84.6%)	6 (40.0%)
Decrease in ALP ≥ 15% at Month 12 – n (%) [3]	14 (77.8%)	10 (76.9%)	2 (13.3%)
ALP < 1.67×ULN and Decrease ≥ 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 ≥ 2.0×ULN.
[3]: The denominator for this calculation is the number of patients with Baseline ALP ≥ 1.67×ULN but < 2.0×ULN.

It can be observed from **Table 32** that both OCA treatment groups showed 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.

7.10 Efficacy Summary

1. Treatment with OCA (10 mg) in a cohort of subjects with early stage PBC who were enrolled with incomplete biochemical response to UDCA resulted in statistically significant improvement from baseline in alkaline phosphatase for the pre-specified endpoint of reduction of ALP to < 1.67 x ULN and 15%, relative to placebo. The percentage of patients achieving the primary endpoint at month 12 was statistically significantly different than placebo [34 of 73 (46.6%) in the OCA 10 mg arm, 32 of 70 (45.7%) in the titration arm and 7 of 73 (9.6%) in the placebo arm]. The effect of OCA on achieving a reduction in ALP was independent of age at diagnosis, duration of PBC, and baseline ALP.

2. Secondary analysis showed that at Month 12, 21 (30%) and 25 (34%) patients from the OCA Titration and OCA 10 mg groups, respectively, achieved an ALP reduction from Baseline ≥ 40% compared with 1 (1%) placebo patient. The numbers of patients normalizing ALP values i.e., 118 U/L in females and 124 U/L males at month 12 are as follows: 1 (1%) patient from OCA titration group, 5 (7%) patients from the OCA 10 mg group, and zero placebo-treated patients.

3. Eighteen patients from the ITT population had elevations in TB above ULN at baseline. For patients with baseline elevations in TB, 2 of 7 in the OCA 10mg arm, 1 of 4 in the titration arm and 0 of 7 in the placebo arm were responders (normalization of TB) at month 12.

4. The number of patients enrolled who were intolerant of UDCA at enrollment (and therefore received monotherapy with OCA during the clinical program) was too small to draw any conclusion regarding the effect of OCA use as monotherapy from this trial. However, combining the data from the phase 2 monotherapy trial (747-201) with the

phase 3 data did show a reduction in ALP in the OCA treated group relative to placebo: 43 patients (41%) OCA and 5 patients (5%) placebo met a formal definition of responder. . See Section 10 for a review of the overall data for use of OCA as monotherapy.

8 PHASE 3 CLINICAL TRIAL AND LTSE - 747-301 - REVIEW OF SAFETY

Double Blind, Placebo Controlled Trial and Long Term Safety Extension of Obeticholic Acid in Patients with Primary Biliary Cirrhosis

8.1 Extent of Exposure

A total of 216 PBC patients were enrolled in the trial, and were randomized as follows:

1. 73 patients received placebo,
2. 73 patients received OCA 10 mg for the total duration of the trial and
3. 70 patients were enrolled in the OCA titration arm and received OCA 5 mg from day 0 to month 6, after which they were eligible for up-titration to 10 mg. Of the 69 patients in the OCA titration arm who were remaining at Month 6. Of these, 36 patients remained at 5 mg for a total duration of 12 months, and 33 patients were up-titrated to OCA 10 mg for the final 6 months of the trial.

Table 33: 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**

Source: CSR 747-301 Table 52 page 188

8.2 Serious Adverse Events

Death

One death occurred in the clinical trial, in an 82 year old male patient randomized to the OCA titration group. The death was due to cardiac failure.

The patient's relevant medical history included PBC, heart failure, atrial fibrillation (since 2005), myocardial infarction x 2, hypertension, and chronic renal impairment (since 1995). The patient had an implantable cardioverter defibrillator at study entry. The patient was randomized to the

OCA titration arm, and initiated on OCA 5 mg. The patient did not uptitrate to OCA 10 mg at month 6 due to general progression of his heart failure. On Day 219 of OCA dosing, the patient experienced an SAE of cardiac failure and was hospitalized. Peripheral edema and pleural effusion were noted upon admission. Of note, the patient's serum creatinine increased from a baseline value of 1.76 mg/dL to 2.13 mg/dL. The event of worsening heart failure was considered resolved and dosing with OCA 5 mg was continued.

On Day 257 the patient had a second event of cardiac failure and was hospitalized and the patient died after this episode. OCA was discontinued 2 days prior to the patient's death. The primary cause of death was noted as congestive cardiac failure and ischemic heart disease. Secondary causes of death were listed as chronic kidney disease and PBC.

Comment:
We agree with the Applicant's assessment that this death is not likely to be treatment related, however the continued enrollment of this patient after the serum creatinine increased to 2.16 mg/dL was inappropriate.

Other Serious Adverse Events (SAEs)
3 (4%) patients in the placebo group experienced 8 SAEs; 11 (16%) patients in the OCA titration group experienced 15 SAEs, and 8 (11%) patients in the OCA 10 mg arm experienced 15 SAEs.

Table 34: Serious Treatment-Emergent Adverse Events by Subject and Treatment Group: Safety Population (N = 216)

Patient ID**	SAE	Time to onset/ AE start day-Dose start day	Duration of the SAE	Action taken	Outcome
PLACEBO					
1	Tibia fracture	220	26	IP interrupted	Recovered and resolved
	Chest pain	268	5	IP interrupted	Recovered
	Dyspnea	268	5	Dose not changed	Resolved
	Sick sinus syndrome	343	3	IP interrupted	Resolved
2	Non cardiac chest pain	285	10	IP interrupted	Resolved
3	Upper GI hemorrhage	75	6	Dose not changed	Resolved
	Variceal hemorrhage	92	2	Dose not changed	Resolved
	Variceal hemorrhage	134	2	Dose not changed	Resolved
OCA titration					
4	Upper gastrointestinal hemorrhage	210	3	IP interrupted	Resolved
5	Ascites	360	4	IP was discontinued on day 288, and was never restarted	Remained on diuretics?
	Hepatic encephalopathy	360	4		Resolved
	Edema	361	3		Remained on diuretics?
	Hepatic	378	13		Resolved

	encephalopathy				
6	Interstitial lung disease	218	10	Dose not changed	Resolved
7	Syncope	46	2	Dose not changed	Resolved
8	Abdominal wall hematoma	89	5	Dose not changed	Resolved
9	Rotator cuff syndrome	305	5	Dose not changed	Resolved
10	Parotitis	88	6	IP interrupted	Resolved
11	Cardiac failure	219	14	Dose not changed	Resolved
	Cardiac failure	257	37	IP withdrawn	Died
12	Varicose vein	86	2	Dose not changed	Resolved
13	Varicose vein	233	2	Dose not changed	Resolved
14	Splenic artery aneurysm	360	2	Dose not changed	No action taken
OCA 10 mg					
15	Osteoarthritis	127	5	IP interrupted	Resolved
	Post procedural Hemorrhage	350	3	IP interrupted	Resolved
16	Pneumonia	249	5	IP interrupted	Resolved
17	Osteoarthritis	316	2	Dose not changed	Resolved
18	Clavicular fracture	102	3	Dose not changed	Resolved
19	Radius fracture	16	6	Dose not changed	Resolved

	Radius fracture	243	2	Dose not changed	Resolved
20	Intervertebral disc protrusion	64	5	Dose not changed	Resolved
	Wrist fracture	240	3	Dose not changed	Resolved
21	Anemia*	14	11	Dose not changed	Resolved
22	Erysipelas	54	21	IP was discontinued prior to SAE	Resolved.

Table source: Adopted from Applicant submission Clinical Study Report 747-301 (Double-Blind Phase) pages 203, 204 and 205 of 3119

*1 patient had anemia which was a result of GI bleeding, requiring blood transfusion

**The actual patient ID numbers have been removed and serial numbers have been subsituted.

8.3 Adverse Events Leading to Study Discontinuation

Of the 216 patients' enrolled 19 (8%) patients discontinued from the trial. Three (2%) patients in the placebo arm; 7 (10%) patients in the OCA titration arm; and 9 (12%) patients in the OCA 10 mg treatment arm discontinued from trial. The majority of TEAEs leading to study discontinuation were attributed to pruritus as noted above.

Table 35: Patient Discontinuations: Randomized Population (N = 217)

Number of Subjects, 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)

Table Source: Copied and electronically reproduced from the Clinical Study Report 747-301 (Double-Blind Phase) page 84 of 3119

Table 36: Subjects with Adverse Events Leading to Study Discontinuation: Safety Population (N = 216)

Patient ID**	Preferred Term	Time to Onset [31]	Duration (days) of AE	Severity	Outcomes
PLACEBO					
1	Headache	43	29	Mild	Resolved
	Abdominal distension	66	6	Moderate	
	Nausea	66	6	Moderate	
	Vomiting	66	6	Moderate	
2	Rash	2	34	Moderate	Resolved
3	Consent withdrawn				Unknown
OCA TITRATION					
4	Hallucination	7	2	Moderate	Resolved
5	Pruritus	221	32	Severe	Resolved
6	Cardiac failure	257	37	Severe	Fatal/patient died
7	Consent withdrawn				Unknown
8	Pruritus	47	27	Severe	Resolved
9	Pruritus	82	38	Severe	Resolved
10	Pruritus	9	153	Severe	Resolved
OCA 10 mg					
11	Pruritus	6	11	Severe	mild pruritus Ongoing
12	Pruritus	86	40	Severe	Resolved

[31] 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.

13	Pruritus	11	9	Severe	Resolved
14	Contusion	67	6	Mild	Resolved
15	Pruritus	52	18	Severe	Resolved
	Withdrew consent				Unknown

Table source: Adapted from Clinical Study Report 747-301 (Double-Blind Phase) page 209 and 201 of 3119

* One patient had diarrhea and later developed hepatic decompensation (ascites, edema and hepatic encephalopathy)

**The actual patient ID numbers have been removed and serial numbers substituted

8.4 Treatment Emergent Adverse Events

Total TEAEs

- 66 patients (90%) from the placebo group reported 452 TEAEs
- 65 patients (93%) from the OCA titration group reported 471 TEAEs
- 69 patients (95%) from the OCA 10 mg group reported a total of 467 TEAEs

Table 37: 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 (%)	Subjects[a] (%)	Subjects[a] (%)	Subjects[a] (%)
All TEAEs	66 (90)	65 (93)	69 (95)
Skin and Subcutaneous Tissue Disorders			
Pruritus	28 (38)	39 (56)	50 (68)
Rash	3 (4)	3 (4)	4 (5)
Eczema	0	4 (6)	2 (3)
General Disorders and Administration Site Conditions			
Fatigue	10 (14)	11 (16)	17 (23)
Oedema peripheral	2 (3)	2 (3)	5 (7)
Pyrexia	1 (1)	0	5 (7)
Infections and Infestations			
Nasopharyngitis	13 (18)	17 (24)	13 (18)
Upper respiratory tract infection	8 (11)	4 (6)	4 (5)
Urinary tract infection	8 (11)	4 (6)	4 (5)
Influenza	4 (5)	5 (7)	4 (5)
Bronchitis	0	4 (6)	1 (1)
Sinusitis	0	1 (1)	4 (5)
Gastrointestinal Disorders			
Nausea	9 (12)	4 (6)	8 (11)
Diarrhoea	8 (11)	2 (3)	8 (11)
Constipation	4 (5)	5 (7)	5 (7)
Abdominal pain upper	5 (7)	5 (7)	4 (5)
Gastrooesophageal reflux disease	4 (5)	2 (3)	4 (5)
Dyspepsia	8 (11)	4 (6)	0
Abdominal discomfort	1 (1)	5 (7)	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	3 (4)	4 (6)	7 (10)
Back pain	8 (11)	4 (6)	4 (5)

Table source: Copied and electronically reproduced from the Applicant's Clinical Study Report 747-301 (Double-Blind Phase) page 192 of 3119

Table 38: 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) (Continued)

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
System Organ Class/ Preferred Term, n (%)	Subjects[a] (%)	Subjects[a] (%)	Subjects[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 subjects; n = number of subjects experiencing event

Table source: Copied and electronically reproduced from the Applicant's Clinical Study Report 747-301 (Double-Blind Phase) page 193 of 3119

The incidence of pruritus, fatigue and arthralgia were increased in each OCA arm relative to placebo, and higher in the OCA 10 mg arm than in the titration arm.

Safety Laboratory Parameters

Five patients in the placebo group experienced liver enzyme elevations of clinical concern compared with the one each in OCA titration and OCA 10 mg treated groups. One placebo patient 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. See the integrated review of safety, Section 9, for a discussion of the changes in liver biochemical tests which did show a difference between treated and placebo patients.

8.5 Safety Parameters of Special Interest

Hepatic-Related Adverse Effects

One (1%) patient in the placebo arm experienced variceal bleeding. Two patients (3%) in the OCA titration arm and one (1%) in the OCA 10 mg arm experienced hepatic related AEs which the Applicant considered unrelated to OCA. One patient in the OCA titration arm experienced ascites, edema, hepatic encephalopathy the second experienced variceal bleeding. The patient in the OCA 10 mg treatment arm experienced mild ascites and anemia (11.8 g/dL→7g/dL) requiring 2 units of blood transfusion, endoscopy was done and patient had congestive gastropathy which was considered as a possible source of bleeding.

Comment:

While there is no clear difference in hepatic-related adverse events in this phase 3 trial, when all the data are taken into consideration, it is possible that OCA, in particular higher OCA doses, may be associated with an increase in hepatic adverse events. See the integrated summary of safety, Section 9, for a discussion of the higher incidence of liver related events on OCA compared to placebo across all studies. Similarly, elevations in transaminases and bilirubin were seen at higher doses; and as discussed in the clinical pharmacology review, Section 11, of this briefing package, liver and systemic exposures to OCA are higher in patients with cirrhosis.

Lipid-Related Effects

Worsening of Dyslipidemia - A decrease in high-density lipoprotein cholesterol (HDL-C) and an increase in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with OCA.

The mean (SD) percent change in HDL-C from baseline to end of study (month 12) was -3.2(18.05) for placebo, -12.42 (17.99) for the OCA titration arm, and -19.34 (19.78) for the OCA 10 mg arm. The mean (SD) percent changes in LDL-C from baseline to the end of the 12 month treatment were as follows: 1.93 (16.03) for the placebo arm, 3.46 (17.8) for the OCA titration arm and 1.15 (21.12) for the OCA 10 mg arm. Seven subjects in the OCA 10 mg group experienced a shift from normal HDLc levels at Baseline to below normal HDLc levels at Month 12 compared to subjects in the placebo group (4 subjects).

Cardiovascular-Related TEAEs

A total of 4 cardiovascular SAEs were reported in 2 patients:

- 1 patient in the placebo group experienced sick sinus syndrome + chest pain;
- 1 patient in the OCA titration group had 2 SAEs of cardiac failure, 1 of which was fatal.

Table 39: Relevant Medical History in Subjects Experiencing Cardiovascular Treatment-Emergent Adverse Events (Palpitations): Safety Population (N = 216)

Patient**	AE	Relevant medical history	Medical history ongoing at baseline
PLACEBO			
1	Palpitation	Hypertension	Yes
OCA titration			
2	Palpitations (2 X events)	Angina pectoris	Yes
3	Palpitations	None	No
OCA 10 mg			
4	Palpitations	Prior heart valve surgery	Yes
5	Palpitations	None	No
6	Palpitations	None	No
7	Palpitations	None	No
8	Palpitations	Atrial fibrillation and hypertension	Yes

Table source: Adapted from Clinical Study Report 747-301 (Double-Blind Phase) page 243/3119
** Actual serial ID number for patients have been removed and substituted with serial numbers

Palpitations were the most common cardiovascular AE noted in the trial. OCA treated patients (3% in the OCA titration arm and 7% in the OCA 10 mg arm) compared to 1% in the placebo treatment arm experienced palpitations. Four percent of patients in the OCA 10 mg arm experienced hypertension compared with 1% in placebo arm and no patient in the OCA titration arm experienced hypertension.

Pruritus

Pruritus was the most common TEAE, with a higher incidence reported in the OCA treatment groups (OCA titration [56%] and OCA 10 mg [68%] versus placebo [38%]). The median time to first onset of pruritus was 50.5 days in placebo, 24 days in the OCA titration arm and 9 days in the OCA 10 mg arm.

Fourteen (50%) patients in the placebo group, 24 (62%) patients in the OCA titration group, and 30 (59%) patients in the OCA 10 mg group required treatment of pruritus. Protocol-defined interventions for pruritus included: bile acid sequestrants, antihistamines, treatment

interruptions, and alternative dosing schedules such as dosing every other day or every third day. Each pruritus event was treated with 1 or more interventions or left untreated.

Table 40: TEAE of pruritus in safety population, N=216

Number of patients N (%)	**Placebo (N = 73)**	**OCA Titration (N = 70)**	**OCA 10 mg (N = 73)**
	Patients N (%)	Patients N (%)	Patients N (%)
Patients reporting at least 1 TEAE of pruritus			
	28 (38)	39 (56)	51 (70)
Patients with any intervention due to pruritus			
	14 (50)	24 (62)	30 (59)
Successful interventions: patients who received any intervention for pruritus and did not discontinue from the study due to pruritus			
	14 (100)	23 (96)	25 (83)
Patients who had an intervention for pruritus and discontinued due to pruritus			
	0	1(4)	5 (17)
Subjects who had no intervention for pruritus who discontinued the study due to pruritus			
	0	0	2

Source: Modified and adapted from the Applicant submission Clinical Study Report 747-301 (Double-Blind Phase) page 226 of 3119

Table 41: Interventions for Management of Treatment-Emergent Pruritus (N=216)

Number of subject (%)	Placebo N= 73		OCA titration N = 70		OCA 10 mg N = 73	
Method of Intervention	**Total Interven-tions**	**Successful Interven-tion for Pruritus**	**Total Interven-tions**	**Successful Interven-tion for Pruritus**	**Total Interven-tions**	**Successful Interven-tion for Pruritus**
Dosing interval change	1 (7)	1 (7)	0	0	4(13)	3(12)
Drug interruption	0	0	1(4)	1(4)	0	0
Dose interval change +concomitant medication	2(14)	2(14)	4 (17)	3 (13)	2 (7)	2 (7)
Received concomitant medication						
*BAS	3 (21)	3 (21)	5 (21)	5 (22)	5(17)	4 (16)
Antihistamine	2 (14)	2(4)	4 (17)	4 (17)	2 (7)	2 (7)
BAS + antihistamine	1 (7)	1 (7)	2 (8)	2 (9)	4(13)	4(16)
Other medications	1 (7)	1 (7)	0	0	1 (3)	1 (4)

Source: Modified and adapted from the Applicant submission Clinical Study Report 747-301 (Double-Blind Phase) page 227 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. 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 (i.e., decrease in study drug frequency), investigational product interruption, or non-drug treatment.

*BAS: bile acid sequestrants

Severe Pruritus[32]:
The incidence of "severe pruritus" was 7% in placebo, 19% in OCA titration arm and 23% in OCA 10 mg arm.

Discontinuations from the study due to pruritus occurred in:

- 1 patient (1%) in the OCA titration group
- 7 patients (10%) in the OCA 10 mg group
- No placebo-treated patients

Starting at OCA 5 mg and titrating up based on clinical response was associated with improved tolerability compared to starting at OCA 10 mg. This was determined by a variety of parameters including: decreased rate of discontinuations due to pruritus (indicating manageable symptoms), decreased overall pruritus severity (days of severe pruritus), delayed time to onset of severe pruritus.

Other Safety Evaluations
Overall, no changes from baseline to month 12 in body weight or BMI were observed in any of the treatment groups, and no clinically meaningful differences in vital signs or ECGs were noted

Bone Fractures
A consult was requested from the Division of Bone, Reproductive and Urologic Products (DBRUP) to provide their opinion and expertise in the evaluation of the results of the DEXA scan performed in 216 subjects in the phase 3 trial, and to determine the significance of a numerically higher rate of fractures observed in OCA-treated subjects relative to placebo-treated subjects in the trial.

Comment:
DBRUP concluded that the DEXA and fracture data provided do not indicate a bone safety issue with OCA.

8.6 Safety Summary

Overall, administration of OCA 5 mg (titrated up to 10 mg) and OCA 10 mg appeared to be safe and generally well tolerated in the majority of patients over a 12-month period, although tolerability issues regarding pruritus were observed. Pruritus was the most common TEAE with a higher incidence and earlier onset with the 10 mg dose. There appeared to be better tolerance to pruritus in the titration arm. The incidence and number of subjects with related TEAEs of

[32] Intense or widespread and interfering with activities of daily living, i.e., causing inability to carry out usual activities, or severe sleep disturbance; the subject may have experienced intolerable discomfort. Medicinal intervention was typically indicated.
Treatment-emergent pruritus, defined as any preferred term including "Prur", was summarized separately by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, treatment group, and preferred term as a subset of all TEAEs.

pruritus was 27 subjects (37%) in the placebo group, 35 subjects (50%) in the OCA titration group, and 48 subjects (66%) in the OCA 10 mg group.

The incidence of TEAEs assessed as related, severe, serious, or leading to study discontinuation was higher in subjects treated with OCA, compared with placebo. With the exception of SAEs, these imbalances were predominantly attributed to pruritus.

TEAEs that occurred with an incidence of ≥5% and were reported more frequently in either of the OCA treatment groups compared with placebo included pruritus, rash, eczema, fatigue, pyrexia, peripheral edema, nasopharyngitis, influenza, bronchitis, sinusitis, diarrhea, constipation, abdominal discomfort, arthralgia, cough, oropharyngeal pain, procedural pain, fractures, palpitations, and hypothyroidism.

Lipid changes, including an early decrease in HDLc, which stabilized and remained within normal range and a transient increase in LDLc, were observed in subjects treated with OCA. Mean LDLc levels in the OCA treatment arms were identical to those of placebo-treated subjects at the end of the 12-month treatment period. A somewhat greater number of subjects (7 subjects) in the OCA 10 mg group experienced a shift from normal HDLc levels at Baseline to below normal HDLc levels at Month 12 compared to subjects in the placebo group (4 subjects).

Cardiovascular events are of special interest in the setting of lipid changes in the OCA treatment groups. No treatment differences were observed for cardiovascular-related AEs or SAEs. A total of 4 cardiovascular SAEs were reported in 3 subjects: 1 subject in the placebo group experienced sick sinus syndrome and 1 subject in the OCA titration group had 2 SAEs of cardiac failure, 1 of which was fatal.

While a distinct safety signal for liver-related biochemistry abnormalities or liver-related clinical adverse events was not seen in the Phase 3 trial, this safety concern did emerge in the integrated safety data, which is discussed below.

9 INTEGRATED SUMMARY OF SAFETY

9.1 Extent of Exposure

A total of 1507 patients and healthy volunteers have been exposed to at least one dose of OCA, of whom 1325 patients have been exposed to cumulative dosing with OCA.

Figure 20: Cumulative exposure to OCA (All OCA treated patients and volunteers, N=1325)

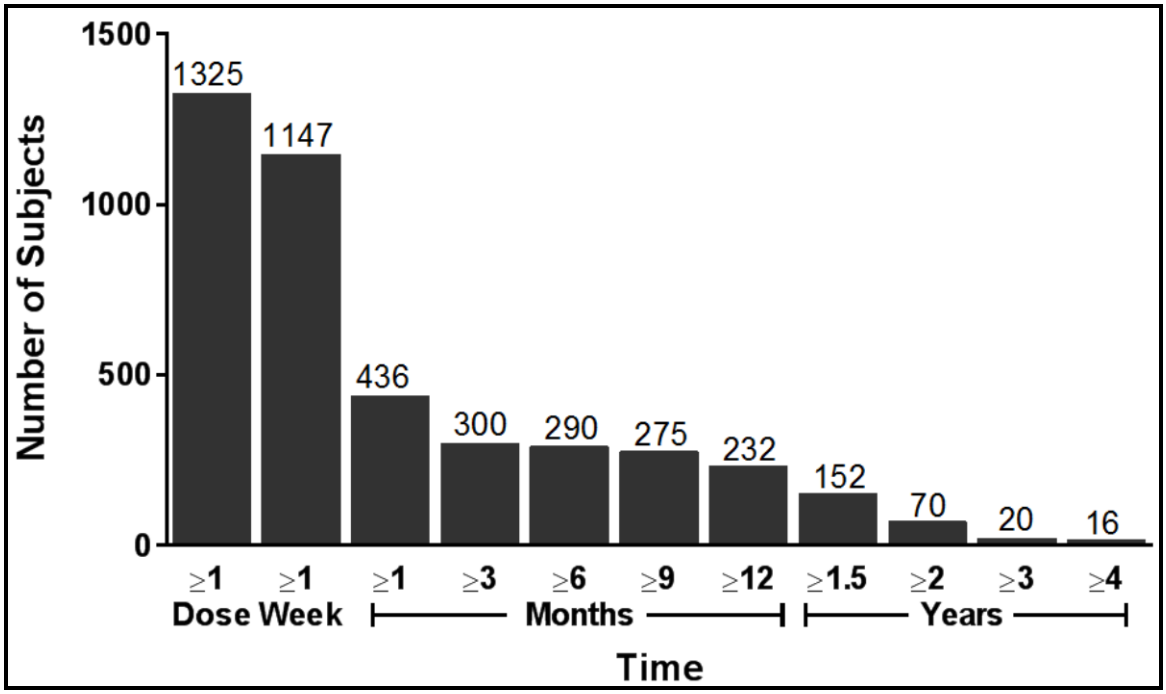
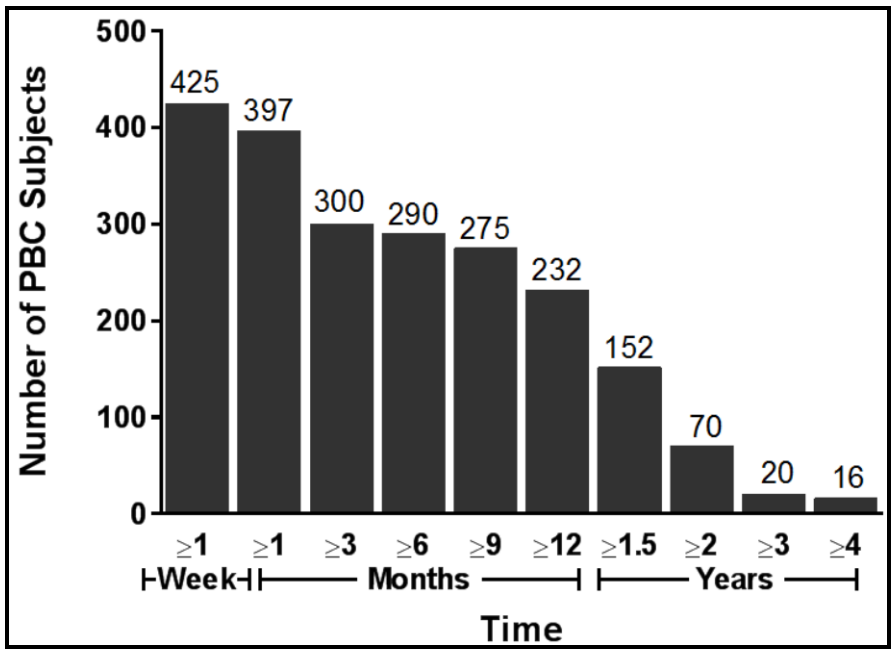


Figure: Electronically copied and reproduced from Applicant submission of Summary of clinical safety, page 37 of 162.

Figure 21: OCA Exposure in Subjects with PBC (All OCA-Treated Subjects with PBC, N = 432)



Safety data cut-off August 31st, 2014. Figure copied and electronically reproduced from Applicant submission of summary of clinical safety page 44-162

9.2 Adverse Events of Special Interest

9.2.1 Pruritus

The incidence, severity and timing of onset of pruritus were not significantly different in the pooled data as in the phase 3 trial and will not be discussed further here.

9.2.2 Dyslipidemia

The AEs in the pooled data sets were similar to those reported in the double blind trials.

9.2.3 Hepatic Related Adverse Events and Liver Enzyme Changes

Liver Enzyme Changes in the Clinical Pharmacology Studies

In an early Phase 1 trial in healthy volunteers, several dose-related increases in ALT and AST were observed (747-102) with OCA. At the 250-mg dose, 50% of subjects experienced both ALT and AST elevations, with the highest ALT level slightly more than 5x ULN. The ALT and AST values declined towards baseline levels after cessation of dosing. In the same study, less marked increases in ALT and AST enzymes were also observed at the OCA 100-mg dose. None of the changes at 100 mg were associated with serum bilirubin elevations.

Hepatic Adverse Events in the Clinical Pharmacology Studies

1. A healthy male volunteer without a prior history of liver disease experienced 2 SAEs (abdominal pain, acute cholecystitis and cholelithiasis) on OCA 25 mg. The SAEs resolved after discontinuation of the drug.
2. A healthy volunteer who had received OCA 10 mg for 28 days, experienced hyperbilirubinemia. The volunteer was discontinued from the trial and the AE resolved without medical intervention.
3. A healthy volunteer who had received OCA 10 mg for 10 days experienced an AE of hypertransaminasemia. OCA dosing was discontinued and the AE resolved without medical intervention.

Hepatic Adverse events in the Lipid Metabolism Trial in PBC patients (747-205)

A 66 year-old female patient with PBC in an open-label trial that assessed effects of OCA on lipid metabolism was on a dose of OCA 10mg when jaundice developed on day 66; OCA was stopped at that time, and jaundice resolved. The patient also developed ascites on day 78, which resolved after treatment with diuretics. This patient had not had a previous event of hepatic decompensation prior to this trial. This decompensation occurred 8 weeks after starting OCA.

Liver Enzyme Changes in Studies in Patients with PBC

In subjects with PBC, OCA treatment has been associated with an increase in liver enzymes and bilirubin. Increases in hepatic TEAEs potentially associated with hepatic decompensation have been seen mainly at higher dose levels (50 mg/day). They have typically occurred within the first 1 to 3 months of treatment and most have resolved or improved after discontinuation of treatment. It is challenging to establish whether these changes are drug-induced or are associated with the natural progression of the underlying PBC.

Hepatic Adverse Events in the Placebo-Controlled Clinical Trials and Open-Label, Long-Term Safety Extension Trials in Patients with PBC (Pooled Results)

A total of 14 OCA-treated patients had 25 TEAEs that were classified within the "standardised MedDRA Queries (SMQ) Hepatic Disorder" across the phase 2 and phase 3 trials 747-201, 747-202 and 747-301. There was a difference in the incidence of TEAEs of Hepatic Disorders between OCA and placebo (5% and 1%, respectively) in this integrated dataset of phase 2/phase 3 trials. Patients who were administered OCA 50 mg had a 2-fold higher incidence of Hepatic Disorders TEAE compared with placebo and all other OCA dose groups. This dose-response relationship was further confirmed by the exposure-adjusted incidence, which adjusts for the multiple doses used in the Phase 2 and 3 (OCA 5 mg, 10 mg 25 mg, and 50 mg) and different trial durations. See **Table 44**.

As noted in Table 42 below, the exposure adjusted incidence of hepatic disorders increased as the dose of OCA increased from OCA 5 mg to OCA 10 mg, to OCA 25mg, and OCA 50 mg in Trial 747-202. In the phase 2 trial 747-202, 3 patients (5%) in the OCA 50 mg group and 1 patient (1%)

in the OCA titration group experienced a severe[33] or serious[34] hepatic SAE/AE (PBC flare, new onset ascites, new onset jaundice, variceal hemorrhage, and hepatic encephalopathy) compared with none in the placebo group. The time to onset of these severe and serious hepatic events in the OCA titration group was 360 days compared to 23 days in the OCA 50 mg group. During the 3 month double-blind, placebo-controlled trial, 9 patients (13%) had a Hepatic Disorder TEAE that was considered by the investigators to be related to OCA, 4 (8%) in the OCA 25 mg treatment group, 1 (3%) patient in the OCA 10 mg arm compared to none in the placebo treated group had hepatic related adverse events and 5 patients had elevations in liver enzymes, One in the 10 mg arm, 4 in the 25 mg arm and 2 on the 50 mg arm. See Table 42.

[33] An AE was considered "severe" if it caused inability to carry out usual activities; the subject may experience intolerable discomfort or pain

[34] An AE or SAR was considered "serious" if, in the view of either the investigator or Applicant, it resulted in any of the following outcomes: death, was life threatening, required in-subject hospitalization or prolonged an existing hospitalization, resulted in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

Table 42: Hepatic-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term Reported: Safety Population - Trial 747-202 (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)
	Subjects (%)	Subjects (%)	Subjects (%)	Subjects (%)
Subjects with hepatic-related AEs	**0 (0)**	**1 (3)**	**4 (8)**	**9 (22)**
Hepatobiliary Disorders				
Primary Biliary Cirrhosis [a]	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				
Feces 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

a The adverse event was PBC flare.
Source: CSR 747-202, Table 55 page 127

Table 43: Hepatic-Related Serious Adverse Events seen in the Placebo-Controlled and Long-Term Safety Extension Trials in Patients with PBC

OCA dose	Adverse event OCA*	Day of onset relative to OCA dosing/ duration of AE	Causality per investigator/ FDA
OCA 25 mg 747-201 LTSE	Choledocholithiasis/ Jaundice	2 years (6 days)	Unrelated/ possibly related
OCA 10 mg 747-301 LTSE	Hyponatremia / Esophageal Varices with bleeding Hepatic Decompensation	2 years (20 days)	Unrelated/ possibly related
OCA 5 mg→10 mg 747-301 LTSE	Upper Gastrointestinal Hemorrhage	344 days (4 days)	Unrelated/ possibly related
OCA 5 mg 301-LTSE	Worsening Of Cholelithiasis	382 (6 days)	Unrelated/ possibly related
OCA 3.3mg 747-201 LTSE	Decompensation of liver No resolution	2 years	Possibly related/ Possibly related
OCA 25mg 747-201 LTSE	hyperbilirubinemia, resolved with drug discontinuation	3 years	Possibly related/ Probably related
OCA 10mg 747-202 LTSE	hyperbilirubinemia, ongoing, not resolved	300 days of OCA dosing	Possibly related/ Possibly related
OCA 10 mg 747-201 LTSE	esophageal variceal hemorrhage, hepatic decompensation, resolved with drug discontinuation	2 years of OCA dosing	Possibly related/ Probably related
OCA 5 mg 747-301 LTSE	hepatic encephalopathy, resolved with drug discontinuation	day 8	Possibly related/ Probably related

Table created by the FDA clinical reviewer from the data provided by Applicant in the Clinical summary of safety

*All these SAEs resulted in drug discontinuation and/or trial discontinuation

Comments:

The investigator considered many of these liver related SAEs as not related to OCA, however after reading the narratives it is our opinion that a causal relation with OCA cannot be ruled out

as OCA has been seen to cause liver injury at higher exposures in the nonclinical data and in phase 1 trials in healthy volunteers elevations in transaminases and bilirubin were seen with higher doses. Also note that exposures are higher in patients with underlying liver disease. See the additional discussion below and the discussion of exposures in patients with cirrhosis in the clinical pharmacology review, Section 11.

There was a higher incidence of SAEs in patients with baseline total and conjugated bilirubin levels > ULN, ALP upper tertile (>331.5 U/L), and Model for End Stage Liver Disease (MELD) > 7 who were treated with OCA. The incidence of these SAEs occurred at higher rates than in the placebo group. There is an exposure-response relationship for these SAEs, with most SAEs occurring in patients receiving OCA 50 mg. Please see Table 42, below *for the exposure adjusted incidence. This may be secondary to the higher systemic and liver exposures seen in patients with moderately advanced liver disease. Since patients with advanced liver disease according to the Rotterdam Criteria were not enrolled in the trials with OCA, the frequency and types of AEs that may occur in patients with advanced liver disease is unknown. Please refer to Section 11 clinical pharmacology review, for a detailed discussion of the exposures in patients with cirrhosis.*

Table 44: Treatment-Emergent Adverse Effects of Special Interest-Hepatic Disorders; Double-Blind, Placebo-Controlled Studies in Subjects with PBC (All Treated Subjects, N = 440)

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

[PEY: Patient exposure years]

Footnote:

[a] In Study 747-301, subjects randomized to OCA 5 mg were assessed at Month 6 for clinical response and tolerability. Subjects who did not achieve the primary composite endpoint and did not have tolerability issues were able to uptitrate to OCA 10 mg.

[b] At each level of summation (overall, system organ class, preferred term), subjects reporting more than one AE are counted only once

Adverse events reported in the placebo group were: non-serious liver function test abnormal and varices esophageal (serious).

Adverse events reported for subjects in the Titration and OCA 10 mg groups were: Ascites, varices esophageal, hepatic pain,

International normalized ratio increased, blood bilirubin increased, hepatic encephalopathy, and spider nevus. Adverse events reported for subjects in the OCA 25 mg and 50 mg groups were: Ascites, biliary cirrhosis primary, hepatomegaly, jaundice, portal hypertension, alanine aminotransferase increased, aspartate aminotransferase increased, and bilirubin conjugated increased.

Table Source: Copied and electronically reproduced from Applicant's summary of clinical safety page 91-162

10 OCA AS MONOTHERAPY EVALUATION

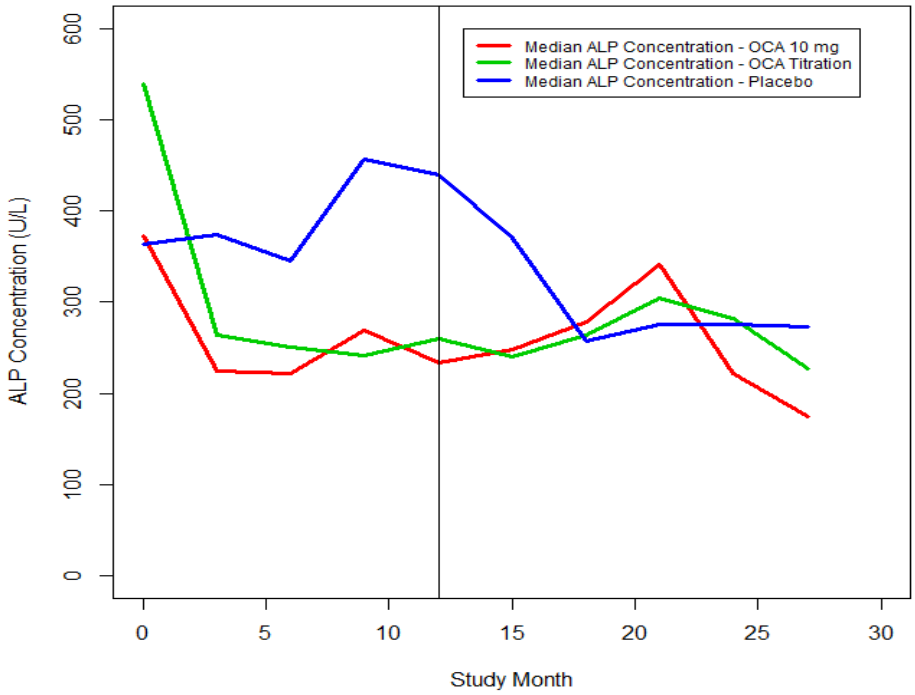
The Phase 3 trial included only 16 (7%) subjects treated with OCA monotherapy. See Table 1 below.

Table 45: Patients on Monotherapy vs. UDCA in Phase 3 trial (747-301) - ITT Population (N = 216)

Number of Subjects	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)	Total (N = 216)
UDCA Use at Baseline, n (%)				
Yes	68 (93)	65 (93)	67 (92)	200 (93)
No	5 (7)	5 (7)	6 (8)	16 (7)

In Trial 747-301, a total of 16 patients received OCA monotherapy: 5 patients in the placebo group, 5 patients in the OCA titration group, and 6 patients in the OCA 10 mg group. At Month 12, 2 of 5 patients in the OCA titration arm were responders and 1 of 6 patients in the OCA 10 mg arm was a responder; no placebo patient responded. It should be noted that these responder rates were the same at Month 6 as well. Figures 7 and 8 below present the median ALP and median TB concentrations, respectively, by randomized treatment group up to the latest data cut. Although the data are highly sparse, it can be seen that ALP concentration levels are reduced by both OCA treatment groups during the first 12 months, most notably during the first three months; these reduced levels remain stable during the LTSE period suggesting durability of response. It can also be seen that ALP levels for placebo patients remain elevated during the first 12 months; once these patients start OCA administration, these levels start decreasing immediately, and ultimately remain stable, during the LTSE period. In regards to TB, these concentrations do not display a consistent pattern.

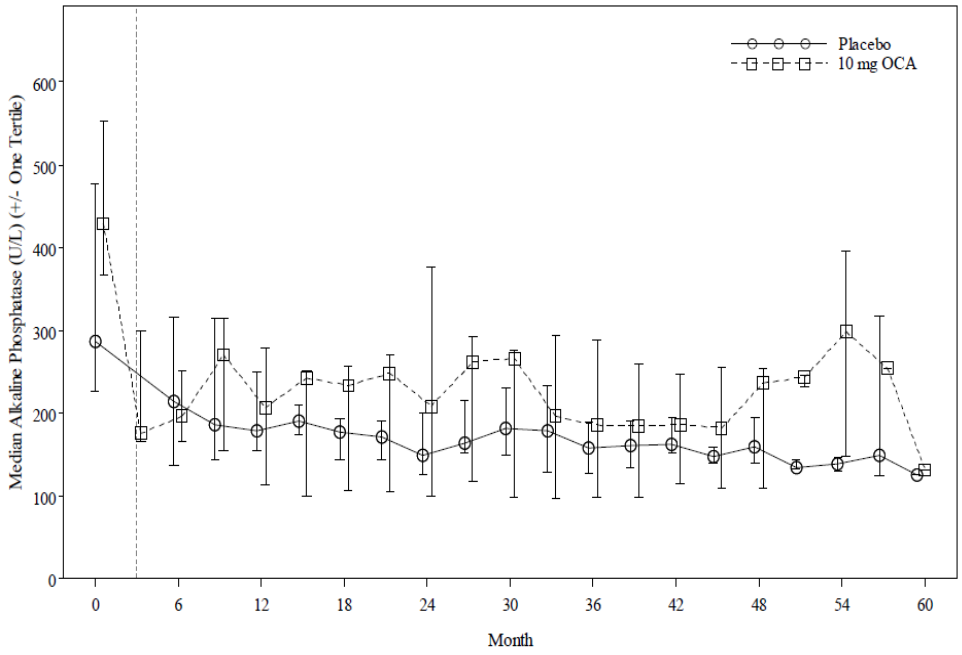
Figure 22: ALP Concentration Levels from Baseline through Ongoing LTSE in Patients Receiving OCA Monotherapy: Trial 747-301



Source: Figure generated by FDA Statistical Reviewer.

As stated in Section 5 above, trial 747-201 exclusively administered OCA as monotherapy. **Figure 23** below presents the median ALP concentrations, respectively, by randomized treatment group, exclusively for 10 mg OCA and placebo, up to the latest data cut. Although the data are highly sparse, it can be seen that ALP concentration levels are reduced by 10 mg OCA during the first 3 months; these reduced levels remain within reduced during the LTSE period suggesting durability of response. It can also be seen that ALP levels for placebo patients start decreasing, and ultimately remain stable, during the LTSE period once these patients start OCA administration.

Figure 23: ALP Concentration Levels from Baseline through Ongoing LTSE in Patients Receiving OCA Monotherapy: Trial 747-201



Source: Figure generated by Applicant and submitted as a response to an Information Request.

In an analysis of a pooled dataset consisting of Phase 2 and Phase 3 trials, the responder rate for monotherapy at 3 months was 38%, which is similar to the 41% responder rate achieved for the combination therapy (OCA plus UDCA). It should be noted that the baseline values of ALP were higher in the monotherapy group as compared to combination therapy group, while the ALP values after 3 months of treatment were similar. There were no new safety signals seen in this population.

Table 46: Efficacy Results for OCA Monotherapy and Combination Therapy with UDCA Based on Pooled Data from Phase 2 and 3 Trials

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

Baseline is defined as the mean of all available evaluations prior to double-blind treatment. Subjects with missing values are considered non-responders.
Source: module 2.5 Table 13.

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11 CONFIRMATORY CLINICAL BENEFIT TRIAL (PHASE 4)

Because the phase 3 trial (747-301) submitted for the marketing application for OCA for treatment of PBC evaluated efficacy based on use of a non-validated endpoints (ALP and TB), the Applicant is required to perform a clinical trial to verify and describe the clinical benefit of OCA in patients with PBC. The design of this ongoing confirmatory trial is described below. The outline of this trial (747-302) is described below.

Phase 3b[35]- Protocol 747-302: A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cirrhosis

Objectives

Primary

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary cirrhosis (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

1. Death (all-cause)
2. Liver transplant
3. Model of end stage liver disease (MELD) score $\geq$ 15 (patients enrolled at $\leq$ 12)
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 $\geq$ 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 confirmed by 2 complimentary imaging modalities

Secondary

1. To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above and also to include liver-related death. To assess the effect of OCA compared to placebo on disease progression via the following:
    a. Liver biochemistry
    b. Markers of inflammation and fibrosis

[35] Note the Applicant called this a phase 3b Trial, but commonly the confirmatory trial is called a phase 4 trial

2. To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.
3. To assess the pharmacokinetics of OCA and its conjugates in a subset of subjects.
4. To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.
5. To assess the safety and tolerability in subjects treated with OCA compared to placebo.

Key inclusion criteria

1. **A mean ALP > 5×ULN and/or mean total bilirubin > ULN and ≤ 3×ULN**
2. Definite or probable diagnosis of PBC (2 of the 3 criteria: AMA positive, liver biopsy consistent with PBC, History of elevated ALP > 6 months)
3. Either is not taking UDCA (no UDCA dose in the past ≥ 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥ 3 months prior to Day 0 (Applicant mentions in protocol 95% patients will be on concomitant UDCA while only 5% patients will be on monotherapy).

Key Exclusion criteria

1. History or presence of other concomitant liver diseases (Definite autoimmune liver disease or overlap hepatitis, Hepatitis C virus infection, Active hepatitis B infection; Primary sclerosing cholangitis, Nonalcoholic steatohepatitis, Gilbert's Syndrome
2. 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. Subjects 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 mg/dL (178 µmol/L)
3. Mean total bilirubin > 3×ULN

Dosage and mode of administration

OCA (5 mg or 10 mg tablets) or placebo

Duration of Treatment
It is estimated that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue 121 total primary endpoint events.

Figure 24: Study Design

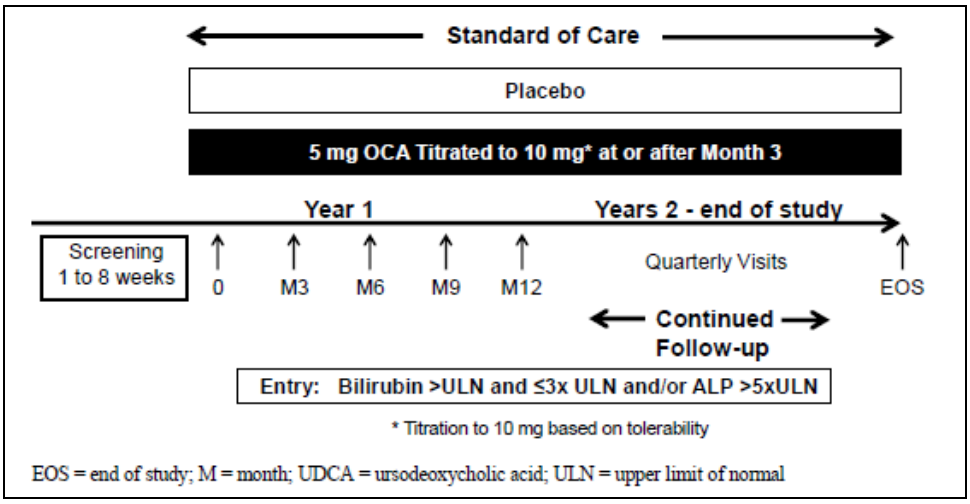


Figure source: Protocol 747-302, page 7 of 128

Discussion of the Potential use of a Non-Concurrent Control Group

During discussion with the Applicant about the confirmatory trial design, the FDA noted that the ability of the Applicant to retain patients in a placebo controlled trial after OCA was marketed was a significant concern. Therefore, the Applicant proposed that as a secondary study objective for supportive analysis purposes, utilize both historical control/observational groups from the UK-PBC and the Global PBC Study Groups. These historical control groups would, separately and in combination, be used as a comparator to the randomized OCA treatment group. The following paragraphs present the outline for the Applicant's proposal.

> Conducting a long-term outcomes study given the paucity of PBC patients, slow disease progression, ethical considerations, and availability of commercialized OCA will impact recruitment and event rates. In long-term trials there is an opportunity to check the assumptions that underlay the original design and sample size calculations, and any assumptions made for powering a study and/or calculating sample sizes can be re-assessed during the conduct of the study without unblinding. Therefore, starting approximately two years after the first patient is randomized, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner every three months. This evaluation will determine if any increases in the number of patients are required in order to obtain the requisite total of 121 adjudicated events (combined across both randomized treatment groups) for the final comparative analysis. Specifically, the pooled number of events will be available during the study in a blinded manner, without any knowledge of the comparative efficacy in the treatment

groups. This method for evaluating the sample size will not inflate the type I error rate, and additional patients may be enrolled as appropriate.

If after four years of accruing patients, despite increases in the number of enrolled patients through the aforementioned sample size re-estimation approach, it is determined that at least an additional two years (i.e., a total study duration of at least 10 years) are needed to randomize sufficient patients to achieve a total of 121 adjudicated events, all patients enrolled from that point forward will receive open-label OCA treatment. Previously randomized patients will continue to be treated in a blinded manner with either OCA or matching placebo. If this modification is implemented, an alternative primary efficacy analysis is pre-specified by the applicant for comparing time to liver transplant or death (all-cause) between all OCA treated patients (i.e., combining all randomized and open-label OCA patients) and all control patients (i.e., combining all randomized placebo, UK-PBC and Global PBC Study Group patients). In order to adequately match patients between these combined groups, and hence mitigate any bias when conducting this comparison, propensity scoring techniques will be utilized.

Note that if a non-concurrent control utilizing data from the UK-PBC and Global PBC Study groups is used as described above the sponsor will need to use a primary endpoint of transplant-free survival as this is the only clinical outcome data that are collected and common to all of these groups.

Additional Discussion

Diagnosis of PBC is based on anti-mitochondrial antibody (AMA) which is positive in 95% of the PBC patients, and therefore there is generally no need for obtaining liver histopathology. Given that there are limited historical data categorizing different PBC stages, the following biochemical classification of disease stage has been utilized instead in clinical practice (Kuipers et al.):

- Early stage disease: normal total Bilirubin, normal albumin, elevated ALP
- Moderately advanced stage disease: either elevated Total Bilirubin or low Albumin
- Advanced stage disease: low Albumin and elevated TB (both)

FDA Comments:
Following the review of the phase 3 trial 747-301, FDA identified the following areas that lack adequate information, which could be answered, however, by the post-marketing trial.

1. *Safety and Efficacy of OCA in patients with advanced liver disease. Since most patients enrolled in trial 747-301 were early stage disease, we are unable to assess whether OCA is safe in patients with moderately advanced disease (evidence of loss of hepatic synthetic function) and advanced stage disease (consistent with cirrhosis). FDA thinks that it will be important to gather information on safety and efficacy of OCA in patients with moderately advanced disease and advanced disease. The currently proposed*

enrollment criteria for the confirmatory trial is either TB > ULN and ≤ 3 × ULN AND/OR ALP > 5 × ULN. While this is a broader range of ALP and TB elevations than was used for the phase 3 trial, the AND/OR criteria for TB and ALP could allow the same early stage patients to be enrolled in this confirmatory trial as were enrolled in the phase 3 trial.

2. *OCA as Monotherapy*
   With the data generated from a phase 3 trial we have scant data on efficacy and safety of OCA as a monotherapy. The design of this confirmatory trial will not generate a significant amount of data on use of OCA as monotherapy, as per the Applicant's trial design, 95% of patients are expected to be on concomitant UDCA.

3. *Continuing Treatment in OCA Nonresponders*
   As the confirmatory trial is currently designed all patients even those who do not have a biochemical response to OCA will stay on OCA for the length of the trial. The Applicant has proposed that there is the potential for other pleiotropic effects based on in vitro data and nonclinical data from a different disease animal model. The potential utility of continuing treatment for patients who do not exhibit a biochemical response to OCA will not be answered with the current trial design.

12 CLINICAL PHARMACOLOGY SUMMARY

See the Clinical Pharmacology Summary in a separate PDF, with a separate Table of Contents.

II. Clinical Pharmacology Background Document

Office of Translational Sciences, Office of Clinical Pharmacology, Division of Clinical Pharmacology 3 and Division of Pharmacometrics

Background Package prepared March 15th, 2016

Clinical Pharmacology Background Package for Gastrointestinal Drugs Advisory Committee (GIDAC)

NDA	207999
Submission Date:	06/29/2015
Brand Name:	Ocaliva®
Generic Name:	Obeticholic acid
Formulation:	Oral tablet
Applicant's Proposed Dosing Regimen:	Starting dose of 5 mg once daily with option of up titration to 10 mg at 3 months based on response and tolerability
Indication:	Treatment of primary biliary cirrhosis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA
OCP Divisions:	Divisions of Pharmacometrics (DPM) and Clinical Pharmacology 3 (DCP3)
DCP3 Reviewers:	Elizabeth Shang, Ph.D. (Primary) Shen Li, Ph.D. (In vitro study review)
DPM Reviewer:	Dhananjay D. Marathe, Ph.D.
PBPK Reviewers:	Yuching Yang, PhD., Ping Zhao, Ph.D.
DCP3 Team Leader:	Sue-Chih Lee, Ph.D.
DPM Team Leader:	Nitin Mehrotra, Ph.D.
PBPK Lead:	Ping Zhao, Ph.D.

Table of Contents

1 EXECUTIVE SUMMARY

The current submission is the original NDA for obeticholic acid (OCA) for the following indication:

> Treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as a monotherapy in adults unable to tolerate UDCA.

OCA is a selective agonist for farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine. FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing synthesis, increasing transport of bile acids out of the hepatocytes, suppressing transport of bile acids into the hepatocytes, and decreasing bile acid re-absorption in enterocytes thus reducing hepatic exposure to bile acids.

Ursodeoxycholic acid (UDCA) is the only drug currently approved in USA to treat PBC.

The Applicant is proposing a starting dose of 5 mg QD (once daily), which should be increased after 3 months, if tolerated, to 10 mg QD to improve response. The to-be-marketed formulation is OCA tablets 5 mg and 10 mg.

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 trials evaluated OCA pharmacokinetics (PK) and short term safety, pharmacodynamics (PD), clinical drug-drug interactions (DDIs), QT prolongation potential (thorough QT study), absolute bioavailability, relative bioavailability, hepatic impairment, food-effect, and agent altering gastric pH on OCA PK. In addition, population PK, exposure-response for efficacy and safety, and physiological PK (PBPK) modeling and simulations were also performed.

The clinical trials conducted in patients with PBC consist of two Phase 2 and one pivotal Phase 3 trial. The Phase 2 trials evaluated 10, 25 and 50 mg QD dosing. The Phase 3 trial evaluated 10 mg QD and a titration arm (5 mg QD for 6 months followed by up-titration to 10 mg QD based on efficacy and tolerability). For efficacy, the Phase 3 trial demonstrated that both 10 mg arm and titration arm were superior to placebo in terms of patients who achieved a pre- defined composite primary endpoint that incorporated changes in ALP and bilirubin levels.

The key points evaluated during the review of this NDA are given below along with the OCP review team's current thinking and recommendations:

1.1 ALP and bilirubin assay findings

The assay methods used to measure ALP and bilirubin (the analytes used to assess response to therapy for the primary efficacy analysis 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. Given the geographic dispersion over several continents of patients enrolled in the international Phase 3 program the applicant elected to use three different labs instead of using one central lab. The labs are accredited by their respective national authorities. Of the three labs, the one that had the best precision and accuracy was used as a reference lab against which the other two labs were compared, and 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 harmonized (corrected) and uncorrected values is less critical. For ALP, the difference between harmonized and raw 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 harmonized in the Phase 3 trial dataset.

1.2 Appropriateness of the Applicant's proposed starting dose of 5 mg QD with titration to 10 mg QD at 3 months for overall population

Based on the dose dependent increase in incidences of pruritus (see **Section 3.3.2.1**) and better tolerability profile with time with a lower starting dose, the Applicant's proposal to start dosing at 5 mg QD (once daily) seems appropriate.

Although, patients in the Phase 3 trial were up-titrated to 10 mg at 6 months, the proposal to initiate up-titration at an earlier time (i.e. 3 months) is supported by data analysis that showed that reduction in ALP reaches a plateau at 3 months with 5 mg once daily dosing, and there was minimal further decrease in ALP from 3 months to 6 months and beyond (see **Figure 7**). Since prior to month 6, the clinical data was collected only at week 2 and at month 3, there is a possibility that the plateau of response of reduction in ALP could have been achieved earlier than 3 months, somewhere between 2 weeks to 3 months, which the current data is unable to capture. So from efficacy perspective alone, one could argue for up-titration at a time earlier than 3 months. But 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 over the three month period (see **Section 3.3.2.1**). Thus, a minimum duration of 3 months will give fair idea of tolerability of starting dose and identification of subjects with tolerability for further up-titration.

The increase in dose from 5 mg to 10 mg QD resulted in additional responders from month 6 to month 12 (see **Table 3**). Also there were 19% patients who were responders (as per the primary composite endpoint criteria) 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. Therefore, 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. (See **Section 3.4.1** for details)

1.3 Dose adjustment for patients with moderate or severe hepatic impairment

Given that the hepatic impairment (moderate and severe) resulted in several fold (4- to 17-fold) increase in plasma exposures of total OCA as compared to healthy volunteers in the dedicated study with a single 10 mg dose, the following dosing schema is proposed: Given the signal of dose-response for pruritus in PBC patients (see **Section 3.3.2.1**), we propose an alternative dosing regimen of 5 mg QW (once weekly) as a starting dose in subjects with moderate or severe hepatic impairment to target comparable initial plasma exposures to subjects with no or mild hepatic impairment. Since the half-life of OCA and its active conjugates is longer in moderate and severe hepatic impairment, a less frequent dosing in such patients is a reasonable option. 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. Please note that this recommendation is different from that made by the Applicant. 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 exposures were predicted to be similar (~2-fold) to healthy controls based on their physiologic pharmacokinetic model. The Applicant stated that dose adjustment in the moderate and severe hepatic impairment population may lead to lower liver exposures which might be suboptimal from efficacy perspective. (See **Section 3.4.2** for details)

1.4 Discontinuation of OCA for lack of biochemical response

Consideration should be given for discontinuation of OCA for the subjects who do not show a reduction in alkaline phosphatase. Currently there is not enough evidence to show how the long term efficacy of transplant-free survival and overall survival would transpire for subjects who do not show response of reduction in alkaline phosphatase with OCA. This uncertainty in long term efficacy should be weighed against the possible unfavorable lipid profile (decrease in HDL, see **Section 3.3.2.2**) and its relation to possible cardiovascular risk due to continued treatment with OCA. Based on the Phase 3 study, the physicians could potentially consider discontinuation of drug if there is a lack of clinically meaningful response (reduction in ALP) after the subject is on a stable dose of OCA for ≥6 months. Since there are different temporal patterns of ALP response in individuals after OCA treatment (see **Figure 12)**, a time point earlier than 6 months on a stable dose may be premature to evaluate and conclude lack of response for decision of treatment discontinuation. (See **Section 3.5** for details)

There is currently an ongoing Phase 3 extension trial with continued dosing of OCA for subjects 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 potential beneficial effects of OCA based on in vitro data and nonclinical data from different disease animal models in order to consider continuation of therapy in the absence of ALP response.

1.5 Evidence for supporting OCA monotherapy in adult subjects unable to tolerate UDCA

There is evidence to support OCA monotherapy for adult subjects 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 a responder rate of 38% for monotherapy at 3 months, which is comparable to that achieved with combination therapy with UDCA (see **Table 8**). There was marked reduction in ALP biomarker with monotherapy and this change was statistically significant ($p<0.0001$; post-hoc analysis on pooled data, see **Figure 14**). Based on this evidence, use of OCA as a monotherapy for subjects who are unable to tolerate UDCA seems reasonable. (See **Section 3.6** for details)

2 CLINICAL PHARMACOLOGY SUMMARY

2.1 Dosing Recommendations and Rationale

2.1.1 Starting Dosage

The recommended starting dosage of OCA is 5 mg orally once daily in adult patients who have failed to achieve an adequate reduction in alkaline phosphatase on a stable dose of UDCA for an adequate duration or who were intolerant to UDCA.

*Rationale: See **Section 3.4.1** for details of evidence to support the starting dose, and **Section 3.6** for details of monotherapy for subjects intolerant to UDCA.*

2.1.2 Dosage Titration

If an adequate reduction in alkaline phosphatase has not been achieved after 3 months of OCA 5 mg once daily, and the patient is tolerating the drug, increase the dose of OCA to 10 mg once daily.

For patients experiencing intolerability due to pruritus, consider one of the following:

- Reduce the dosage:
    - 5 mg every other day, for patients intolerant to 5 mg once daily
    - 5 mg once daily, for patients intolerant to 10 mg once daily
- Alternative dosing schedules, such as dosing every other day, every third day or every seventh day
- Interruption of dosing for up to 2 weeks followed by restarting at a reduced dose or on an alternative dosing schedule.
- Addition of an antihistamine or a bile acid sequestrants

For patients who continue to experience persistent or severe pruritus, consider discontinuing treatment with OCA.

*Rationale: The up-titration of dose at 3 months was proposed by the applicant even though the Phase 3 study evaluated up-titration of dose (from 5 mg to 10 mg once daily) at 6 months. See **Section 3.4.1** for details of evidence to support the titration schedule. Also various alternative dose titrations were employed by the Applicant during the conduct of their Phase 3 trial, including dose interruptions or dosing every day or every third day etc. to address the issue of tolerability. These dosing regimens as part of alternative titration strategy appear reasonable.*

2.1.3 Administration Instructions

Take OCA with or without food.

Take bile acid binding resins at least 4 hours before or 4 hours after (or at as great an interval as possible) OCA.

Rationale: Food effect study showed that plasma exposure of OCA and glyco-OCA (an active metabolite of OCA) were ~15% higher and tauro-OCA (another active metabolite of OCA) was ~5% lower in fed condition as compared to the fasting condition. These differences in exposure are not clinically meaningful and thus OCA can be administered without regard to meals.

Regarding bile acid binding resins (bile acid sequestrants; BAS), since the BAS can bind to and reduce the bioavailability of OCA, the Phase 3 study protocol specified that subjects taking a BAS should stagger their dosing of OCA (and UDCA) and BAS by at least 4 hours. With these dosing instructions, modestly lower trough concentrations of OCA were observed at Month 6 and Month 12 in subjects taking BAS. This was associated with a modest attenuation of efficacy for the 5 mg dose group but no meaningful effect for the 10 mg dose group. Thus, the same approach of staggered dosing of BAS is acceptable.

2.1.4 Use in Renal Impairment

No dose adjustment is needed when OCA is used in patients with serum creatinine clearance > 50 mL/min/1.73m^2. No data are available as to how severe impairment would impact the systemic exposure to OCA and its conjugates.

Rationale: Renal excretions of OCA and conjugates are low (<3% in the mass balance study). Population PK analysis did not identify renal function (eGFR) as a significant covariate for OCA clearance/ exposure for patients with renal impairment (eGFR ranged from 52 to 433 mL/min/1.73 m^2). However, patients with eGFR <50 mL/min/1.73 m^2 were not enrolled in the study.

2.1.5 Dosage Adjustment in Hepatic Impairment

No dose adjustment to the starting dose is needed in patients with mild hepatic impairment. However, we recommend that the starting dose of OCA for moderate and severe hepatic impairment (Child-Pugh B and C) should be 5 mg once weekly, rather than once daily. If an adequate reduction in alkaline phosphatase has not been achieved after 3 months of OCA 5 mg once weekly, and the patient is tolerating the drug, the OCA dose should be increased to 5 mg twice weekly and then subsequently to 10 mg twice weekly depending on response and tolerability.

Rationale: The alternative starting dose of 5 mg QW (once weekly) was arrived at based on plasma exposure matching in subjects with moderate or severe hepatic impairment to those with no or mild hepatic impairment using simulations with the physiologic PK model. See ***Section 3.4.2*** *for details of dose adjustment rationale.*

2.2 Pharmacokinetics

Like bile acids, OCA and its major active metabolite conjugates (glyco-OCA and tauro-OCA) also undergo extensive enterohepatic recirculation. Therefore, the PK profiles exhibit multiple peaks within a day following once daily dosing as meals will 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 (EC_{50} of 24 nM, 84 nM and 45 nM for glyco-OCA, tauro-OCA and OCA respectively). For the OCA conjugates, the systemic concentration is adjusted for the molecular weight difference to obtain the OCA-equivalent concentrations, i.e.,

Glyco-OCA (adjusted) = unadjusted glyco-OCA concentration (ng/mL) × 0.8805

Tauro-OCA (adjusted) = unadjusted tauro-OCA concentration (ng/mL) × 0.7969

2.2.1 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.

2.2.2 Distribution

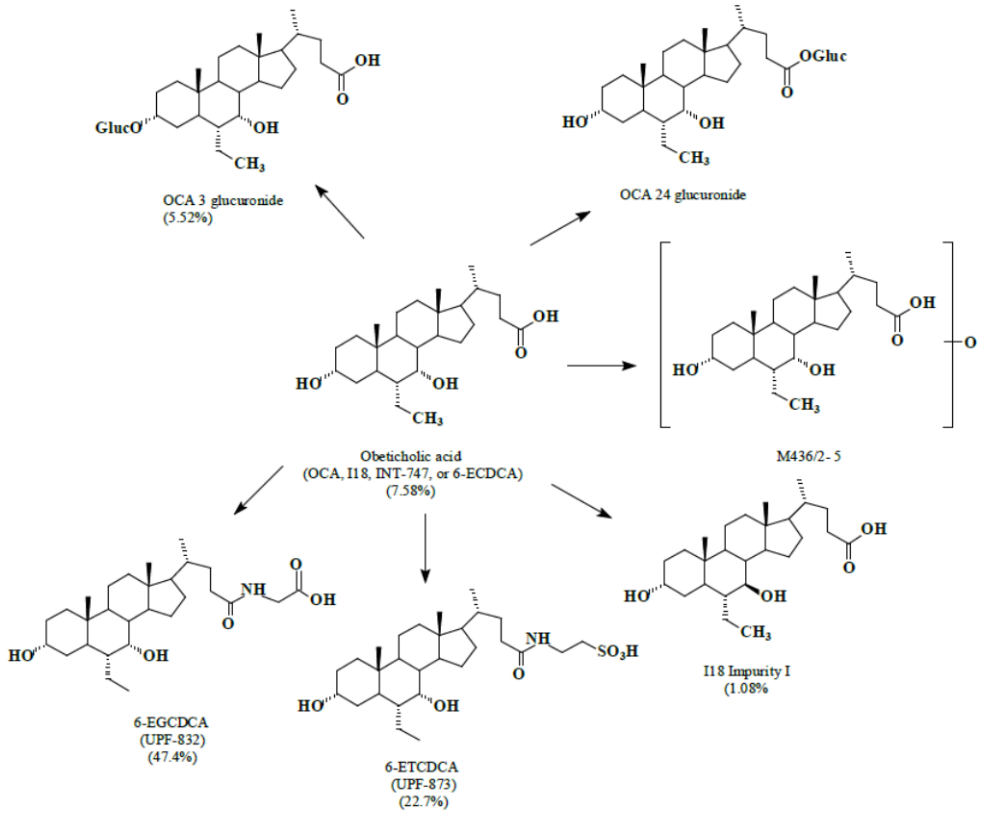
OCA and its conjugates are highly bound to human plasma proteins (> 99.0%). After intravenous (IV) administration of 0.1 mg OCA, the volume of distribution of OCA was 618 L. Liver concentration is predicted to be much higher (~20-fold) than the plasma concentration in healthy subjects based upon a PBPK model.

2.2.3 Metabolism and Elimination

OCA is not metabolized by CYP enzymes. Major active metabolites, glyco-OCA and tauro-OCA, are present in the plasma at much higher concentrations (AUCtau ~14- and ~12-fold, respectively) compared to the parent drug, following 10 mg QD dosing.

The proposed human metabolic pathways are shown in **Figure 1**.

Figure 1: Applicant's proposed metabolic pathway of OCA in human plasma



Gluc = glucuronic acid,

The mean %AUC_{0-t} values were present in the figure.

Following an oral administration of 25 mg [^{14}C]-OCA, about 87% of the dose is excreted in feces through biliary secretion. Less than 3% of the dose is excreted in the urine with no detection of OCA.

The effective half-life of OCA is about 24 hours.

2.2.4 Specific Populations

Gender, age, and race had no impact on the pharmacokinetics of OCA based on the pop-PK analysis. Population PK analysis dataset consisted of 301 female and 505 male subjects, age ranging from 18 to 71 years and had 10 Asian, 233 Black, 554 White and 9 Other subjects.

Body weight was a significant predictor of OCA pharmacokinetics, with lower OCA exposure expected with higher body weight. The body weight effect is not expected to cause a meaningful impact on efficacy as concentrations of total OCA are predicted to be above the estimated IC_{50} for efficacy (reduction in ALP) after daily administration of OCA at 5 mg and 10 mg doses. Also in the Phase 3 study, there was no trend of up-titration occurring preferably in higher body weight subjects (associated with lower concentration) over lower body weight subjects with titrations based on response and tolerability. Thus, the impact of body weight is not clinically meaningful to suggest dose recommendation based on body weight.

2.2.5 Drug-Drug Interactions

2.2.5.1 Effect of other drugs on the pharmacokinetics of OCA

Effect of CYP inhibitors: Because OCA is not a substrate for CYP enzymes, CYP enzyme inhibition/induction by other drugs is not expected to affect the PK of OCA.

Effect of transporter inhibitors: OCA, glyco-OCA, and tauro-OCA are weak substrates for P-gp. Coadministration with drugs that are P-gp inhibitors is not expected to have a significant effect on the PK of OCA or its conjugates.

Effect of gastric acid reducing agents: The solubility of OCA is pH-dependent. Administration of 10 mg OCA with omeprazole 20 mg QD for 4 days resulted in 19% increase in steady-state Cmax and AUC of OCA. Similar increase was also observed with glyco-OCA and tauro-OCA. No dosage adjustment for OCA is needed when it is coadministered with omeprazole 20 mg QD. The Applicant did not study the effect of omeprazole 40 mg on the systemic exposure to OCA and its metabolites.

Effect of resin binding agents: Bile acid sequestrants, colesevelam and cholestyramine, bind to OCA, glyco-OCA, and tauro-OCA. In Phase 3 trials, bile acid sequestrants were given at least 4 hours before or 4 hours after OCA administration to minimize the interaction.

2.2.5.2 Effect of OCA on other drugs

CYP inhibition by OCA

In vitro studies indicated that clinical relevant inhibition of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 by OCA, glyco-OCA, or tauro-OCA at the systemic level is not anticipated. However, a potential in-vivo drug interaction via inhibition of CYP3A4 in the gut cannot be ruled out.

Effect on PK of midazolam, a CYP3A4 substrate: Multiple doses of OCA 10 mg QD resulted in changes in systemic exposures to midazolam, however, multiple doses of OCA 25 mg QD resulted in increase of AUC (26%) and Cmax (17%) of midazolam. Dose adjustment of CYP3A substrates is not needed when co-administering OCA 10 mg with a CYP3A substrate.

Effect on PK and PD of warfarin, a CYP2C9 substrate: Based on in vitro studies, OCA is not expected to affect the PK of drugs that are CYP2C9 substrates. In an in vivo drug interaction study, co-administration of warfarin with multiple doses of OCA 10 mg and 25 mg QD resulted in 13% and 18% increase in systemic exposure to S-warfarin, respectively. However, as the maximum INR decreased by 11%, monitoring INR and adjusting dose of warfarin accordingly is recommended when warfarin is co-administered with OCA 10 mg QD.

Effect on omeprazole, a CYP2C19 substrate*:* Following multiple doses of OCA 10 mg QD, AUC and Cmax of omeprazole increased by 33%. Systemic exposure to hydroxyl-omeprazole is also increased. Similar effect was found at OCA 25 mg QD. The mechanism for this increase is unknown. Dose adjustment of CYP2C19 substrate is not needed when co-administering OCA 10 mg with a CYP2C19 substrate.

CYP induction by OCA

In vitro studies showed that there is low potential for induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 enzymes by OCA, glyco-OCA, or tauro-OCA at therapeutic concentrations of OCA.

Effect on dextromethorphan, a CYP2D6 substrate: In general, CYP2D6 is believed to be not inducible. Nonetheless, the Applicant conducted a study to look into the potential for CYP2D6 induction by OCA. Following multiple doses of OCA 10 mg and 25 mg QD, no significant effect on systemic exposure to dextromethorphan or dextrorphan was found.

CYP down regulation

In *in vitro* studies, down-regulation of CYP1A2 mRNA by OCA, glyco-OCA, and tauro-OCA was observed in a concentration-dependent manner.

Effect on the PK of caffeine, a CYP1A2 substrate: Following multiple doses of OCA 10 mg QD, AUC_{inf} and Cmax of caffeine increased by 42% and 6%, respectively. Further increase in systemic exposure to caffeine was noted when it was administered following OCA 25 mg QD. The interaction is likely to be due to CYP1A2 down regulation by OCA. Therefore, therapeutic monitoring and dose adjustment of CYP1A2 substrates that have a narrow therapeutic range is needed when they are co-administered with OCA.

Transporter inhibition

In vitro studies showed that there is potential for OCA and its conjugates to inhibit OATP1B1 and OATP1B3, but not other transporters such as P-gp.

Effect on PK of digoxin, a P-gp substrate: As expected, no significant effect on systemic exposure to digoxin was observed following multiple doses of OCA 10 mg and 25 mg QD. Renal clearance of digoxin remained the same.

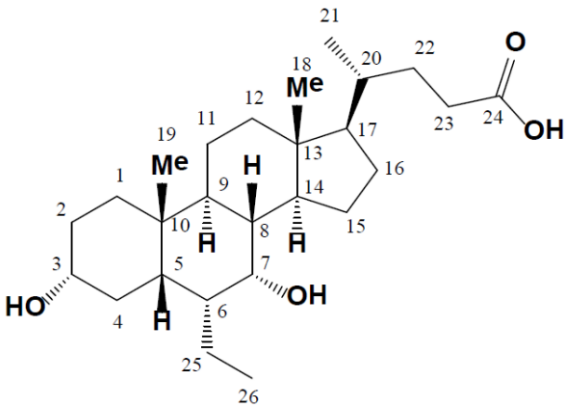
Effect on PK of rosuvastatin, a substrate for OATP1B1, OATP1B3 and BCRP: Following multiple doses of OCA 10 mg QD, AUC_{inf} and Cmax of RSV increased by 22% and 27%, respectively. while changes in AUC_{inf} and Cmax of the metabolite N-desmethyl-RSV was negligible. Similar findings were observed at OCA 25 mg QD. Although in vitro study and the known effect of FXR activation point to potential increase in systemic exposure to OATP substrates, only a small increase in exposure to rosuvastatin was observed.

3 RELEVANT DETAILS OF CLINICAL PHARMACOLOGY

3.1 Highlights of physico-chemical properties of drug substance / drug product

1. Structural formula: $C_{26}H_{44}O_4$.

Figure 2: Chemical Structure of Obeticholic Acid



2. Established name: Obeticholic acid
3. Other names: 6α-ethyl chenodeoxycholic acid (6-ECDCA); INT-747; or DSP-1747
4. Molecular Weight: 420.63 g/mol

Obeticholic acid is a Biopharmaceutics Classification System (BCS) Class II drug.

3.2 Design features of the clinical studies used to support dosing claims

The clinical development program for OCA consists of seventeen clinical pharmacology Phase 1 studies; two double-blind, placebo-controlled, 3-month Phase 2 studies; one double-blind, placebo-controlled Phase 3 study; and the open-label, long-term safety extension phases for the Phase 2 and Phase 3 studies. There were additional two Phase 2 studies, one for the treatment of portal hypertension and another to investigate the effect of OCA on lipoprotein metabolism in subjects with PBC. The relevant clinical studies supporting the main dosing claims in the NDA are listed in **Table 1**.

Population PK analysis was performed using the PK data for OCA, glyco-OCA and tauro-OCA from sixteen Phase 1 and Phase 2 studies. Exposure-response analyses were carried out with the data from Phase 3 study 747-301 with observed trough concentrations as exposure metric.

PBPK analysis was performed based upon PK data from five Phase 1 and Phase 2 studies. Review of PBPK analysis can be found in Appendix.

Table 1: Summary of relevant clinical studies

Study Type	Study No.	OCA Dosing Regimen and Duration	No. of Subjects in Study
Studies in PBC Patients			
Phase 2 randomized, double-blind, placebo-controlled study	747-201	Monotherapy study for 3 months 10 and 50 mg QD multiple doses (Day 1-85)	59
	747-202	Study with concomitant UDCA for 3 months 10, 25 and 50 mg QD multiple doses (Day 1-85)	165
Phase 3 randomized, double-blind, placebo-controlled efficacy/safety study	747-301	10 mg QD for 12 months or 5 mg QD for 6 months followed by titration to 10 mg QD for next 6 months based on efficacy/tolerability	217

Source Data: Section 2.7.6, Table 1

3.3 Exposure-Response (E-R)

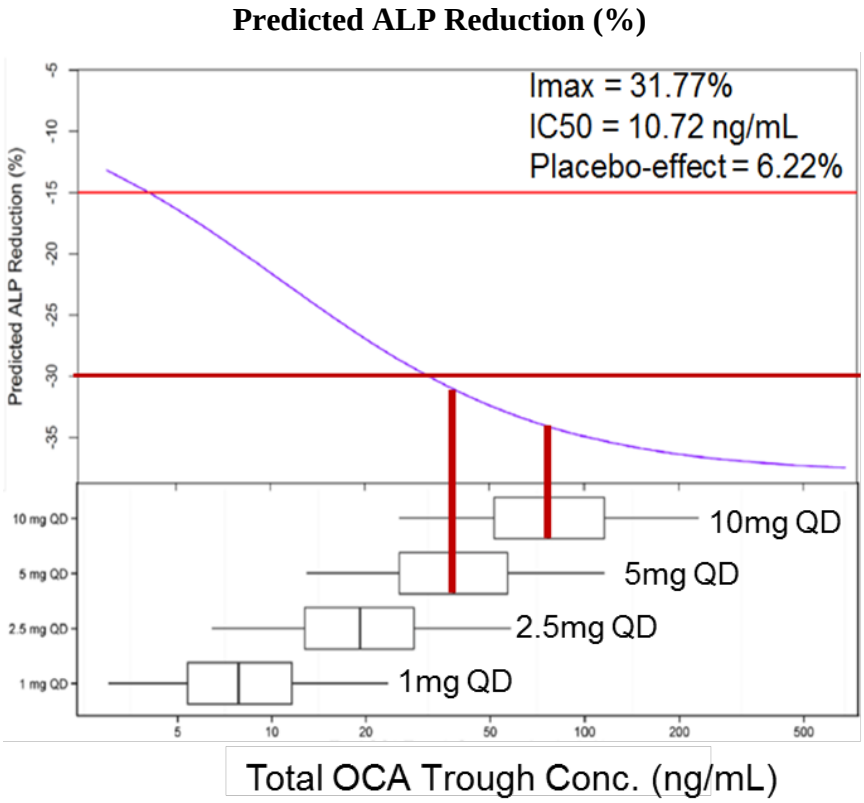
3.3.1 E-R relationships (dose-/concentration-response) for efficacy

3.3.1.1 Clinical Marker/Endpoint

The Applicant evaluated the exposure-response (E-R) relationship of reduction in ALP in PBC subjects with total OCA concentration as the exposure metric, using data at 6 months for treatment regimens of 5 mg and 10 mg QD OCA in study 747-301 (**Figure 3**).

For percent change from baseline in ALP, a maximum inhibition model (I_{max} model) was fitted. I_{max} and IC_{50} values for the model were 31.8% and 10.7 ng/mL, respectively (**Figure 3**). Placebo effect showed a decrease in ALP of 6.2%. These results indicate that a 5 mg and 10 mg dose of OCA, with average concentrations >40 ng/mL, is predicted to cause at least on average a 30% decrease in ALP and there is plateauing of reduction in ALP with higher concentrations. Also doses greater than 10 mg are not predicted to result in additional meaningful benefit in ALP reduction, which was consistent with the Phase 2 data (747-201 and 747-202).

Figure 3: E-R relationship of reduction in ALP with total OCA concentrations



Boxplots in the above figure represent the predicted trough exposure levels of total OCA based on the final population PK model.

Symbols represent composite endpoint predicted based on prediction of ALP and bilirubin.

Blue line represents simple I_{max} fit.

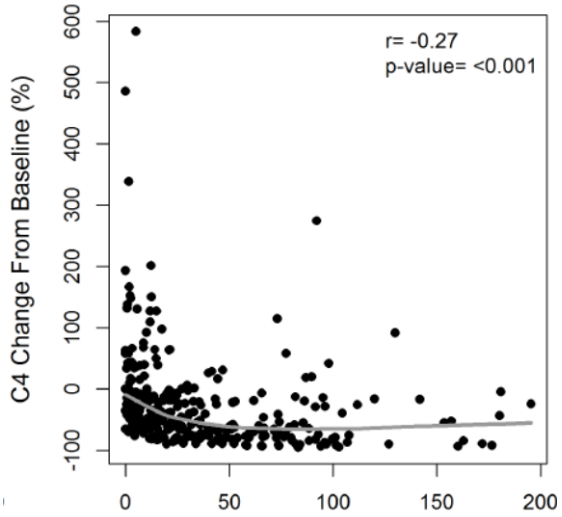
For predicted ALP reduction: IC_{50}=10.72 ng/mL, I_0 (placebo effect) = -6.22%, I_{max} = 31.77%.

Source Data: Applicant's Population PK/PD and Simulation Report, Adapted from Figures 10.1

3.3.1.2 Biomarker

The Applicant evaluated the exposure-response (E-R) relationship of 7α-hydroxy-4-cholesten-3-one (C4), a bile acid precursor and a marker of FXR activation, in healthy subjects with data from Study 747-105 (**Figure 4**). C4 levels are the marker of bile acid synthesis. Average values of C4 over the assessment period were used in the analysis. The analysis showed that C4 levels decreased with increasing total OCA exposure, indicating the exposure dependent reduction in bile acid synthesis. Reduction in C4 seems to plateau at total OCA concentrations ~50 ng/ml.

Figure 4: E-R relationship of change in C4 from baseline with total OCA concentrations (C_{avg}) in healthy subjects



Source Data: Applicant's Population PK/PD and Simulation Report, Figure 9.1

3.3.2 E-R relationships (dose-/concentration-response) for safety

3.3.2.1 Safety Events

Pruritus was the most common adverse event with OCA treatment and there were multiple instances of discontinuations from the study that were attributed to pruritus in the Phase 2/3 studies. During the conduct of clinical studies, the PK samples were collected at longer times, e.g. at the end of 6 months and 12 months in Phase 3 study, while the discontinuations happened at earlier times. Thus E-R for pruritus and discontinuations would be biased because of drop-out of these patients prior to their visit for PK sampling. Hence, evaluation of E-R relationship for pruritus and discontinuations was not carried out. Instead the evaluation of dose-response was done to infer about these safety signals. Evidence from various Phase 2 studies showed a clear dose-response relationship for pruritus as well as discontinuations due to pruritus with more events at higher doses (**Table 2**).

Table 2: Dose-response relationship for pruritus and discontinuations due to pruritus in Phase 2 studies

Population/AE	Placebo	OCA 10 mg	OCA 25 mg	OCA 50 mg
Alcoholic cirrhotic portal hypertension (Study 204: OCA dosed for ~7 days)				
All grade pruritus		**10%** (2/20)	**31%** (4/13)	
PBC subjects (Study 202: Phase 2, + UDCA, OCA dosed for 3 months)				
Related TEAE pruritus	**45%**	**47%**	**81%**	**80%**
Discont. due to pruritus	**0%** (0/38)	**8%** (3/38)	**8%** (4/48)	**24%** (10/41)
PBC subjects (Study 201: Phase 2, no UDCA, OCA dosed for 3 months)				
Related TEAE pruritus	**26%**	**70%**		**88%**
Discont. due to pruritus	**0%** (0/23)	**15%** (3/20)		**38%** (6/16)

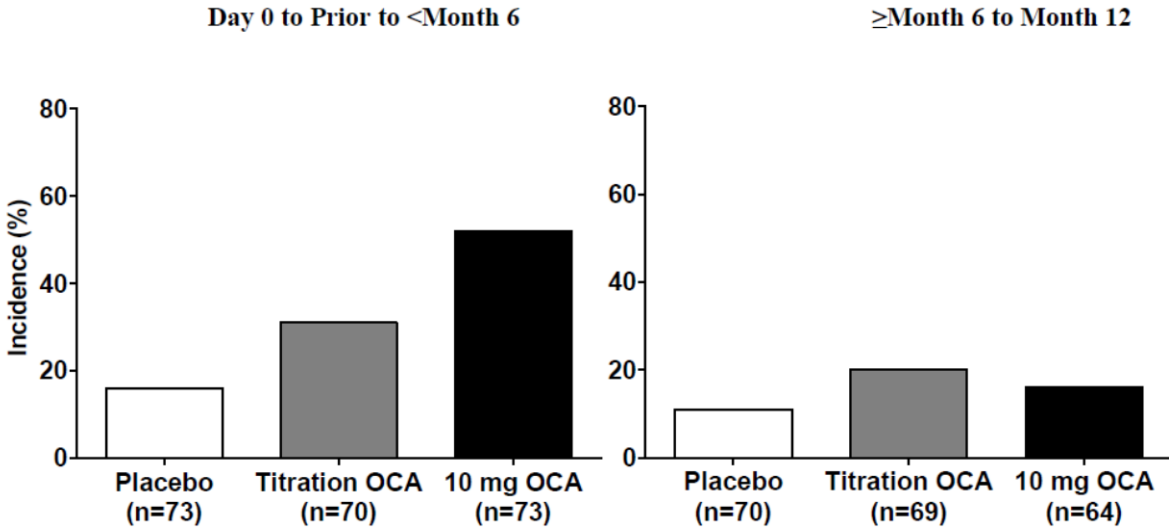
TEAE= Treatment Emergent Adverse Events
Discont.=Discontinued

Phase 3 study also showed a dose-response relationship for treatment emergent adverse events leading to discontinuations, 3% (2/73) in placebo, 7% (5/70) in OCA titration arm (5 mg QD starting dose with up-titration to 10 mg QD based on efficacy/tolerability) and 11% (8/73) in OCA 10 mg arm. There was a dose-response relationship for pruritus related discontinuations too, with 0% in placebo, 1% (1/70) in OCA titration arm and 10% (7/73) events in the OCA 10 mg arm. The median time to first onset of severe pruritus in OCA 10 mg arm was 11 days (< 2 weeks) and the range for the time of discontinuations due to pruritus was 6 to 86 days (< 3 months).

The incidence of new or worsened pruritus was lower in the 6-12 month study period compared to the 0-6 month study period across all treatment arms: 16% versus 11% in the placebo arm, 31% versus 20% in the titration arm, and 52% versus 16% in the 10 mg arm respectively (**Figure 5**). Thus, based on the incidence of new or worsened pruritus, pruritus improved with continued treatment.

However, there is an important caveat that treatment emergent AEs of pruritus that occurred during the 0-6 month period and were ongoing during the 6-12 month period were not counted as new events during the latter period. Thus there could be a certain bias introduced in incidences for the 6-12 month period. Nevertheless, at the very least, the incidences of number of events did not increase in the second 6 month period compared to the first 6 month period, which indicates that the hazard of pruritus events was constant or diminishing with time.

Figure 5: Incidence of new onset or worsened treatment-emergent pruritus events during 0-6 months and during 6-12 months in Phase 3 study

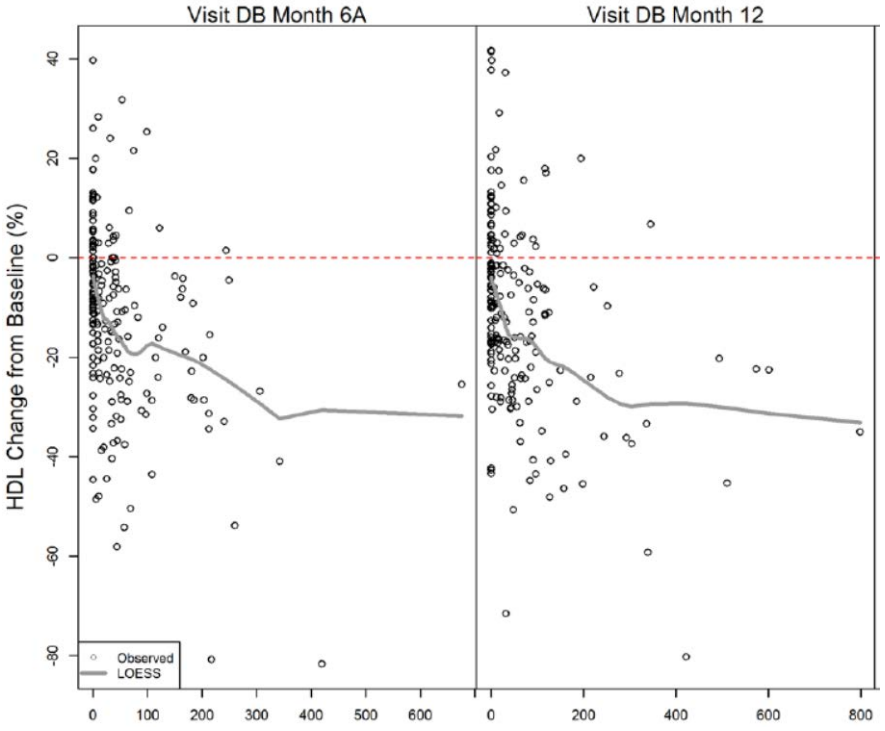


Source Data: CSR 747-301, Figure 39

3.3.2.2 Biomarkers

A relationship of response of change in HDL with observed trough concentrations of total OCA was assessed with data from Phase 3 study 747-301. Higher total OCA concentrations were associated with more reduction in HDL from baseline. The concentration dependent reduction in HDL was observed for the entire concentration range (**Figure 6**).

Figure 6: Relationship of change in HDL from baseline with total OCA concentration



Source Data: Applicant's Population PK/PD and Simulation Report, Figure 9.5

3.4 Appropriateness of dose and dosing regimen proposed by the Applicant

The Applicant's proposed dosing regimen of 5 mg QD starting dose, followed by up-titration to 10 mg QD at 3 months based on response and tolerability for the overall population is acceptable. However, for subjects with moderate and severe hepatic impairment, the Applicant proposal of no adjustment in dosing regimen is unacceptable. We recommend a dosing regimen of 5 mg QW (once weekly) as the starting dose, followed by subsequent dose up-titrations at 3 months to 5 mg twice weekly and further to 10 mg twice weekly based on efficacy and tolerability in this subpopulation.

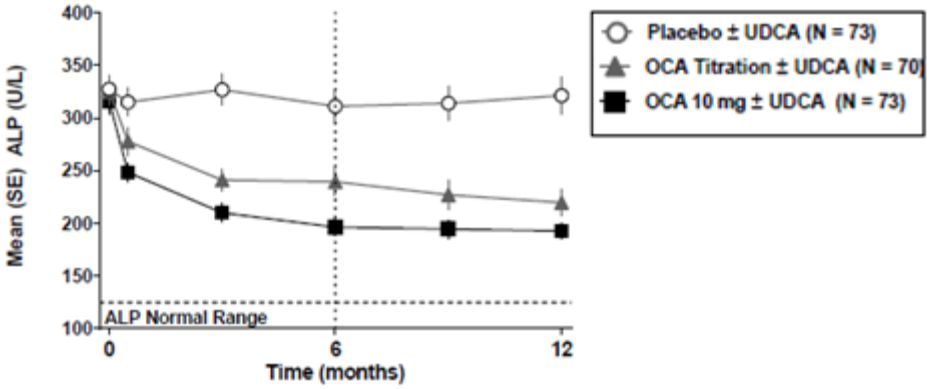
3.4.1 General Population: PBC patients without moderate or severe hepatic impairment

Based on the dose dependent increase in incidences of pruritus (see **Section 3.3.2.1**) and better tolerability profile with time with a lower starting dose, 5 mg QD (once daily) is a more appropriate starting dose over 10 mg QD dosing for the general population. This is consistent with Applicant's proposal and is acceptable to the OCP review team.

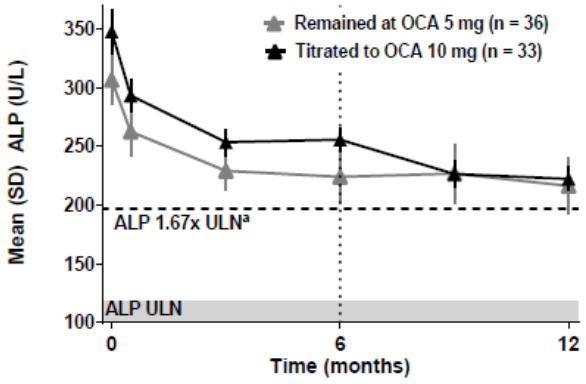
Although, patients in the Phase 3 trial were up-titrated to 10 mg at 6 months, the proposal to initiate up-titration at an earlier time (i.e. 3 months) is supported by data analysis that showed that reduction in ALP reaches a plateau at 3 months with 5 mg once daily dosing, and there was minimal further decrease in ALP from 3 months to 6 months and beyond at a mean level (**Figure 7**). Since prior to months 6, the clinical data was collected only at week 2 and at month 3, there is a possibility that the plateau of response of reduction in ALP could have been achieved earlier than 3 months, somewhere between 2 weeks to 3 months, which the current data is unable to capture. So from efficacy perspective alone, one could argue for up-titration at a time earlier than 3 months. But 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 over the three month period (see **Section 3.3.2.1**). Thus, a minimum duration of 3 months will give fair idea of tolerability of starting dose and identification of subjects with tolerability for further up-titration.

Figure 7: Time profiles of mean ALP in the ITT population for Phase 3 trial 747-301 across the three randomized arms (panel A) and ALP levels and change in ALP within the titration arm for subjects remaining at 5 mg QD vs. those titrated to 10 mg QD OCA at month 6 (panel B and C). Panel A shows that OCA treatment resulted in improvement in ALP levels as early as 2 weeks and resulted in statistically significant improvement versus placebo ($p \leq 0.0001$) in ALP levels at month 6 and 12. Panel B shows that for subjects in OCA titration arm, who were up-titrated to 10 mg QD, there was further decrease in ALP levels from month 6 to month 12, with mean ALP at baseline, month 6 and month 12 being 348 U/L, 256 U/L and 222 U/L respectively.

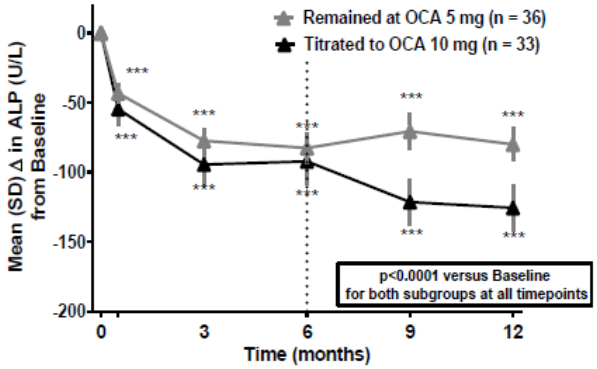
A. ALP levels across three arms



B. ALP levels in titration arm



C. Change in ALP in titration arm



Source Data: Section 2.5, Figure 11 and CSR 747-301, Figure 24

The increase in dose from 5 mg to 10 mg QD resulted in additional responders from month 6 to month 12 (**Table 3**). Also there were 19% patients (out of patients on 5 mg QD dosing for 1 year) who were responders (as per the primary composite endpoint criteria) 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. Therefore, 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.

Table 3: Categorization of subjects as responders (+) / non-responders (-) based on criteria of achievement of primary composite endpoint at 6 months and at 12 months for different treatment arms in Phase 3 study

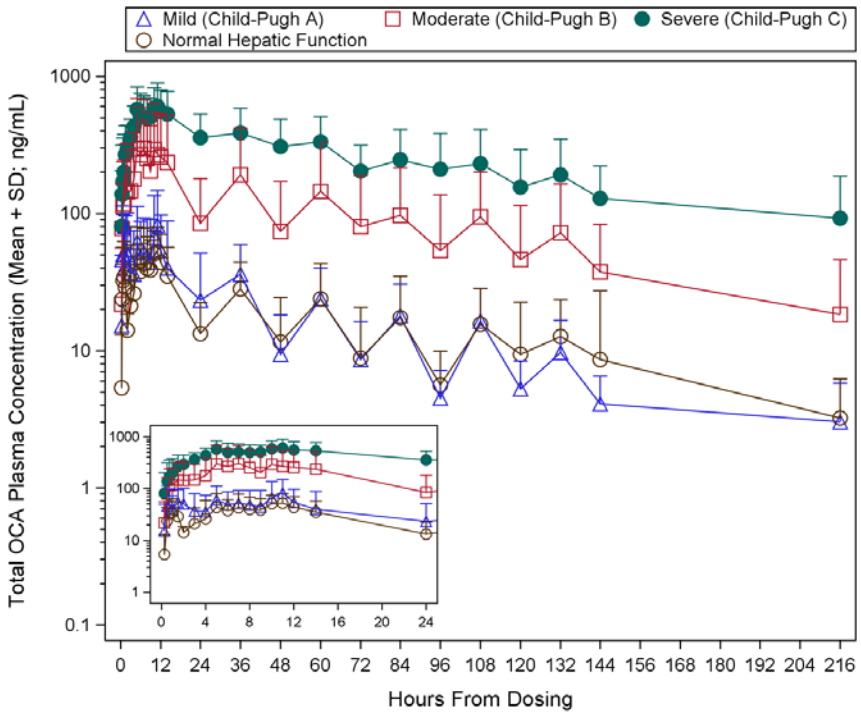
Treatment	Primary Endpoint at 6M / 12M			
	- / -	- / +	+ / -	+ / +
Placebo (N=73)	66 (90.4%)	2 (2.7%)	0 (0%)	5 (6.9%)
5 mg (N=37)	11 (29.7%)	2 (5.4%)	7 (18.9%)	17 (45.9%)
5 mg→10 mg (N=33)	20 (60.6%)	13 (39.4%)	0 (0%)	0 (0%)
10 mg (N=73)	32 (43.8%)	4 (5.5%)	7 (9.6%)	30 (41.1%)

3.4.2 Specific Population: Patients with moderate or severe hepatic impairment

In the dedicated hepatic impairment study (747-103) with a single dose of 10 mg, the systemic exposure ($AUC_{0\text{-}9\ days}$) to total OCA was 1.1-, 4.2-, and 17.3-fold in subjects with mild, moderate and severe hepatic impairment, respectively, when compared to normal healthy volunteers. The mean total OCA concentration-time profiles in this study are shown in

Figure 8 and the mean PK parameters (Cmax and AUCt) for total OCA in plasma for normal healthy volunteers and subjects with various categories of hepatic impairment are quantified in **Table 4**.

Figure 8: Mean plasma concentration-time profile (Semi-log) of total OCA following a single oral dose of 10 mg OCA (inset shows expanded view of first 24 hours)



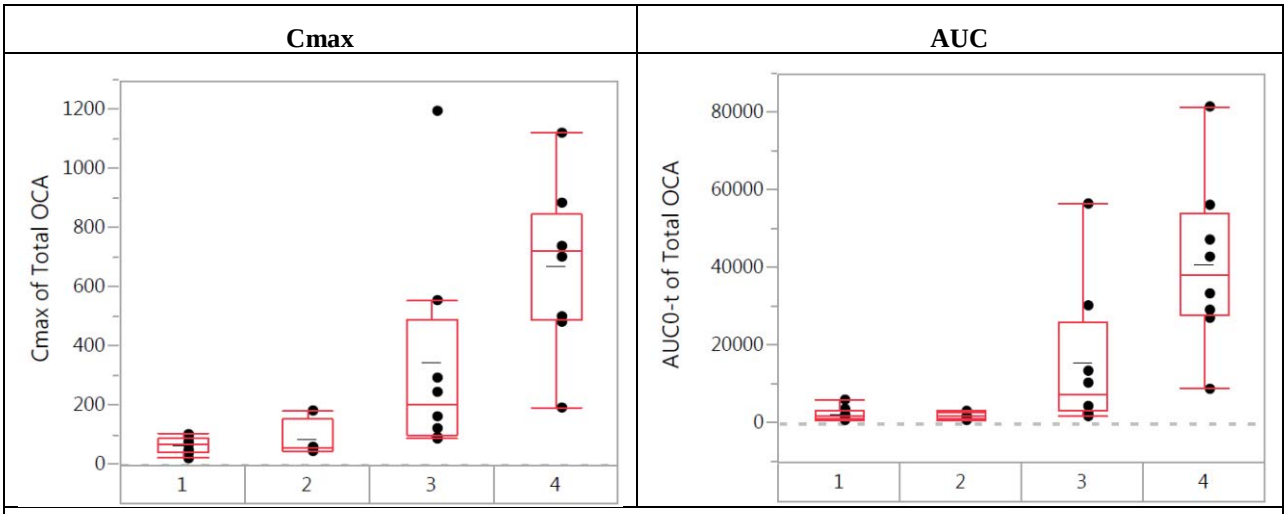
Source Data: Adapted from data for Figure 8 in Section 2.7.2

Table 4: Mean (SD) PK parameters of plasma total OCA

Parameters	Normal Hepatic Function (N=8)	Mild (N=8)	Moderate (N=8)	Severe (N=8)
Cmax (ng/mL)	68.3 (27.6)	107 (65.1)	348 (377)	674 (281)
AUC0-t (hr*ng/mL)	2480 (1810)	2770 (2060)	15700 (19100)	41000 (21900)

The distribution of individual Cmax and AUC0-t of total OCA is shown in **Figure 9**. The summary statistics of ratios of systemic exposure (Cmax and AUCt) of OCA and its conjugates in hepatic impairment categories to that in normal healthy volunteers are shown in **Table 5**. There was no apparent association of change of unbound free fraction percentage (%Fu) of OCA and tauro-OCA with the increased degree of hepatic impairment. Mean %Fu of glyco-OCA increased in patients with severe hepatic impairment.

Figure 9: Individual Cmax and AUC of total OCA in patients with mild, moderate and severe hepatic impairment vs normal subjects.



1=normal; 2=mild; 3=moderate; 4=severe

Black line = mean; black dot = individual values

Box plot shows 25% quantile, median, and 75% quantile with whiskers extending to the upper and lower data point values excluding outliers.

Source Data: Reviewer's analysis

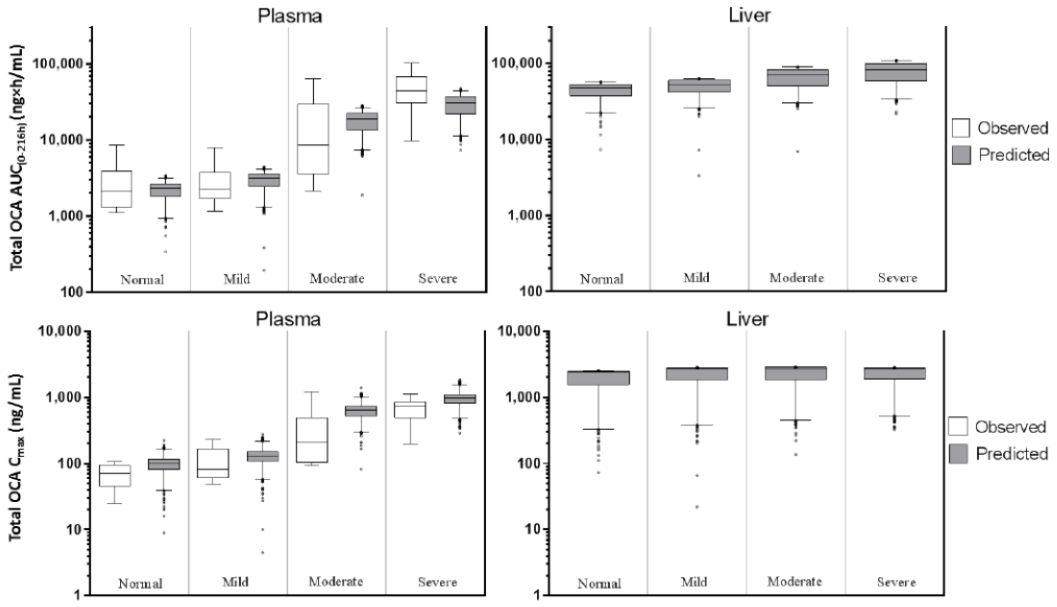
Table 5: Statistical comparison of AUC0-t and Cmax of OCA and its conjugates in hepatic impairment (747-103)

		OCA		**Glyco-OCA**		**Tauro-OCA**		**Total OCA**	
Comparison	Param-eters	GMR*	90% CI	GMR	90% CI	GMR	90% CI	GMR	90% CI
Mild vs Normal	AUC	1.38	72.8 - 261	1.27	64.7 - 250	7.09	29.6 – 170	1.13	56.5 – 225
	Cmax	1.35	79.8 - 228	1.43	79.5 - 256	8.72	40.4 – 188	1.49	86.3 – 256
Moderate vs Normal	AUC	2.41	127 - 456	3.33	169 – 654	6.86	286 – 1640	4.20	211 – 838
	Cmax	1.91	113 - 323	3.73	208 - 670	5.63	261 – 1220	3.76	218 – 647
Severe vs Normal	AUC	7.03	372 - 1330	11.40	579 - 2240	36.80	1540 – 8830	17.30	867 – 3440
	Cmax	4.70	278 - 796	8.12	452 - 1460	21.40	991 - 4630	9.75	566 - 1680

*GMR= Geometric mean ratio

To further evaluate the relevance and impact of such differences in plasma concentrations, the Applicant developed a physiologic PK model to quantify the fold changes in liver concentrations of OCA and its conjugates under hepatic impairment scenario. The details of the physiologic PK model can be found in the PBPK model review in Appendix. Per the model, the Applicant states that even though the plasma exposure is several fold high, the liver exposure in severe hepatic impairment is predicted to be similar (~2-fold) to healthy controls and thus dose adjustment is not needed in this subpopulation (**Figure 10**). The Applicant stated that dose adjustment in the moderate and severe hepatic impairment population may lead to lower liver exposures which might be suboptimal from efficacy perspective.

Figure 10: Observed (systemic) and PBPK model predicted (systemic and liver) AUC and Cmax of systemic and liver concentration of total OCA by liver function in subjects from Study 747-103



Observed data values are based on n =8 subjects by group of hepatic impairment; Predicted data values are based on 200 iterations Monte-Carlo simulations in 8 subjects by group of hepatic impairment; Boxplot whiskers represent 1st and 99th percentile.

AUC = area under the curve; C_{max} = maximum concentration; HEPIMP = hepatic impairment; n = number of subjects; OCA = obeticholic acid

Source Data: Applicant's Physiologic PK model report, Figure 4-2

Overall, the Applicant's model fits show that even though there is some over-prediction of plasma concentration in moderate hepatic impairment, the plasma concentrations in severe hepatic impairment are well captured and reproduced by the model. Thus the model can be reasonably useful for simulating various dosing scenarios to predict the plasma concentrations and possibly liver concentrations (with certain caveats as described in PBPK model review in Appendix A) under various degrees of hepatic impairment. Thus, the model was used to carry out simulations with different dosing regimen for normal subjects and subjects with hepatic impairment. **Table 6** shows the model predicted steady state C_{avg} values for plasma and liver concentrations in subjects with normal hepatic function (with 5 mg QD dosing) and subjects with mild/moderate/severe hepatic impairment (with 5 mg QD and 5 mg QW dosing). Various other dosing regimens were also simulated and the plasma and liver exposure predictions for these are documented in **Table 5** of Appendix A (**Section 4.3** of PBPK review, Appendix A).

Without any dose adjustment for hepatic impairment as proposed by the Applicant, the dosing regimen of 5 mg QD 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 (**Table 6**).

Table 6: Predicted steady state Cavg values for plasma and liver concentrations of total OCA in subjects with different categories of hepatic impairment under different dosing regimen

Exposure Parameter	Hepatic Function	Dose & Dosing Interval	
		5 mg QD	5 mg QW
Plasma $C_{ss, avg}$ (ng/mL) Median [5th-95th]	Normal	**63.3** [57-64]	
	Mild HI	**85.9** [77-87]	
	Mod. HI	602 [511-608]	**85.9** [74-87]
	Severe HI	1090 [899-1100]	**156** [130-157]
Liver $C_{ss, avg}$ (ng/mL) Median [5th-95th]	Normal	**1260** [1140-1270]	
	Mild HI	**1410** [1300-1430]	
	Mod. HI	2180 [1890-2210]	312 [274-315]
	Severe HI	2840 [2390-2870]	407 [346-410]

Source Data: Adapted from Applicant's response to Clinical Pharmacology information request

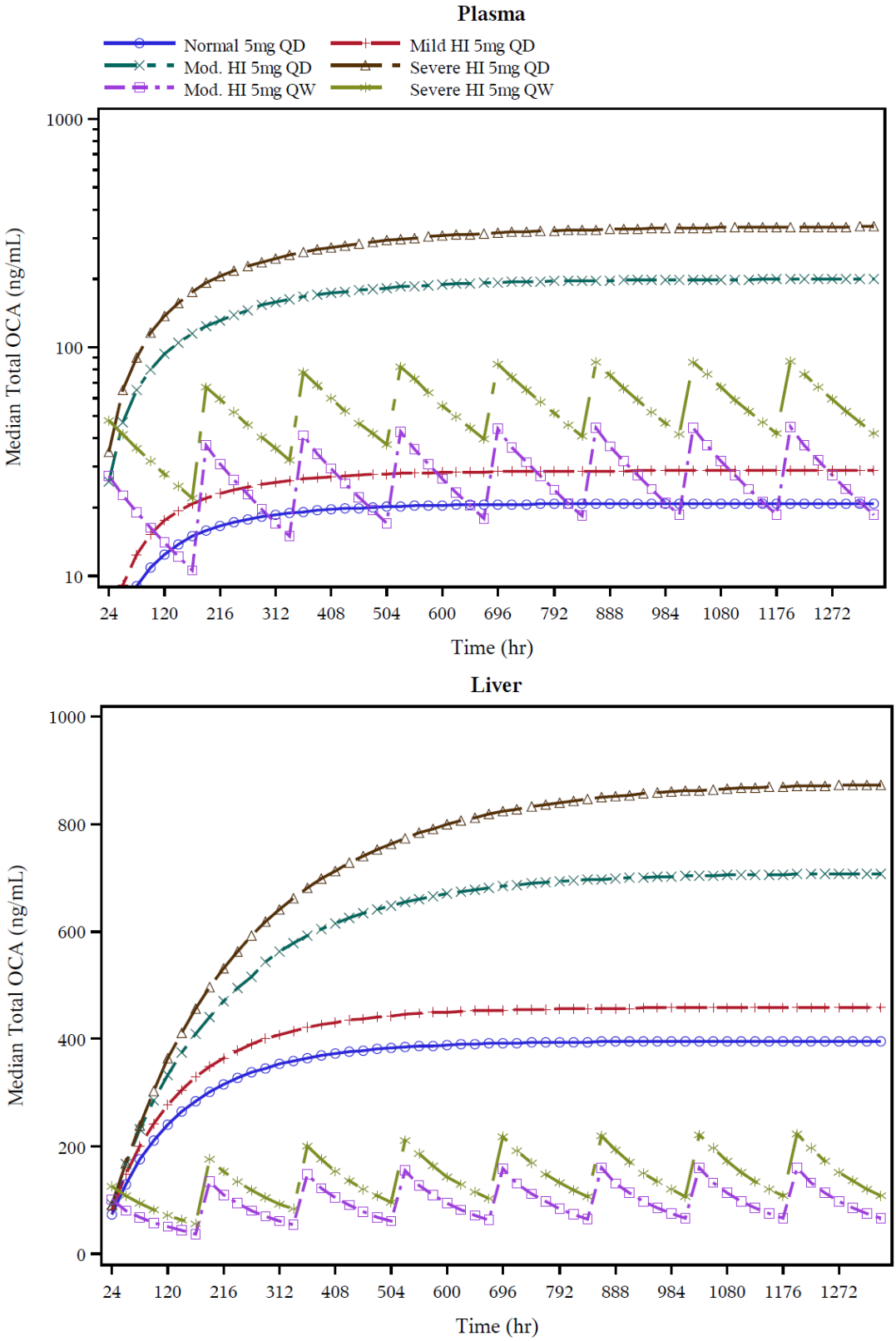
We considered following aspects for this scenario:

- There was a known dose-response relationship for pruritus (see **Section 3.3.2.1**).
- It is not entirely known whether the pruritus is driven by plasma exposures or liver exposures and/or other susceptibilities independent of exposure.
- Even if the pruritus events were to be driven by liver exposures, it is unknown whether there is a shallow or steep E-R relationship of pruritus with liver exposures to consider the 2-fold changes to be clinically relevant or not.

Thus, in the absence of dose adjustment, there is potential for high plasma exposures (and potentially liver exposures) leading to safety/discontinuation issues in case of PBC patients with moderate/severe hepatic impairment (Child Pugh B/C). Since there was no time-dependent worsening of tolerability on same dose/exposure (**Figure 5**), 50% of severe pruritus onset occurred within 2 weeks of dose initiation, and all of the discontinuations due to pruritus in the 10 mg QD arm occurred within the first three months (see **Section 3.3.2.1**), initial dosing regimen in moderate or severe hepatic impairment to match exposures to those of normal or mild hepatic impairment PBC subjects will likely avoid potential safety/discontinuation issues and allow identification of subjects who may qualify for up-titration at ≥3 months.

The dosing regimen of 5 mg QW (once a week) for moderate and severe hepatic impairment in this scenario gives the ability to achieve matching plasma exposures with the no impairment or mild hepatic impairment subjects (**Table 6** and **Figure 11**). Further up-titration to 5 mg BIW (twice weekly) and subsequently to 10 mg BIW (twice weekly) depending on tolerability and efficacy can then be followed to further increase the liver concentrations and meet individual efficacy goals.

Figure 11: Predicted median plasma (top panel) and liver (bottom panel) concentrations of total OCA in subjects with different categories of hepatic impairment (normal/mild/moderate/severe) with 5 mg QD dosing and additionally subjects with moderate and severe hepatic impairment with 5 mg QW dosing



Source Data: Analysis of simulation dataset submitted by the Applicant in response to Clinical Pharmacology information request

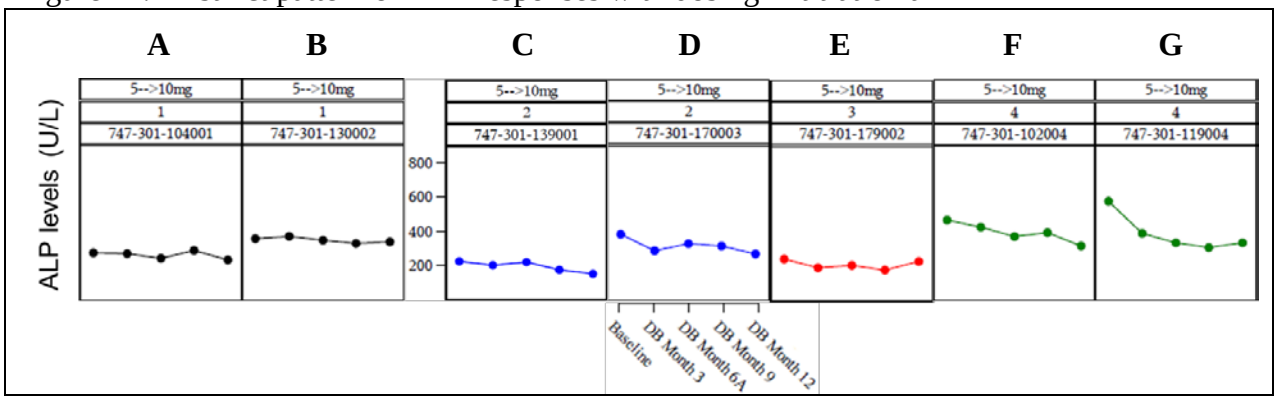
3.5 Discontinuation of OCA for lack of biochemical response

Consideration should be given for discontinuation of OCA for the subjects who do not show response of reduction in alkaline phosphatase. See **Section 1.4** that discusses the current thinking of the OCP review team.

The data in the Phase 3 trial was analyzed to evaluate the pattern of gain or loss of efficacy in subjects at different time points (esp. 3, 6, 9 and 12 months) during the treatment period. The analysis of some of the representative individual profiles suggested that there is a huge variability in pattern of response with either the continued same dosing or up titration to a higher dose in the treatment period. For example, within the titration arm where subjects were dosed at 5 mg QD for the first six months, followed by up-titration to 10 mg QD for the next six months for a part of those subjects depending upon efficacy and tolerability, there were following distinct patterns of responses (**Figure 12**):

- Some subjects did not have reduction in ALP within first six months and continue to not have any reduction in ALP in the next six months even after dose up titration to 10 mg (panel A-B)
- Some subjects do not have reduction in ALP within the first six months, but show reduction in ALP upon dose up-titration in the next six months (panel C)
- Some subjects do show reduction in ALP within the first 3-6 months on 5 mg dose, but do not show further reduction in ALP upon up titration to 10 mg (panel D)
- Some subjects show reduction in ALP with 5 mg dose, but there is reversal of this reduction in the next six months while they are up-titrated to 10 mg (panel E)
- Some subjects show reduction in ALP in the first six months and achieve 15% reduction in ALP by 6 months and continue to show further reduction in ALP when they are up titrated to 10 mg dose (panel F)
- Some subjects show reduction in ALP in the first six months and achieve 15% reduction in ALP by 6 months but do not show further reduction in ALP upon up titration to 10 mg (panel G).

Figure 12: Distinct pattern of ALP responses with dosing in titration arm



Based on these different patterns, we can categorize subjects as responder/non-responder at 6 months (6M) and at 12 months (12M) for response criteria such as 15% reduction in ALP

(**Table 7A**) or achievement of primary composite endpoint (**Table 7B**).

Table 7: Categorization of subjects as responders (+) / non-responders (-) based on (A) criteria of 15% reduction in ALP from baseline at 6 months and at 12 months and (B) criteria of achievement of primary composite endpoint at 6 months and at 12 months, for different treatment arms in Phase 3 study

A.

Treatment	ALP 15% reduction at 6M / 12M			
	- / -	- / +	+ / -	+ / +
Placebo (N=73)	47 (64.4%)	8 (11%)	5 (6.9%)	13 (17.8%)
5 mg (N=37)	3 (8.1%)	4 (10.8%)	7 (18.9%)	23 (62.2%)
5 mg→10 mg (N=33)	5 (15.2%)	8 (24.2%)	1 (3.0%)	19 (57.6%)
10 mg (N=73)	13 (17.8%)	2 (2.7%)	4 (5.5%)	54 (74.0%)

B.

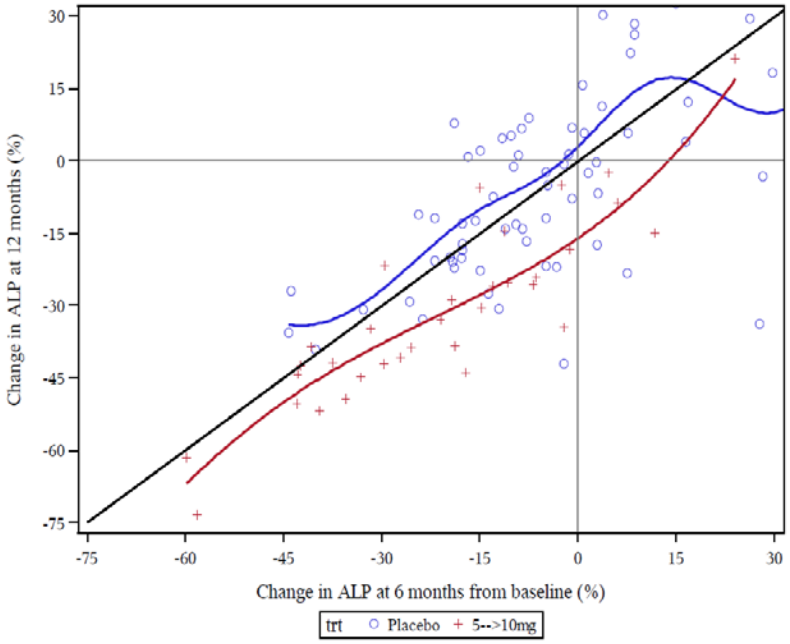
Treatment	Primary Endpoint at 6M / 12M			
	- / -	- / +	+ / -	+ / +
Placebo (N=73)	66 (90.4%)	2 (2.7%)	0 (0%)	5 (6.9%)
5 mg (N=37)	11 (29.7%)	2 (5.4%)	7 (18.9%)	17 (45.9%)
5 mg→10 mg (N=33)	20 (60.6%)	13 (39.4%)	0 (0%)	0 (0%)
10 mg (N=73)	32 (43.8%)	4 (5.5%)	7 (9.6%)	30 (41.1%)

The **Table 7B** shows that a substantial proportion (39.4%) of patients (who got up-titrated to 10 mg QD) that did not achieve responder criteria at 6 months, but with the up-titration (5 mg→ 10 mg), they were able to achieve responder status by 12 months (13 subjects for primary endpoint criteria). Also some of the subjects did become responders by 6 months, but lost their responder status by 12 months even in spite of continuing on the same dose that they achieved the response on (7 subjects for primary endpoint criteria). Thus, there may be value in affording the up-titration to those individuals who may have achieved responder status at short time, and thus did not get up-titrated, but lost their efficacy due to may be disease progression or lack of sustained response.

Furthermore, on an average, there was an increase in ALP response as seen by further reduction in ALP levels from 6 months to 12 months in treatment arm where subjects were up-titrated from 5 mg to 10 mg at six months (**Figure 13**). This is evidenced by the majority of points lying below the line of identity in the plot of reduction in ALP at 12 months vs. reduction in ALP at 6 months. Conversely, majority of points in the placebo arm remain above the line of identity, indicating that the placebo response of reduction in ALP did not sustain from month 6

to month 12. Based on this plot, depending on the threshold of reduction in ALP that can be deemed to be clinical significant and distinguishable from placebo response, an appropriate criteria can be suggested (e.g. minimum 15% reduction in ALP from baseline) to determine whom to discontinue potentially because of lack of efficacy (lack of clinically relevant reduction in ALP) after they are titrated to 10 mg dose and evaluated for ≥6 month duration on this dose. Since there are different temporal patterns of ALP response in individuals as shown in **Figure 12**, a time point earlier than 6 months on a stable dose may be premature to evaluate and conclude lack of response for decision of treatment discontinuation.

Figure 13: Change in ALP at 6 and 12 months after treatment



3.6 Evidence for supporting OCA monotherapy in adult subjects unable to tolerate UDCA

There is evidence of ALP reduction when considering pooled data from phase 2 and 3 trials that supports OCA monotherapy in adult subjects unable to tolerate UDCA.

The Phase 3 study had only ~7.5% subjects treated with OCA as a monotherapy. So the evidence for monotherapy was evaluated based on response at the 3-month timepoint in a pooled dataset derived from the two Phase 2 trials (747-201, 747-202) and the Phase 3 trial (747-301). 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 (**Table 8**). The responder definition was the same as the one used for the primary efficacy analysis in study 747-301. Also the data showed marked change in ALP biomarker with monotherapy and this change was statistically significant ($p<0.0001$; post-hoc analysis on pooled data, **Figure 14**). The baseline values of ALP were higher in monotherapy as compared to combination therapy, while the ALP values after treatment were similar at 3 months. Based on this evidence, use of OCA as a monotherapy for subjects who are unable to tolerate UDCA seems reasonable.

Table 8: Efficacy results for OCA monotherapy and combination therapy with UDCA based on pooled data from study 747-201, study 747-202 and Phase 3 study 747-301

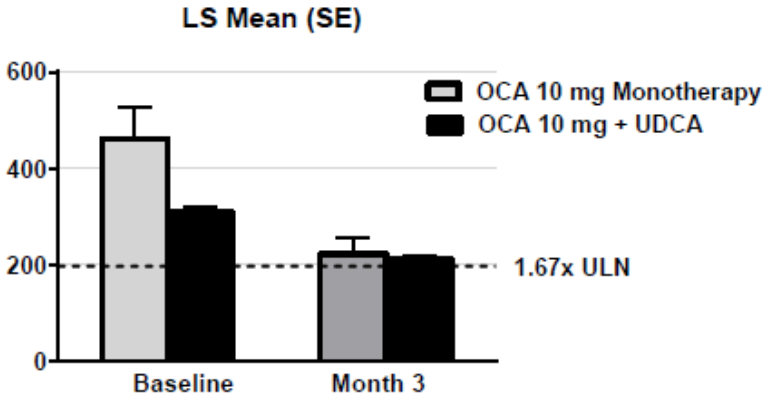
Month 3	Composite Endpoint: ALP <1.67x ULN and Total Bilirubin ≤ULN, and ALP Decrease of ≥15% from Baseline	
	Responder	CMH p-value[a]
Monotherapy		
Placebo (N = 28)	1 (4)	NA
OCA 10 mg (N = 26)	10 (38)	0.0010
Combination (+ UDCA)		
Placebo (N = 106)	5 (5)	NA
OCA 10 mg (N = 105)	43 (41)	<0.0001

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

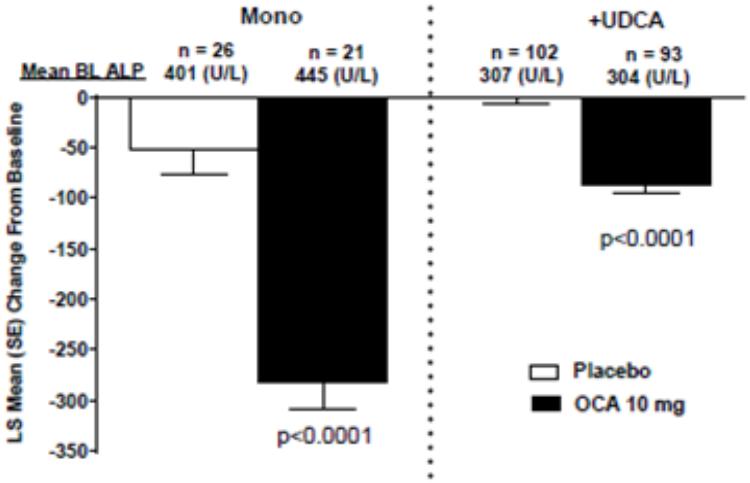
Source Data: Section 2.5, Table 13

Figure 14: ALP levels (panel A) and change in ALP from baseline (panel B) with OCA monotherapy and combination therapy with UDCA, based on pooled data from study 747-201, study 747-202 and Phase 3 study 747-301

A. LS Mean ALP (U/L) Values at Baseline and Month 3



B. LS Mean Change in ALP (U/L) From Baseline to Month 3



Source Data: Section 2.5, Figures 12, 13

3.7 Single dose and multiple dose PK parameters

3.7.1 Healthy subjects

3.7.1.1 Single dose - Plasma

The single dose PK of OCA in healthy subjects was characterized in three Phase 1 studies: 747-101, 747-102 (Day 1) and 747-105. The sensitivity (LLOQ) of analytical method used in 747-101 was 100 ng/mL for all three analytes (OCA, glyco-, and tauro-OCA), 200 times higher than the most sensitive method used for 747-105 (LLOQ = 0.5 ng/mL for all three analytes). The PK results of 50, 100, 250, 500 mg of OCA from Study 747-101 were not reviewed. The sensitivities of analytical method used in 747-102 were 1, 5, and 1 ng/mL for OCA, glyco- and tauro-OCA, respectively. Since Study 747-102 studied higher doses, the assay sensitivity difference comparing to Study 747-105 is not an issue.

Study 747-105 is a single-dose (Day 1; 5, 10 or 25 mg OCA) and multiple-dose (Days 4-17; 5, 10 or 25 mg OCA once daily) PK study under fasting condition, i.e. subjects were fasted for 10 hours before the dose followed by PK sampling. The mean concentration-time profiles (linear and semi-log) of OCA, glyco-OCA, and tauro-OCA following single oral dose administration are presented in **Figure 15**. Note that the single dose PK sampling time in this study was up to 60 hours, which was not long enough to estimate terminal T1/2.

3.7.1.2 Multiple doses - Plasma

The multiple-dose PK of OCA in healthy subjects was characterized in two Phase 1 studies: 747-102 and 747-105. The mean concentration-time profiles of OCA, glyco-OCA, and tauro-OCA following 5, 10, and 25 mg QD OCA are presented in

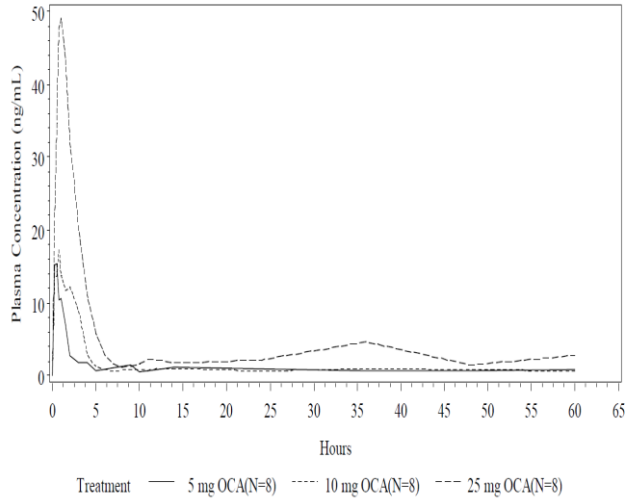
Figure 16.

The multiple-dose PK of OCA, glyco-, and tauro-OCA following 5, 10, and 25 mg QD for 14 days are summarized in **Table 9**. Note that in this study, the multiple doses started 4 days after the subjects received a single dose of OCA.

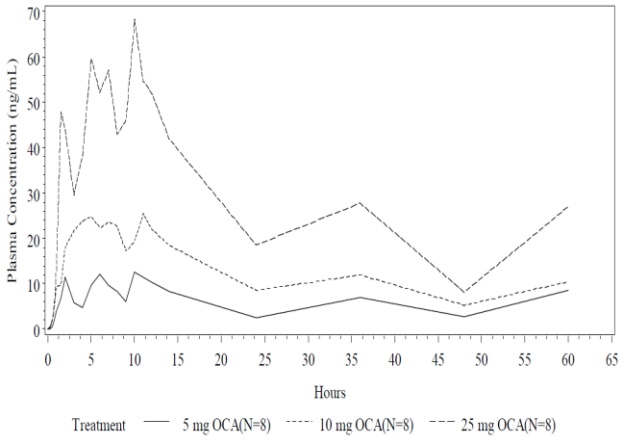
In the multiple-dose period, the sampling time after the last dose was up to 528 hours post-dose. However, all the subjects had plasma concentrations of OCA and its conjugates below LLOQ at Hour 480 and beyond. Due to extensive enterohepatic recirculation, the terminal T1/2, and CL/F of glyco- and tauro-OCA were not estimable.

Figure 15: Mean concentration-time profiles for OCA and its metabolites in plasma following single oral administration of 5, 10, and 25 mg

OCA – Linear Scale



Glyco-OCA – Linear Scale



Tauro-OCA – Linear Scale

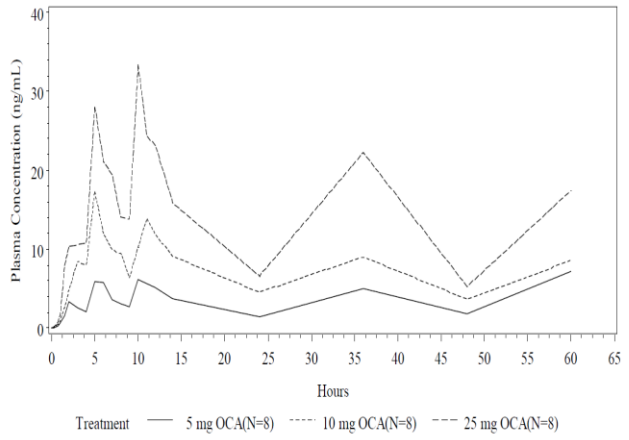
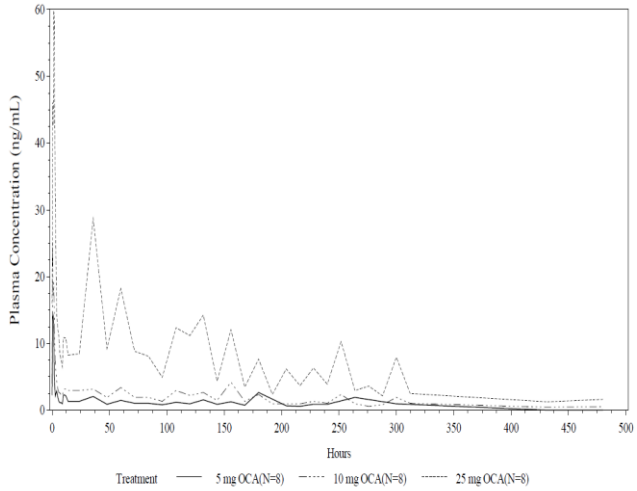
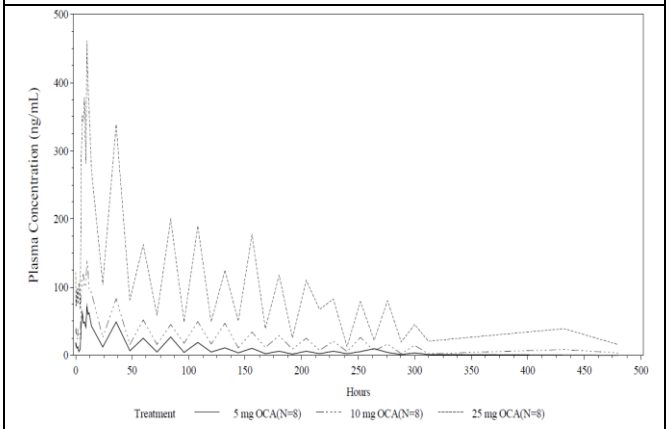


Figure 16: Mean concentration-time profiles for OCA, glyco-OCA, and tauro-OCA in Plasma following multiple oral doses of 5, 10, and 25 mg QD OCA, on Day 17 (Study 747-105)

OCA – Linear Scale



Glyco-OCA – Linear Scale



Tauro-OCA – Linear Scale

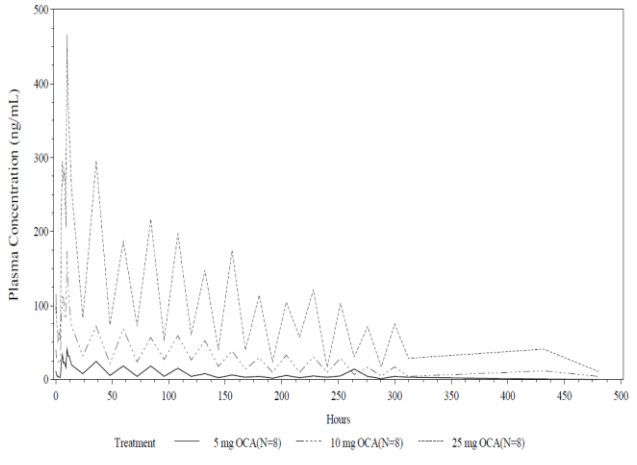


Table 9: Mean (CV%) of multiple doses plasma PK parameters by dose level (Study 747-105)

Analyte PK Parameter	n	5-mg OCA (N = 8)	n	10-mg OCA (N = 8)	n	25-mg OCA (N = 8)
OCA						
C_{max} (ng/mL)	7	21.9 (47.2)	8	38.0 (47.5)	7	104 (36.3)
t_{max} (h)[a]	7	1.0 (0.3-4.0)	8	1.5 (0.3-3.0)	7	1.5 (0.5-3.0)
AUC_{0-24} (ng·h/mL)	7	58.9 (39.1)	8	111 (15.4)	7	340 (35.5)
Rac AUC_{0-24}	5	1.9 (15.4)	7	2.1 (33.9)	7	2.0 (13.0)
Rac C_{max}	7	1.3 (51.1)	8	1.6 (59.7)	7	1.5 (36.1)
Glyco-OCA						
C_{max} (ng/mL)	7	79.8 (82.5)	8	157 (32.5)	7	506 (29.0)
t_{max} (h)[a]	7	10 (6-12)	8	10 (6-11)	7	10 (5-11)
AUC_{0-24} (ng·h/mL)	7	839 (86.6)	8	1755 (36.7)	7	5579 (39.0)
Rac AUC_{0-24}	7	4.5 (25.7)	8	6.4 (67.7)	7	6.8 (35.4)
Rac C_{max}	7	3.6 (34.1)	8	6.4 (68.8)	7	6.8 (36.1)
$MRAUC_{0-24}$	7	11.1 (43.3)	8	13.8 (27.3)	7	14.5 (16.7)
MRC_{max}	7	3.0 (34.6)	8	4.1 (41.1)	7	4.5 (29.8)
Tauro-OCA						
C_{max} (ng/mL)	7	45.1 (108.6)	8	182 (38.3)	7	484 (36.8)
t_{max} (h)[a]	7	10 (6-12)	8	10 (6-11)	7	10 (8-11)
AUC_{0-24} (ng·h/mL)	7	415 (111.7)	8	1651 (32.4)	7	4910 (33.6)
Rac AUC_{0-24}	7	4.3 (40.2)	8	9.4 (28.3)	7	13.6 (30.6)
Rac C_{max}	7	4.3 (51.5)	8	10.1 (28.3)	7	11.4 (25.5)
$MRAUC_{0-24}$	7	4.6 (71.9)	8	12.3 (38.2)	7	13.1 (52.5)
MRC_{max}	7	1.4 (58.7)	8	4.7 (52.1)	7	4.4 (61.7)
Total OCA						
C_{max} (ng-eq/mL)	7	108 (90.3)	8	285 (27.7)	7	836 (18.7)
t_{max} (h)[a]	7	10 (6-12)	8	10 (6-11)	7	10 (5-11)
AUC_{0-24} (ng-eq·h/mL)	7	1128 (91.4)	8	2972 (28.6)	7	9165 (26.3)
Rac AUC_{0-24}	7	4.2 (23.6)	8	6.6 (42.5)	7	7.8 (32.7)
Rac C_{max}	7	3.4 (50.3)	8	6.9 (45.0)	7	7.0 (34.1)

AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours; C_{max} = maximum concentration (observed); C_{min} = minimum concentration over a 24-hour dosing interval; CV% = percent coefficient of variation; glyco-OCA = glycine 6α-ethyl-chenodeoxycholic acid; $MRAUC_{0-24}$ = ratio of conjugate to OCA for AUC_{0-24}; MRC_{max} = ratio of conjugate to OCA for C_{max}; ng-eq = nanogram-equivalents; OCA = obeticholic acid; Rac = accumulation ratio; tauro-OCA = taurine 6α-ethyl-chenodeoxycholic acid; t_{max} = time to C_{max}

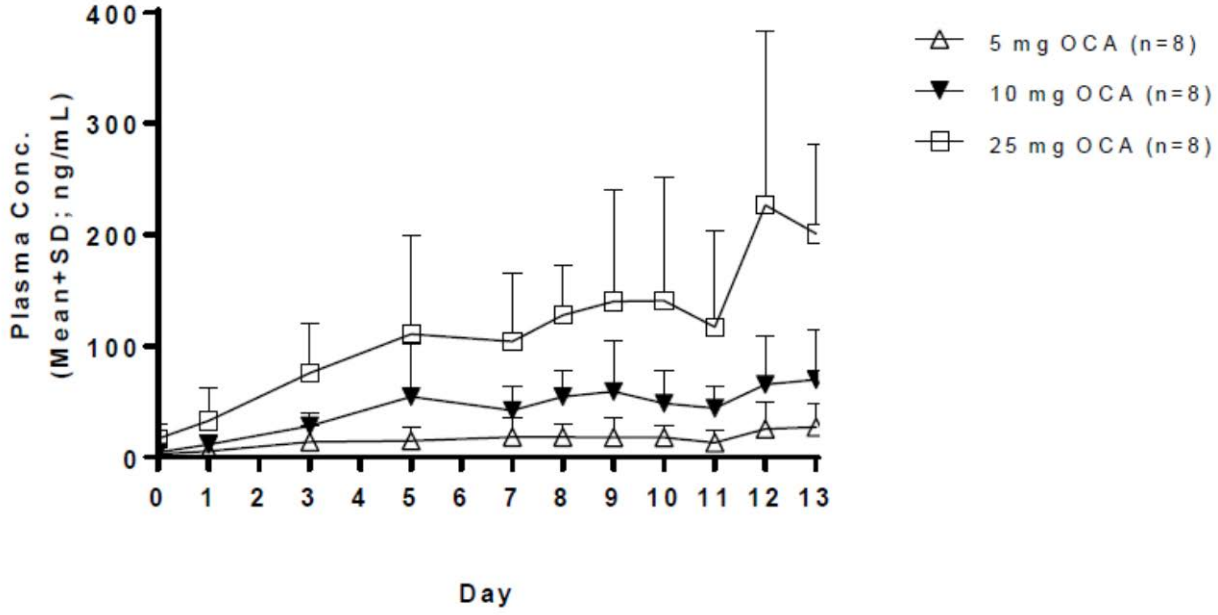
[a] Median and range

Source: CSR 747-105, Section 14, Table 14.2.3.2, Table 14.2.3.4, Table 14.2.3.6, and Table 14.2.3.8

Time to steady-state

Based upon the visual inspection of trough concentration-time profile from Day 4 to Day 17 (**Figure 17**) in Study 747-105, OCA reaches SS by Day 9 (5-day of QD dosing), while total OCA appears to be close to SS by Day 13 (9 days of QD dosing) for the lower doses.

Figure 17: Mean (+SD) of trough total OCA plasma concentration versus time profile following 5, 10, and 25 mg QD OCA for two weeks.

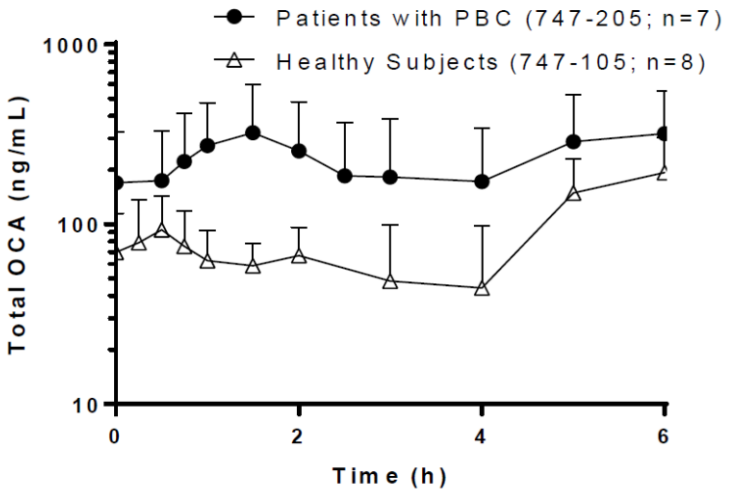


Note: Day 0 in the plot is Day 4 in the study

3.7.2 PK of the drug in healthy volunteers vis-a-vis in patients with PBC

A direct comparison between the PK of OCA in healthy volunteers and patients is not feasible because of the limited PK samples collected in patients with PBC. With this caveat in mind, a cross-study comparison was performed and the mean concentration-time profiles of first 6 hours between patients with PBC (Study 747-205) and healthy subjects (Study 747-105) were shown in **Figure 18**. Study 747-105 evaluated healthy subjects dosed with 10 mg QD OCA for 14 days. Study 747-205 evaluated PK profiles over the first 6 hours after last dose administration of OCA dosed with 10 mg QD OCA for 8 weeks in PBC patients. Study 747-301 evaluated trough PK concentrations for PBC patients dosed for 24 weeks (6 months). The comparative data from study 747-205 and study 747-105 showed an overall similar profile, but with modestly higher systemic exposure for PBC patients compared to healthy volunteers. However, the limited number of subjects in these studies and the high variability in the systemic exposures limits the interpretation of these results. In this comparison, the difference in Cmax of total OCA between patients (mean/SD of 409/299 eq-ng/mL) and healthy subjects (mean /SD of 285/27.7 eq-ng/mL) was two-fold.

Figure 18: Mean (SD) Steady-State Plasma Concentration-Time Profile of Total OCA in Subjects with Primary Biliary Cirrhosis (Study 747-205) and Healthy Subjects (Study 747-105) After Daily Administration of 10 mg OCA (Semi-log)



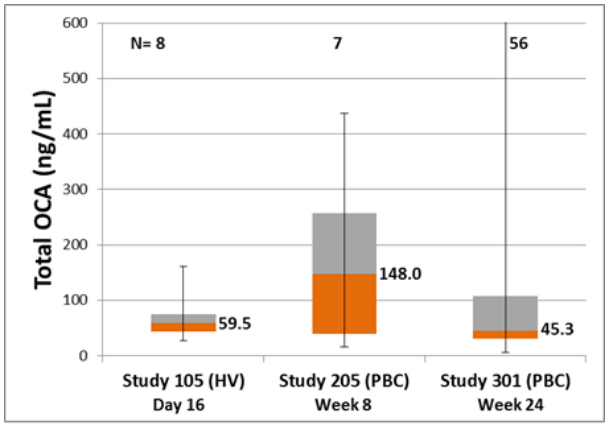
Source data: Figure 7, Section 2.7.2

Study 747-301 evaluated trough PK concentrations for PBC patients dosed for 24 weeks (6 months) with 5 mg and 10 mg QD OCA. The mean trough concentrations of total OCA in patients from Study 747-301 were 1.6 fold than healthy subjects (Study 747-105) after 10 mg QD (**Table 10**), while the median trough concentrations were similar between these two populations (**Figure 19**). Overall, there was substantial overlap between the concentrations in the two populations. The inter-subject variability seems to be greater in patients than that in healthy subjects.

Table 10: Descriptive statistics of OCA and its conjugates trough concentrations (ng/mL) at Month 6 (Study 747-301), and Day 14 (Study 747-105) by treatment

	OCA	Glyco-OCA	Tauro-OCA	Total OCA
	Month 6, Patients			
5 mg (N=63)	3.73 (4.62)	39.2 (43.0)	31.8 (44.7)	63.6 (70.1)
10 mg (N=57)	4.90 (4.96)	50.7 (60.9)	42.5 (103)	83.4 (114)
	Day 14, Healthy			
5 mg (N=7)	1.30 (0.398)	12.4 (11.2)	7.70 (8.18)	18.4 (16.7)
10 mg (N=8)	2.91 (0.811)	26.4 (15.3)	31.8 (11.0)	51.5 (20.7)

Figure 19: Boxplot of trough concentration of total OCA in study 747-105 (healthy volunteers), study 747-105 (PBC patients) and Phase 3 study 747-301 (PBC patients) after daily administration of 10 mg OCA for 14 days, 8 weeks and 24 weeks respectively.



3.7.3 Inter-subject variability of PK parameters in volunteers and patients, and major causes of variability

Inter-subject variability

Table 11 shows that the inter-subject variability of systemic exposure (AUCtau) following multiple dose administration of OCA. The larger inter-subject variability is likely due to the extensive hepatic recirculation. The number of subjects in the study is small affecting the variability assessment.

Table 11: Inter-subject variability (N) of OCA systemic exposures (Cmax and AUCtau) after multiple oral doses of 5, 10, 25, 50, 100, and 250 mg QD in healthy subjects.

		Study 747-105			Study 747-102			
Analyte	Dose (mg)	5 mg (N=7)	10 mg (N=8)	25 mg (N=7)	25 mg (N=8)	50 mg (N=8)	100 mg (N=16)	250 mg (N=7)
OCA	**Cmax**	**47**	**48**	**36**	**35**	**40**	**48**	**78**
	AUC(0-24)	**39**	**15**	**36**	**52**	**56**	**48**	**115**
Glyco-OCA	**Cmax**	**83**	**33**	**29**	**40**	**45**	**40**	**63**
	AUC(0-24)	**87**	**37**	**39**	**36**	**66**	**40**	**49**
Tauro-OCA	**Cmax**	**109**	**38**	**37**	**55**	**60**	**75**	**52**
	AUC(0-24)	**112**	**32**	**34**	**56**	**74**	**75**	**51**

3.7.4 Degree of linearity or non-linearity in PK parameters based on the dose-concentration relationship

Single doses

Following single dose of 5 mg, 10 mg, and 25 mg OCA, dose-proportionality was concluded for Cmax and AUC0-t and all analytes (OCA, glyco-OCA and tauro-OCA) with the exception

of AUCt for OCA which increased in a more than dose-proportional manner. Due to its extensive hepatic enterohepatic recirculation, AUC0-t determined by 60 hours PK sampling does not reflect the total systemic exposure following single doses.

Multiple doses

Following multiple-dose administration of 5, 10, and 25 mg QD for 14 days, dose-proportionality was concluded for the parent drug only. For the conjugates and total OCA, Cmax and AUC0-24h increased more than proportionally with dose.

3.7.5 Change in PK parameters with time following chronic dosing

PK of OCA and its conjugates do not appear to change with time because as OCA is not a substrate of CYP enzymes. The metabolism of OCA is through conjugation. Thus, the PK of OCA should not change either by auto-induction or auto-inhibition. The changes of PK parameter with time was not well characterized in phase 1 single and multiple doses studies as the sampling time in single dose study was only up to 60 hours. Due to extensive hepatic recirculation and the sampling time limitation, the AUCinf was not estimable in the single dose studies.

Following multiple doses of 5, 10, and 25 mg OCA for 14 days, the systemic exposures (Cmax and AUC0-24h) are greater than that of single doses across all dose levels (**Table 12**).

Table 12: Ratios of AUC0-24h (RAUC) between Day 14 and Day 1 for various doses of OCA (Study 747-105)

DOSE (mg)	Analytes	N	Mean	CV%
5	OCA	5	1.9	15.4
	Glyco-OCA	7	4.5	25.7
	Tauro-OCA	7	4.3	40.2
10	OCA	7	2.1	33.9
	Glyco-OCA	8	6.4	67.7
	Tauro-OCA	8	9.4	28.3
25	OCA	7	2.0	13.0
	Glyco-OCA	7	6.8	35.4
	Tauro-OCA	7	13.6	30.6
RAUC=AUC0-24,ss/AUC0-24,Day1				

4 APPENDIX A: PHYSIOLOGICAL-BASED PHARMACOKINETIC (PBPK) MODELING REVIEW

Application Number	NDA207999
Drug Name	Obeticholic Acid
Primary PBPK Reviewer	Ping Zhao, Ph.D., Yuching Yang, Ph.D. and Dhananjay Marathe, Ph.D.
Secondary PBPK Reviewer	Nitin Mehrotra, Ph.D.

1. Objectives

The main objective of this review is to evaluate the submitted physiologically-based pharmacokinetic (PBPK) modeling information that predicted the exposure of obeticholic acid (OCA) in the systemic circulation and the liver in healthy subjects and patients with hepatic impairment and to determine the adequacy of the model to support dosing recommendations of OCA in subjects with hepatic impairment.

To support its conclusion that no dose adjustment is required in patients with hepatic impairment, the applicant provided the PBPK modeling and simulation information.

2. Pertinent Background

In a phase I study, subjects with varying degrees of hepatic impairment (severity based on Child-Pugh scores, CP scores) were given a single oral dose of 10 mg OCA [4]. Plasma exposure of OCA, glyco-OCA, tauro-OCA and total OCA are higher in subjects with hepatic impairment than in subjects with normal hepatic functions (**Table 1**). For example, mean AUCt (AUC from time zero to the time of the last measurable concentration) of total OCA in plasma were approximately 1.1-fold, 4.2-fold, and 17-fold higher in subjects with mild, moderate, and severe hepatic impairment, respectively, compared with subjects with normal hepatic function. The magnitudes of exposure change appear to differ among OCA, glyco-OCA and tauro-OCA. In subjects with severe hepatic impairment, the magnitudes of increase in AUCt were 7, 11, and 37-fold for OCA, glyco-OCA, and tauro-OCA, respectively.

The observed higher plasma concentrations of OCA and endogenous bile acids in subjects with severe hepatic impairment from Study 747-103 [4] appear to be consistent with plasma levels of OCA and endogenous bile acids found in other studies. In a phase 2 study (Study 747-204), 10 or 25 mg of OCA were administered to patients with portal hypertension for 6-12 days, a condition defined by the applicant as hepatic impairment. On the last day of the treatment, plasma maximal concentration (Cmax) of total OCA were about 5 to 6-fold higher than the central values observed in healthy subjects receiving the same doses [1]. Fisher et al also measured endogenous bile acid levels in explanted liver samples from cholestasis (end-stage chronic cholestasis) and non-cholestasis (cirrhosis of alcoholic/chronic hepatitis) patients with end-stage liver dysfunction [5]. Compared with subjects with normal hepatic function, there was a substantial increase in serum endogenous total bile acid concentrations in patients with hepatic impairment (17 and 23-fold for noncholestatic and cholestatic patients, respectively, [5]). The authors also reported a modest increase in liver concentrations of total bile acids (2 and 4-fold higher for noncholestatic and cholestatic patients, respectively) [5].

To evaluate that liver exposure of OCA in subjects with hepatic impairment, the applicant conducted modeling and simulation using a physiologically-based pharmacokinetic (PBPK) model, and predicted approximately 2-fold increase in total OCA in subjects with severe hepatic impairment [1]. Based on model predictions, the applicant suggested that significant elevation of total OCA in plasma does not represent exposure changes of OCA at the site of action for efficacy or safety (i.e., liver) in subjects with hepatic impairment [1]. In its proposed prescription information [6], the applicant stated that “Limited data exist in patients with moderate or severe hepatic impairment therefore caution should be exercised. The systemic exposure of obeticholic acid is increased in patients with moderate and severe hepatic

impairment when compared to healthy controls and patients with mild hepatic impairment. Based on limited data, TRADENAME was generally well tolerated in patients with hepatic impairment. No dose adjustment is required in patients with hepatic impairment." (Section 8.7 of the proposed label), and "Despite higher systemic plasma exposure levels of obeticholic acid in patients with hepatic impairment, liver exposure was predicted to be similar to healthy controls based on a physiologic pharmacokinetic model. No dose adjustment is required in patients with hepatic impairment" (Section 12.3 of the proposed label).

Table 1: Geometric least square mean ratio (%) of plasma exposure of OCA, glyco-OCA, tauro-OCA, or total OCA following a single oral 10-mg OCA dose in subjects with hepatic impairment to those in subjects with normal hepatic function (Source, Tables 11, 14, 18, 21, Tables 14.2.1.1-4 4, [4]).

		OCA		**Glyco-OCA**		**Tauro-OCA**		**Total OCA**	
Hepatic functions [a]	Parameters	Geometric least square mean ratio (%)	90% CI	Geometric least square mean ratio (%)	90% CI	Geometric least square mean ratio (%)	90% CI	Geometric least square mean ratio (%)	90% CI
Mild/ Normal	AUCt [b]	138	73-261	127	65-250	71	30-170	113	57-225
	AUC 24	146	80-268	132	68-254	76	34-171	123	65-34
	Cmax	135	80-28	143	80-256	87	40-188	149	86-256
Moderate/ Normal	AUCt [b]	241	127-456	333	169-654	686	286-1643	420	211-838
	AUC 24	315	172-578	393	204-758	663	296-1485	440	232-837
	Cmax	191	113-323	373	208-670	563	261-1217	376	218-647
Severe/ Normal	AUCt [b]	703	372-1330	1138	579-2236	3684	1537-8830	1728	867-3444
	AUC 24	830	462-1490	1142	593-2200	3298	1473-7385	1527	804-2901
	Cmax	470	278-796	812	452-1458	2142	991-4627	975	566-1680

[a] Mild (Child-Pugh A); moderate (Child-Pugh B); severe (Child-Pugh C) and normal hepatic function. [b] AUCt: AUC from time zero to the time of the last measurable concentration.

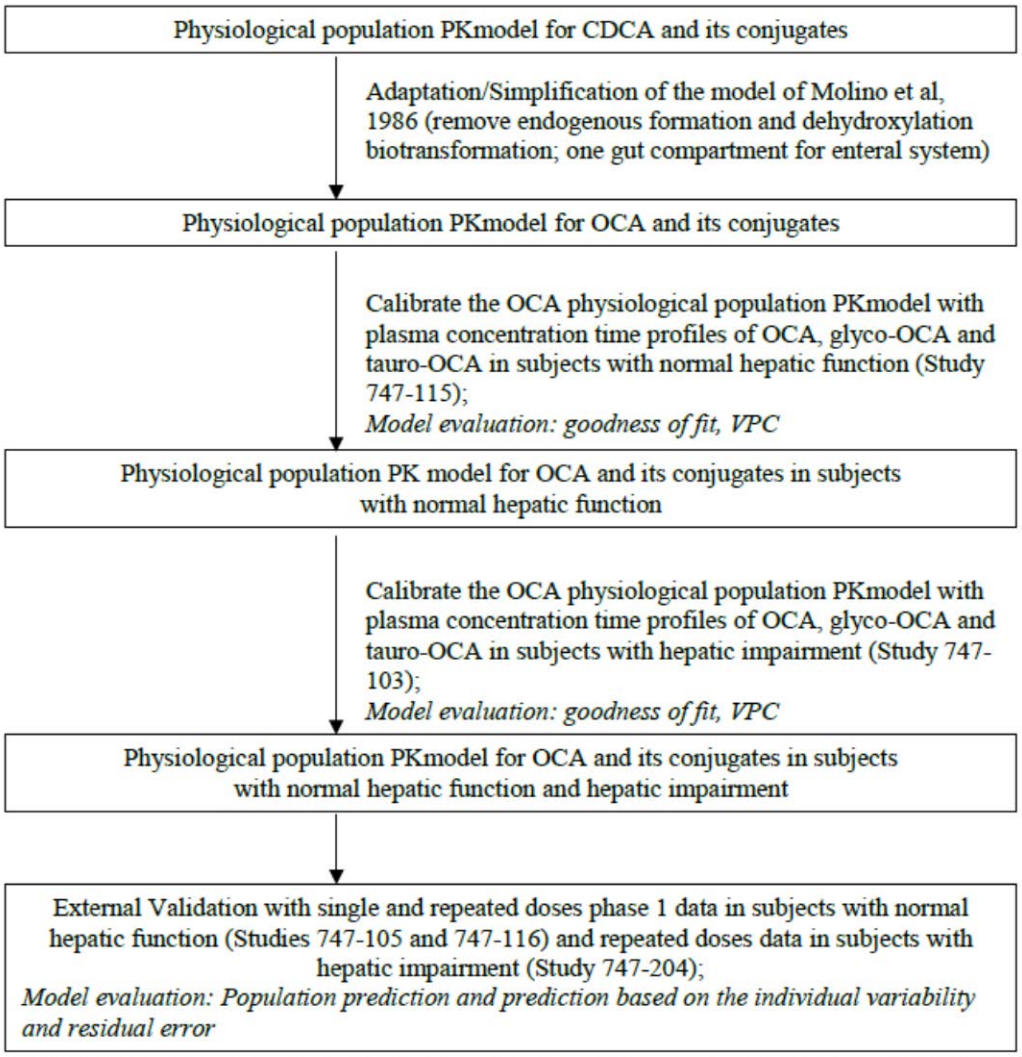
CI= Confidence Interval

The primary objective of this review is to assess the adequacy of the applicant's PBPK models that were used to predict hepatic exposures of OCA and its metabolites and to support their labeling claims with regard to OCA dosing regimen in subjects with varying degrees of hepatic impairment.

3. Methods

A previously developed multi-compartment PBPK model for chenodeoxycholic acid (CDCA), an endogenous bile acid [7], was adopted and modified by the applicant to construct PBPK models for OCA and its conjugates. The applicant used Phoenix® NLME™ 1.3 (Pharsight, A Certara Company, Cary, North Carolina, USA) to perform PBPK modeling and simulations. **Figure 1** represents a workflow of the development and application of integrated models for OCA and its conjugates.

Figure 1: Workflow of the development of integrated OCA and its conjugates (Source: Figure 3.1, [1])



Glyco-OCA = Glycine conjugate of OCA; OCA = obeticholic acid; PK= pharmacokinetic; tauro-OCA = taurine conjugate of OCA; VPC = visual predictive check

3.1. Model fitting

The model [1] includes description of the relationships between plasma concentration and time, a variance component characterizing between subject variability (BSV) in model parameters, and residual unexplained variability using additive and proportional model. The model had the following form:

$$Cp_{ij}=C(D_i,t_j,\theta_i)+\varepsilon_{ij}$$

$$\theta_i=(\theta_{i1,\ldots}\theta_{im})$$

where Cp_{ij} is the concentration at j^{th} time for subject i, D_i represents dosing history for subject i, θ_i is the vector of m model parameters for subject i, and ε_{ij} is random error associated with a concentration at the j^{th} time for subject i. BSV was modeled assuming a log-normal distribution as follows:

$$\theta_{in}=\theta_{TVn}\,exp(\eta_{in})$$

$$(\eta_1 \ldots \eta_m) \sim MVN(0, \Omega)$$

Where θ_{TVn} is the population typical value for the n^{th} model parameter, and η_{in} (ETA) is the random inter-subject error or BSV on the n^{th} parameter for subject *i* that jointly follow a multivariate normal distribution (*MVN*) with mean zero and variance Ω. This model for BSV assumes that estimated parameters are log-normally distributed. Due to the high level of complexity of the model, BSV was incorporated on absorption rate constant K_a and rate from gallbladder to gut.

Residual variability was assumed to have an additive component and a component proportional to the prediction:

$$y_{ij} = \hat{y}_{ij} * (1+\varepsilon_{1ij}) + \varepsilon_{2ij}$$

where y_{ij} and $\hat{y}_{ij}$ represent the j^{th} observed and predicted plasma drug concentration for the i^{th} participant, and ε is the random residual variability. Each ε ($\varepsilon 1$ and $\varepsilon 2$) is normally distributed with mean 0 and variance σ_2.

3.2. Model evaluation

The model was evaluated using several diagnostic plots [1]:

- Observed total OCA plasma concentration data versus population predicted data (PRED) and individual predicted data (IPRED)
- Observed total OCA data and PRED versus time from the first dose
- Observed OCA, glyco-OCA, tauro-OCA versus PRED and IPRED
- Conditional weighted residual (CWRES) of OCA and conjugates versus PRED and time
- 200 iterations corrected visual predictive check (VPC) on the observed concentrations

3.3. CDCA model and assumptions

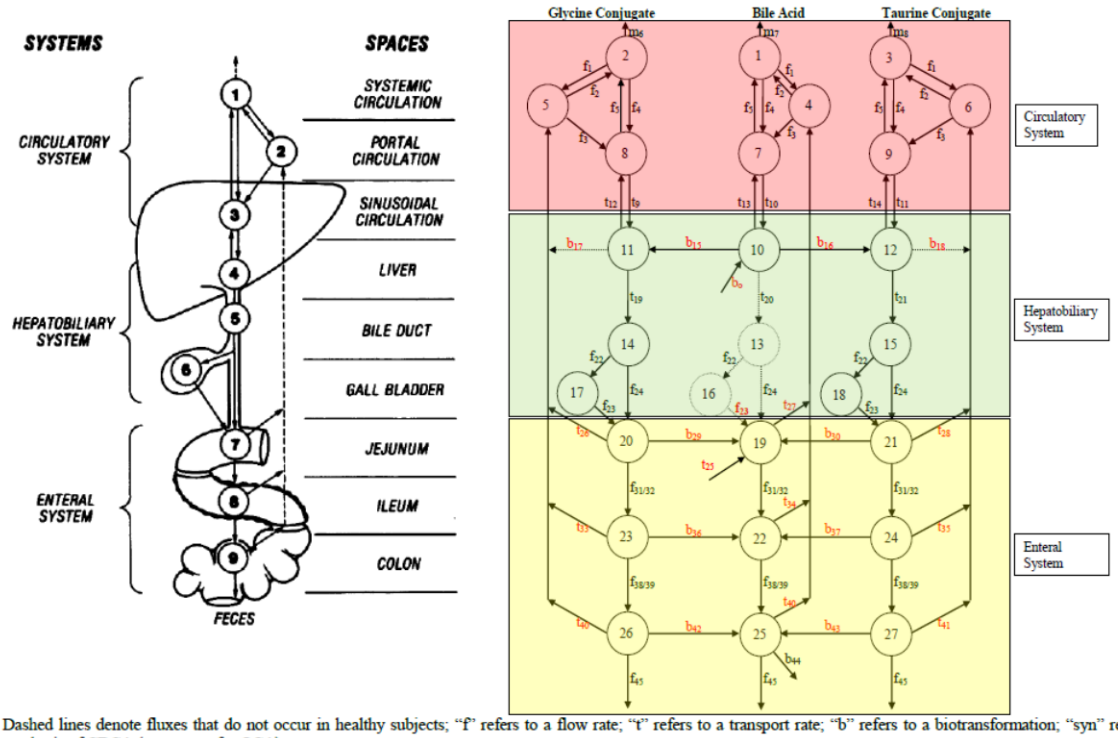
The system model for CDCA and metabolites included three systems: circulatory, hepatobiliary, and enteral systems ([7], **Figure 2**). Within each system, physiology compartments were defined and were interconnected according to either blood flow or kinetic processes relevant to permeation, biotransformation, and active transport of CDCA and its conjugates.

This model was evolved from an earlier model describing cholic acid and conjugates [8]. Key assumptions include:

Circulatory system:

- Total mass of CDCA species was set at 1.9 mmol (0.74 g)
- Portal-systemic shunting is not applicable for healthy individual
- Hepatic first-pass extraction values were 0.8 for conjugates and 0.6 for CDCA. First pass extraction was lower for CDCA than for cholic acid conjugates [8], resulting in higher CDCA serum concentrations

Figure 2: Physiologic PK model for CDCA and conjugates (Source: Figure 1-5, [1])



Dashed lines denote fluxes that do not occur in healthy subjects; "f" refers to a flow rate; "t" refers to a transport rate; "b" refers to a biotransformation; "syn" refers to de novo synthesis of CDCA (set to zero for OCA)

CDCA= chenodeoxycholic acid; OCA= obeticholic acid

Hepato-biliary system:

- Synthesis rate was 0.22 µmol/min
- Biotransformation to glycine conjugate was 3 times that of taurine conjugation
- Biliary excretion of unconjugated CDCA was negligible (set to zero)
- Glyco-CDCA in hepatocytes was mainly from reabsorption from duodeno-jejunal and ileal space; minor input was from newly conjugated glycol-CDCA. New, unconjugated CDCA was either from reabsorption or from de novo synthesis from cholesterol
- Tauro-CDCA in hepatocytes was mainly from reabsorption from ileal space; minor input was from newly conjugated tauro-CDCA (See above)
- Both glyco- and tauro-CDCA are actively transported into bile via bile salt excretory pump (BSEP, [1]). This was not specified in the model
- Duration of meal induced gall-bladder contraction was 120 min
- Gall-bladder contraction was delayed until 10 min after the beginning of the meal
- Duration of meal induced (digestive) change in intestinal motility was 210 min
- The ratio between digestive and fasting motility flow rates was 2.4
- Bile exiting from the common duct to duodenum-jejunum space had a rate about twice that of accumulation into the gallbladder
- During gall-bladder contraction all the bile contained in the common duct and in gall-bladder entered directly into the intestine
- Rate of de-conjugation of glycine conjugate was five times higher than that of taurine conjugate
- Negligible conversion of CDCA to ursodeoxycholic acid

Enteral system:

- Passive absorption (proximal intestinal absorption) assumed for CDCA and glyco-CDCA, not for tauro-CDCA within duodeno-jejunal space
- The majority of glyco- and tauro-CDCA are transported in ileum by apical sodium dependent bile acid transporter (ASBT) and then into the portal system via the organic solute transporters (OSTs). These transporters were not specified in the model [1]
- No de-conjugation of CDCA conjugates in duodeno-jejunum
- 15% glyco-CDCA entered ileal space and was de-conjugated to form CDCA, which is effectively absorbed; tauro-CDCA was assumed to be reabsorbed without de-conjugation
- No absorption was assumed in colon. All CDCA are dehydroxylated to lithocholic acid
- No fecal output of CDCA species

3.4. OCA model and assumptions

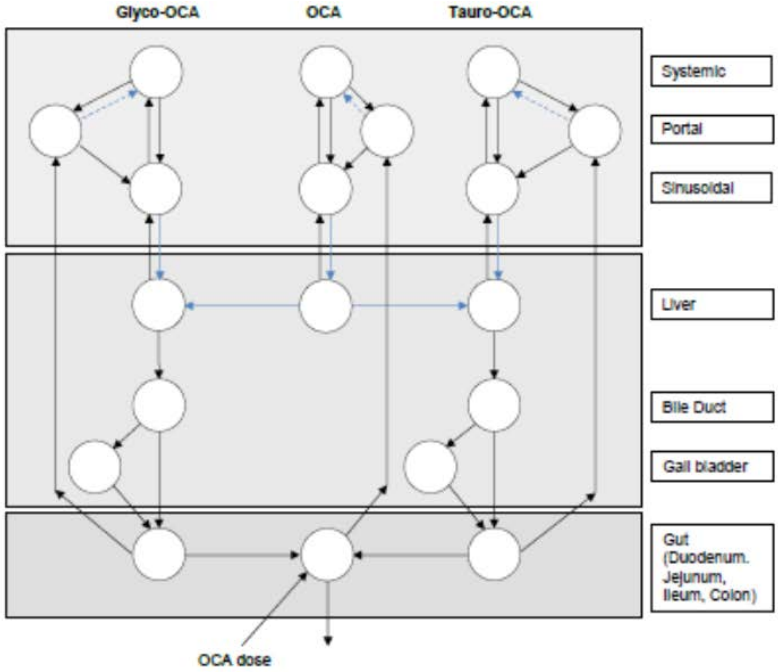
Systems model for OCA and conjugates is simplified by lumping all enteral spaces into a single gut space (**Figure 3**). According to the applicant, values and units for volume of spaces in CDCA model [7] remain unchanged, and volume of gut compartment (0.920 L) corresponds to the sum of duodenum/jejunum, ileum, and colon compartments described by Molino et al [7]. Physiological flow rates from CDCA model were fixed with the exception of flows from bile duct to gallbladder and from bile duct to gut, which were modified to accommodate the simplification of the gut compartment (fixed typical values for system parameters).

- Gallbladder emptying time was assumed to be 90 min since the beginning of the meal
- OCA does not have zero order synthesis
- Dehydroxylation of OCA was not assumed because of steric hindrance
- Oral administration of OCA is represented as input into the gut compartment

3.5. OCA model for healthy subjects

Biotransformation and transport rates were fitted to observed plasma concentration-time profiles of OCA, glyco-OCA and tauro-OCA (**Figure 1**, Study 747-115). Plasma concentrations below the limit of quantitation (BLQ) of OCA, glyco- OCA and tauro-OCA were imputed to half of the lowest limit of quantitation (LLOQ). Both non-BLQ and inputted data from four Phase 1 studies and one Phase 2 study were used in this analysis.

Figure 3: Conceptual representation of the models for OCA, glyco-OCA and tauro-OCA (Source: Figure 3-2, [1])



Solid arrows correspond to flows or rates present in both normal and hepatic impaired subjects; dashed blue arrows correspond to portal systemic shunting (in subjects with hepatic impairment only); blue arrows represent the flows or rates changing with hepatic impairment. In this model, the volume of liver also changes with hepatic impairment.

3.6. OCA model adapted for hepatic impairment

Anatomical/physiological changes described by Johnson et al [9] were considered for system parameters of the model to describe OCA disposition in subjects with varying degrees of hepatic impairment. Child-Pugh (CP) A, B, and C were used to categorize mild, moderate, and severe hepatic impairment. These changes include portal-systemic shunting (as a result of increased portal blood pressure) and reduction in liver volume (**Table 2**). The magnitudes of decrease in hepatic uptake (active transport from sinusoidal space to the liver space) and increase in tauro-conjugation rates (decrease in glycine/taurine conjugation ratio) were fitted to observed plasma concentration-time profiles of OCA and conjugates in subjects with hepatic impairment taking a single oral dose of 10 mg OCA in Study 747-103 (**Table 3**).

Table 2: Effect of cirrhosis on liver volume and hepatic flow fixed in the model (Source: Table 3.2.1, [1])

Parameters	**Percentage change relative to healthy subjects** [b]		
	Child-Pugh A	**Child-Pugh B**	**Child-Pugh C**
Average liver volume	-10.9%	-29.0%	-39.0%
Hepatic arterial flow [a]	+40.8%	+62.5%	+91.5%
Hepatic portal flow [a]	-9.0%	-36.5%	-44.6%

[a] *The mesenteric arterial flow does not change. The balance of flows was achieved by setting the hepatic venous flow as the sum of hepatic arterial and portal flow, and the portal shunt flow as the mesenteric arterial less the hepatic portal flow.*

[b] *Numerical values of % change in liver volume and blood flows are slightly different from Table III of Johnson et al [9].*

Table 3: Model parameters associated with anatomical/physiological changes in subjects with hepatic impairment (Source: Table 3.2.2, [1])

Parameters	**Parameters fitted using data in subjects with hepatic impairment in 747-103**		
	CP-A	**CP-B**	**CP-C**
Decreased hepatic uptake [a]	tvCL_sinu_liver*exp (Hepup2)	tvCL_sinu_liver*exp (Hepup3)	tvCL_sinu_liver*exp (Hepup4)
Increased conjugation [a]	tvCLf_tauro*exp(tconj2)	tvCLf_tauro*exp(tconj3)	tvCLf_tauro*exp(tconj4)

[a] *tvCL_sinu_liver and tvCLf_tauro are transport rate from sinusoidal space to liver and tauro conjugation rate constant (units: hr^{-1}) in healthy subjects*

3.7. Model verification

Models for OCA and conjugates were verified using plasma OCA pharmacokinetic data from study 747-105 (healthy subjects), 747-116 (healthy subjects), and 747-204 (subjects with hepatic impairment).

3.8. Model application

Total OCA was calculated as the sum of OCA, glyco-OCA and tauro-OCA in nM units. Exposure metrics derived from simulations were AUC, Cmax and average concentration (C_{avg}=AUC_{0-24}/24). Simulated liver exposures to total OCA was plotted with changes from baseline of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) measured systemically at the end of treatment (day 6 to day 12) in the Phase 2 study 747-204.

Based on FDA's request, applicant also used PBPK model to simulate the dosing interval needed to match the steady-state plasma exposures in subjects with mild, moderate, or severe hepatic impairment to those achieved with 5 mg once daily (q.d.) dosing in healthy subjects. Simulated plasma PK profiles of total OCA (every 24 hours) for subjects receiving 5 mg OCA include q.d., every other day (q2d), once weekly (q.w.), every two weeks (q2w), and every 17.3 days (q.17.3.d) [2]. Liver exposures for these dosing regimens were also simulated.

3.9. Additional analyses

Comparisons were made between observed levels of total CDCA in study 747-103 (plasma), Fisher et al [8] (plasma and liver), and applicant's simulations (plasma and liver). In subjects with end-stage cholestasis, subjects with end-stage non-cholestasis cirrhosis, and subjects with normal liver function, mean total endogenous bile acid levels were 215 μM (explant liver samples), 119 μM (reviewer calculated, explant livers), and 57 μM (reviewer calculated) respectively in the liver, and 123 μM, 93 μM, and 5 μM (reviewer calculated), respectively in serum [8]. Reviewer calculated total CDCA based on digitized percentage of total bile acid in liver and serum for each of the three groups [8]. An FDA in house digitizing software was used for these calculations [9].

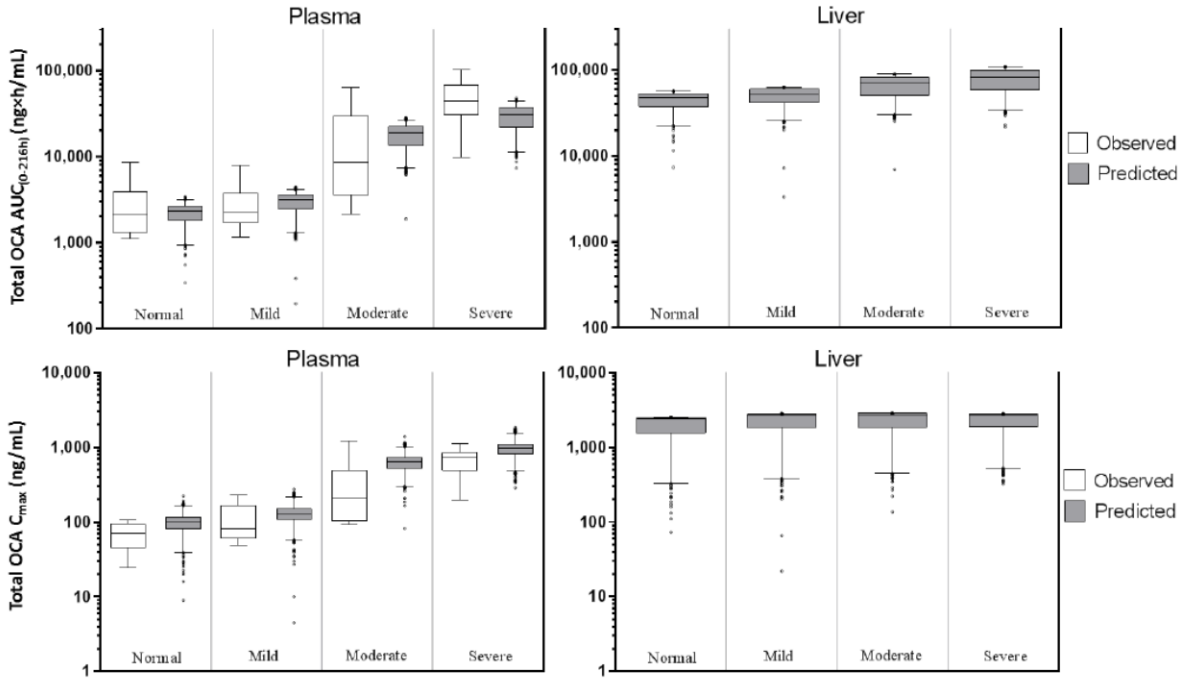
4. Results

4.1. Does PBPK model adequately describe plasma pharmacokinetics of OCA and metabolites in subjects with normal hepatic function and subjects with varying degrees of hepatic impairment?

Yes, simulated plasma concentration-time profiles of OCA and conjugates in subjects with normal hepatic function and in subjects with portal hypertension generally described observed data.

A comparison of observed plasma exposure data (AUC and Cmax) of total OCA from Study 747-103 and simulated data with best-fit model for OCA after a single dose of 10 mg q.d. is shown in **Figure 4** (left panels) for subjects with normal hepatic function and subjects with various degrees of hepatic impairment. Although there is some over-prediction of plasma total OCA for moderate impairment scenario, the model seems to reasonably characterize the extreme scenarios bracketed by normal and severe hepatic impairment category. The corresponding predictions of liver concentrations for each of these hepatic impairment scenarios are shown on the right panels of **Figure 4** (See more on 4.2 below).

Figure 4: AUC and Cmax of systemic and liver concentration of total OCA by liver function in subjects from Study 747-103 (Source: Figure 4-2, [1])



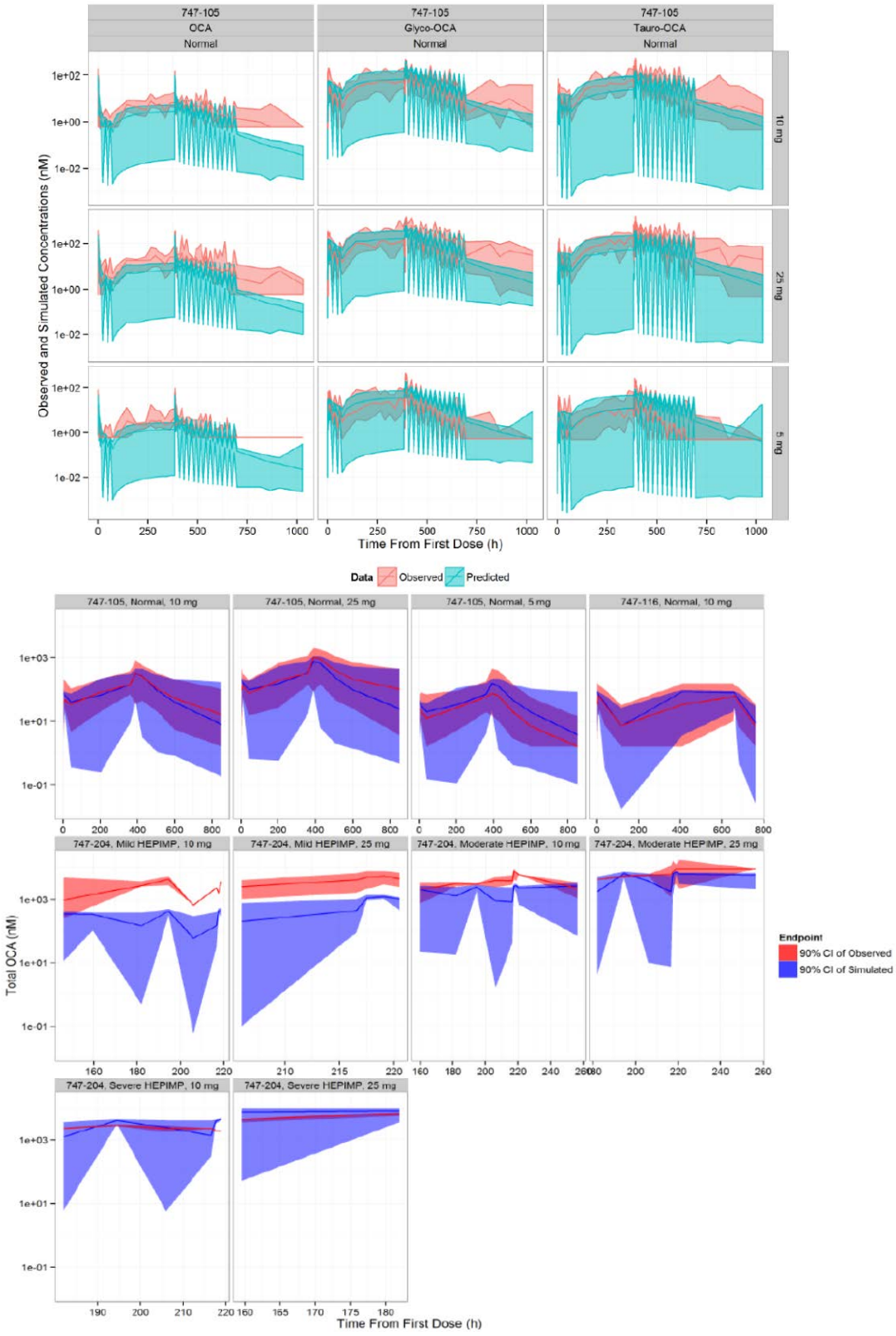
Observed data values are based on n =8 subjects by group of hepatic impairment; Predicted data values are based on 200 iterations Monte-Carlo simulations in 8 subjects by group of hepatic impairment; Boxplot whiskers represent 1st and 99th percentile.

AUC = area under the curve; C_{max} = maximum concentration; HEPIMP = hepatic impairment; n = number of subjects; OCA = obeticholic acid

Figure 5 shows VPC plots for verification dataset (Studies 747-105, 106, and 204) that was not being used during model development. For Study 747-105, there is a systematic bias of under-prediction (e.g., predictions for 10 and 25 mg, and OCA PK predictions for 5 mg). For hepatic impairment, there is an apparent under-prediction of total OCA in subjects categorized as mild

hepatic impairment based on Child-Pugh score in Study 747-204. The applicant hypothesized that these portal hypertension patients who were categorized CP-A may have physiological changes that are characteristic of moderate-severe hepatic impairment (See **4.4** for more discussion on target population). Model estimated magnitude of percent decreases in hepatic uptake of OCA species were 12%, 84%, and 91%, (exponential of -0.132, -1.86 ,and -2.37, respectively for "Hepup", Table 3) in subjects with mild, moderate, and severe hepatic impairment, respectively; model estimated magnitude of fold-increases in tauro-conjugation were 1.0- (no change), 2.9-, and 4.8-fold (exponential of 0.00481, 1.05, and 1.56, respectively for "tconj", Table 3) in subjects with mild, moderate, and severe hepatic impairment, respectively. Increases in absorption rate constant (K_a) and flow from bile to gall-bladder were also estimated. Of note, VPCs for all model building and verification datasets show high variability in plasma concentrations.

Figure 5: Visual predictive check (VPC) plots of OCA PBPK model for observed data not used during model development (updated Figures 7.13 and 7.14 [1,2])



4.2. Can applicant's PBPK models be used to simulate liver exposure of OCA and metabolites?

Yes. However, it has to be acknowledged that both CDCA model and OCA model have many limitations and certain assumptions have not been confirmed (See **4.4**). Nonetheless, sufficient evidence seems to support the use of OCA PBPK models to predict hepatic exposures of OCA and metabolites to support dosing recommendations of OCA in subjects with hepatic impairment.

First, the applicant was able to predict systemic and liver CDCA in healthy subjects and subjects with liver dysfunction. In response to FDA's 08242015IR, the applicant first stated that they re-produced modeling results based on Molino's CDCA model using Phoenix software (Phoenix CDCA model, [2]). Using the Phoenix CDCA model, the applicant conducted additional simulations to predict plasma and liver CDCA. For simulations of CDCA in subjects with severe hepatic impairment, effects of severe hepatic impairment on hepatic uptake and taurine conjugation estimated from OCA model were directly applied for respective pathways for CDCA, and changes in system parameters (e.g., shunting and decreased liver volume) were the same as OCA simulations (**Table 2**). **Table 4** shows that model predicted plasma CDCA exposures are generally consistent with that observed in subjects with normal liver function and subjects with severe liver impairment from several studies [3, 8, 12]. More importantly, the Phoenix CDCA model predictions appear in-line with observed liver CDCA exposure in subjects with normal hepatic function and in subjects with end-stage cholestasis or cirrhosis (non-cholestasis). Of note, systemic CDCA levels seem to vary significantly across different studies.

Table 4: Comparison of observed and simulated CDCA exposure in plasma and liver

	Endogenous bile acid concentrations (μM)	Observed	Simulated[b]
Fisher et al, 1996 [8]			
Normal hepatic function	Serum	1.45 [a]	-
	Liver	23.58 [a]	-
End-stage chronic cholestasis	Serum	53.98 [a]	-
	Liver	86.20 [a]	-
End-stage cirrhosis	Serum	57.88 [a]	-
	Liver	71.02 [a]	-
Stiehl et al 1990 [12]			
Stage I, II cirrhosis	Serum	3.1	-
	Liver	-	-
Stage IV cirrhosis	Serum	38.6	-
	Liver	-	-
study 747-103 [3]			
Normal hepatic function	Plasma	3.49	5
	Liver	-	69
Severe hepatic impairment (CP-C)	Plasma	61.9	47
	Liver	-	89

[a] Calculated based on the percentage of total endogenous bile acids digitized from Figures 2 (liver) and 5 (serum) from [8]. [b] Simulated using Phoenix CDCA model [2].

Second, modeling of both CDCA and OCA utilizes information of both compounds and a common systems model, which supports PBPK modeling for bile acids in general. The applicant also claimed that absorption, distribution, metabolism, and excretion (ADME) properties are generally comparable between CDCA and OCA, based on in vitro data as well as parameter estimated using respective PBPK models.

Last but not the least, observed plasma data of OCA and conjugates in subjects with varying degrees of hepatic impairment (Study 747-103) were critical for this analysis.

4.3. Should OCA dose be adjusted in subjects with hepatic impairment?

Yes, based on predicted plasma and liver exposures of OCA in subjects with hepatic impairment following different dosing schedules of OCA, and dose-response for pruritus (see main text of Question Based Review), a less frequent dosing schedule is recommended as starting dosing regimen in patients with moderate and severe hepatic impairment. If additional efficacy is desired, patients can be up-titrated via a combination of higher dose and more frequent dosing regimen depending on tolerability.

The FDA reviewers requested the applicant to provide simulations of plasma and liver OCA exposures in subjects with hepatic impairment following different OCA dosing schedules [2]. Predicted total OCA exposures in plasma and liver for subjects with normal hepatic function and subjects with hepatic impairment receiving 5 mg OCA q.d., q2d, q.w., q2w, and q.17.4.d are presented in **Table 5**. For patients with severe hepatic impairment, plasma total OCA exposure with 5 mg q.w. dosing is predicted to be similar to that for subjects with normal hepatic function and mild hepatic impairment receiving 5 mg OCA q.d.

Table 5: PBPK model simulated average plasma and liver steady state concentrations (Css,ave) for total OCA after a 5 mg q.d., q2d, q.w., q2w, and q.17.3.d (QD, Q2D, QW, Q2W, Q17.3D) dose of OCA stratified by hepatic function (Source: Table 2, [2]). Values are median [5th, 95th]

Hepatic Function	Dosing Interval				
	QD	Q2D	QW	Q2W	Q17.3D
Plasma $C_{ss,ave}$ (ng/mL) Median [5^{th}-95^{th}]					
Normal	63.3 [56.5-64.1]	31.6 [28.4-32.1]	9.06 [8.3-9.2]	4.54 [4.1-4.6]	3.66 [3.3-3.7]
Mild Impairment	85.9 [77.2-87]	43 [38.8-43.5]	12.3 [11-12.4]	6.13 [5.6-6.2]	4.97 [4.5-5]
Moderate Impairment	602 [511-608]	301 [256-304]	85.9 [74.1-86.8]	43 [36.2-43.4]	34.7 [28.3-35.3]
Severe Impairment	1090 [899-1100]	544 [443-551]	156 [130-157]	77.7 [63-78.4]	63.0 [49-63.6]
Liver $C_{ss,ave}$ (ng/mL)					
Normal	1260 [1140-1270]	627 [575-636]	180 [166-182]	89.9 [82.1-90.9]	72.8 [65.4-73.7]
Mild Impairment	1410 [1300-1430]	706 [648-714]	202 [183-204]	101 [92.3-102]	81.8 [74.9-82.8]
Moderate Impairment	2180 [1890-2210]	1090 [945-1100]	312 [274-315]	156 [134-158]	126 [105-128]
Severe Impairment	2840 [2390-2870]	1420 [1180-1440]	407 [346-410]	203 [168-205]	164 [131-166]

4.4. What are the limitations of PBPK model for OCA and CDCA?

Hepatic impairment causes multiple physiological changes that directly or indirectly affect the ADME processes of a drug [9,11]. Although many changes have been quantitatively or semi-quantitatively incorporated into PBPK modeling framework [9,11], predictive performance of these models in prospectively predicting the effect of varying degrees of hepatic impairment on a drug's pharmacokinetics has not been established [13]. This is further complicated by clinical practice of categorizing hepatic impairment using CP score, which is a composite score of multiple clinical measures. For example, two patients of different liver disease origins may be categorized to have the same CP score. System models for hepatic impairment subjects developed according to CP categorization inherently carry large uncertainty when being used to predict the effect of hepatic impairment on drug exposure.

Molino et. al. [7] acknowledged deficiencies of the CDCA model, including a simplified enterocyte space, a simplified sinusoidal compartment ignoring zonation, the combination of duodeno-jejunum which was not able to explain immediate postprandial increase, pressure changes and fluid absorption by gall-bladder, fixed ratio of conjugation with glycine and taurine whereas taurine conjugation may vary depending on taurine pool, and ignorance of food-bile acid interaction in intestinal lumen. Of note, the CDCA model was used only to simulate total CDCA in small intestine and serum total CDCA during digestion of a meal, of which observed data are available [7]. Thus Molino model did not include some key elements such transporter regulation which is essential to estimate bile acid exposure in liver, and should not be considered as a model that has been fully verified.

Molino's CDCA model was then modified to simulate the pharmacokinetic profiles for OCA and its two conjugates in plasma and liver. However, discrepancies among the terminology and units make it difficult to compare CDCA model parameters listed in Molino's report (Tables 5 and 7, [7]) and that summarized in [1]. For example, one should be able to compare the flow constant (f22) in the report (0.003 L/min, [1]) to the transfer coefficient (f22, 0.003 per min, table 5 of ref [7]) or flow (bile duct to gall-bladder, 0.06 L/min, table 7 of ref [7]) used in Molino's paper [7]. Also related to transparency of the model modification, one should be able to identify how many parameters were actually modified by comparing the original CDCA model parameters and the updated OCA parameters. For example, transport rates for glyco-CDCA and tauro-CDCA from sinusoidal to liver are the same, but these rates are different for OCA conjugates.

Many assumptions for both CDCA and OCA models, though plausible, cannot be confirmed or adequately justified (i.e., negligible biliary excretion of parent CDCA and OCA, assumption on hepatic first-pass extraction of OCA, rate of de-conjugation of glycine conjugate was 3-times higher than that of taurine conjugate, percentage of glyco-CDCA entering ilium). With regard to hepatic impairment, the model assumed increased tauro-conjugation by hepatic impairment (**Table 3**) that is not bile acid specific. Of note conflicted observations of the total glycine to taurine ratio were reported for patients with liver disease. For example, a decreased total glycine to taurine ratio was reported in PBC patients [14], and Linnet (1982) reported that total glycine to taurine ratio was significantly lower in subjects with extrahepatic cholestasis (median 1.1) than in subjects with cirrhosis (median, 2.0) and in subjects with normal hepatic function (median, 1.7) [15].

Other discrepancies identified include:

- The combined volume of jejunal, ileal, and colonic spaces was 0.9 L, instead of 0.92 L. Flow constants for f1, f3, f4, and f5 are 16.1, 94.3, 5.9, 450 L/h.

- Gallbladder emptying after meal was assumed to be 90 min for OCA model [1] but was stated to be 120 min in response to the information request [2]. The same value was 120 min for CDCA [7].
- The same parameters were tested for the value of 210 min for Phoenix CDCA model [2] to match the original simulation of the effect of food on CDCA pharmacokinetics, whereas the original work reported the use of 120 min [7].

5. Conclusion

The applicant's model was informed by plasma concentrations of OCA and conjugates observed in subjects with varying degrees of hepatic impairment (relatively rich model development dataset) and was able to generally capture OCA exposure observed in subjects with normal hepatic function and with hepatic impairment (verification datasets). The applicant also predicted plasma and liver exposures of CDCA in subjects with normal hepatic function and in subjects with severe hepatic impairment (cholestasis and non-cholestasis). Despite several limitations recognized for modeling of both OCA and CDCA and the lack of predictability of PBPK for hepatic impairment [13], the applicant's prediction of liver OCA exposures using PBPK is considered useful in supporting dosing recommendations of OCA in patients with hepatic impairment.

Although the magnitude of elevation in liver OCA concentrations in subjects with severe hepatic impairment was predicted to be less than that in plasma concentrations, there were significantly higher plasma OCA exposures in subjects with moderate and severe hepatic impairment compared to patients with normal liver function. With the evidence of dose-response relationship for pruritus (and related discontinuations, see main text of Question Based Review) and unknown relationship of plasma/liver exposures to pruritus, a conservative approach of adjustment of starting dose in subjects with severe hepatic impairment to match plasma exposures to those subjects with normal hepatic function, followed by subsequent up-titrations of dose and dosing frequency, appears reasonable.

6. References

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